Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

[FR Doc. 85-29671 Filed 12-11-85; 12:43 pm]

BILLING CODE 6714-01-M

5

FEDERAL ELECTION COMMISSION

"FEDERAL REGISTER" NO: 85-29583.

PREVIOUSLY ANNOUNCED DATE AND TIME: Tuesday, December 17, 1985, 10:00 a.m. (open session).

THE FOLLOWING ITEM HAS BEEN ADDED TO THE AGENDA: Request by the Larouche Campaign To Make an Oral Presentation.

PERSON TO CONTACT FOR INFORMATION: Mr. Fred Eiland, Information Officer 202-523-4065.

Marjorie W. Emmons,

Secretary of the Commission.

[FR Doc. 85-29648 Filed 12-11-85; 11:45 am]

BILLING CODE 6715-01-M

6

FEDERAL ENERGY REGULATORY COMMISSION

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: December 3, 1985, 49 FR 49658.

PREVIOUSLY ANNOUNCED TIME AND DATE OF MEETING: 9:00 a.m., December 10, 1985.

CHANGE IN THE MEETING: The following item was added:

Item No., Docket No. and Company

RP-1—TA82-1-21-001, *et al.*, Columbia Gas Transmission Corporation

Kenneth F. Plumb,

Secretary.

[FR Doc. 85-29701 Filed 12-11-85; 2:15 pm]

BILLING CODE 6717-02-M

7

FEDERAL MARITIME COMMISSION

TIME AND DATE: 10:00 a.m., December 18, 1985.

PLACE: Hearing Room One, 1100 L Street, NW., Washington, DC 20573.

STATUS: Parts of the meeting will be open to the public. The rest of the meeting will be closed to the public.

MATTERS TO BE CONSIDERED:

Portions open to the public:

1. Agreement No. 203-010852: Discussion Agreement in the Far East-U.S. Atlantic Trades among Nippon Yusen Kaisha, Mitsui O.S.K. Lines, Ltd., and Yamashita-Shinnihon Steamship Co., Ltd.

2. Docket No. 85-19: Tariff Publication of Free Time and Detention Charges Applicable to Carrier Equipment Interchanged With Shippers or Their Agents—Consideration of comments filed in response to Notice of Proposed Rulemaking, and certain other pleadings.

Portions closed to the public:

1. Consideration of the application for an ocean freight forwarder license filed by Four Winds International, Inc.

2. Consideraton of Matson Navigation Company Tariff FMC-F No. 18 applicable between ports in the State of Hawaii, and protests thereto.

3. Consideration of a proposed 2.5 percent overall rate increase filed by Matson Navigation Company in the Hawaiian Trade, and the status of pending Docket No. 85-3: Matson Navigation Company Proposed Overall Rate Increase of 2.5 percent between United States Pacific Coast Ports and Hawaii Ports.

4. Special Docket No. 1343: Application of OOCL-Seapac Services, Inc. for the benefit of Minnesota Mining and Manufacturing Co.—Consideration of the record.

5. Special Docket No. 1349: Application of Australia-New Zealand Container Line for the benefit of Meadowsfreight New Zealand Ltd.—Consideration of the record.

CONTACT PERSON FOR MORE INFORMATION: Bruce A. Dombrowski, Acting Secretary, (202) 523-5725.

Bruce A. Dombrowski,

Acting Secretary.

[FR Doc. 85-29703 Filed 12-11-85; 2:19 pm]

BILLING CODE 6730-01-M

8

SYNTHETIC FUELS CORPORATION

SUMMARY: Interested members of the public are advised that a meeting of the Board of Directors of the United States Synthetic Fuels Corporation will be held at the time, date and place specified below. This public announcement is made pursuant to the open meeting requirements of section 116(f)(1) of the Energy Security Act (94 Stat. 611, 637; 42 U.S.C. 8701, 8712(f)(1)) and section 4 of the Corporation's Statement of Policy on Public Access to Board meetings. During the meeting, the Board of Directors will consider a resolution to close the meeting pursuant to Article II, section 4 of the Corporation's By-Laws, section 116(f) of the said Act and sections 4 and 5 of the said policy.

Open Session

I. Call to Order—Chairman's Opening Remarks
II. Approval of Board Minutes
III. Report of Compensation Committee on Officer Election
IV. Review of Paraho-Ute Project's Compliance with Requirements of the Third General Solicitation
V. Review of Updated Information from the Northern Peat Project
VI. Consideration of the Seep Ridge Project
A. Approval of the Deep Ridge Environmental Monitoring Plan Outline
B. Approval of an Award of Financial Assistance to the Seep Ridge Project
VII. Review of Loan Guarantee Documentation for the Parachute Creek Project
VIII. Consideration of Directors' Financial Interests
IX. Resolution to Close the Meeting

Closed Session

X. Review of Loan Guarantee Documentation for the Parachute Creek Project
XI. Status Report on Cathedral Bluffs Project

TIME AND DATE: 10:15 a.m., December 17, 1985.

PLACE: 2121 K Street, NW, Room 503 and 403, Washington, DC 20586.

PERSON TO CONTACT FOR INFORMATION: If you have any questions regarding this meeting, please contact Ms. Karen Hutchison, Director-Media Relations, at (202) 822-6455.

Dated: December 10, 1985.

United States Synthetic Fuels Corporation.

March Coleman,

Assistant General Counsel-Corporate and Litigation.

[FR Doc. 85-29608 Filed 12-10-85; 4:56 pm]

BILLING CODE 000-00-M

9

TENNESSEE VALLEY AUTHORITY

[Meeting No. 1361]

TIME AND DATE: 10:30 a.m., (EST), Tuesday, December 17, 1985.

PLACE: TVA West Tower Auditorium, 400 West Summit Hill Drive, Knoxville, Tennessee.

STATUS: Open.

Agenda

Approval of minutes of meeting held on November 26, 1985.

Discussion Items

1. A follow-up report on implementation of recommendations from the 1984 Groundwater Assessment discussed at the September 12, 1984, Board meeting, the results and recommendations from the First Tennessee Development District groundwater demonstration, and the products which have resulted from these projects.

Action Items

B—Purchase Awards

B1. Requisition 50—Spot coal for Cumberland Steam Plant.

B2. Negotiation GB-451985—Turbine diaphragms for Widows Creek Fossil Plant "A" units 1-3.

B3. Negotiation GC-453816—Steam gland conversion packages for Kingston and Shawnee fossil plants.

C—Power Items

C1. Supplement to Contract No. TV-62311A between Tennessee Emergency Management

Agency and TVA for cooperation in the development and implementation of radiological emergency plans as required by the Nuclear Regulatory Commission and the Federal Emergency Management Agency.

* C2. Proposed agreements with Shamrock Coal Company relating to mining of a portion of TVA's Red Bird coal reserves located in Clay County, Kentucky

D—Personnel Items

*D1. Personal services contract with Management Analysis Company, San Diego, California, to provide the services of William Bibb, as a loaned employee, to serve as Site Director of TVA's Browns Ferry Nuclear Power Plant located at Athens, Alabama.

*D2. Personal services contract with Paul R. Ray & Company, Inc., Atlanta, Georgia, to assist in filling the positions of Site Director, Browns Ferry Nuclear Plant, and Manager, Engineering and Construction.

E—Real Property Transactions

E1. Filing of condemnation cases.

E2. Modification of deed to Chattanooga Yacht club affecting a 5.9-acre portion of Chickamauga Reservoir land located in Hamilton County, Tennesee, to provide for abandonment of a filling condition and sufferance of the existing clubhouse encroachment—Tract No. XCR–83.

E3. Grant of 30-year easement to Union County, Tennessee, for the construction, operation, and maintenance of public recreational facilities affecting approximately 15.8 acres of Norris Reservoir land located in Union County, Tennessee—Tract No. XTNR–106RE.

E4. Grants of permanent easement to (1) State of Alabama for the construction, operation, and maintenance of a highway—Tract No. XTWDRT–4H, 16.9 acres; (2) Board of Water and Sewer Commissioners of the City of Florence, Alabama, for the construction, operation, and maintenace of a water treatment plant—Tract No. XTWDRT–5WP, 8.5 acres; and (3) the City of Florence, Alabama, for public recreation purposes—Tract No. XTWDRT–2RE, 82.0 acres; all easements affecting Wilson Dam Reservation land located in Lauderdale County, Alabama.

F—Unclassified

F1. Agreement between TVA and the Retirement system covering arrangements for loan by TVA to the Retirement System's Voluntary Retirement Savings and Investment Plan for Members of the Retirement System—Interest Fund II.

F2. Subagreement No. 41 under the TVA/U.S. Department of Energy Memorandum of Understanding No. TV–48296A covering arrangements for fabrication and test of a 36-volt lithium alloy/iron monosulfied battery for electric vehicle application.

F3. Technical Assistance Plan and Interagency Agreement Between TVA and U.S. Department of Energy covering arrangements for specialized technical assistance by DOE relating to startup and continued safe operation of TVA's nuclear power plants (Agreement No. TV–68345A); and Subagreement No. 1., "TVA Weld Quality Evaluation, Watts Bar Unit 1."

F4. Appointment of Director, Office of Small and Disadvantaged Business Utilization, as TVA's Advocate for Competition in connection with TVA's Automatic Data Procesing procurements that are subject to regulation under the Brooks Act.

*Items approved by individual Board Members. This would give formal ratification to the Board's action.

CONTACT PERSON FOR MORE INFORMATION: Craven H. Crowell, Jr., Director of Information, or a member of his staff can respond to requests for information about this meeting. Call (615) 632–8000, Knoxville, Tennessee. Information is also available at TVA's Washington Office (202) 245–0101.

Dated: December 10, 1985.

J.G. Stewart.

Manager of Corporate Administration and Planning.

[FR Doc. 85–29637 Filed 12–11–85; 10:51 am]

BILLING CODE 8120–01–M

federal register

Friday
December 13, 1985

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 610

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. 80N-0208]

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations in response to the report and recommendations of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel). The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, antitoxins, and immune globulins. On the basis of the Panel's findings and recommendations, FDA is proposing to classify these products in Category I (safe, effective, and not misbranded), Category II (unsafe, ineffective, or misbranded), or Category IIIB (off the market pending completion of studies permitting a determination of effectiveness). Products recommended for Category IIIA (formerly defined as on the market during further studies in support of effectiveness) will be reviewed by the Vaccines and Related Biological Products Advisory Committee for reclassification into Category I or II. In the near future, FDA will publish a notice of opportunity for hearing (NOH) to revoke the licenses for products in Category II and Category IIIB. Comments and additional data will be requested in the NOH.

DATES: Comments on the proposed classification of products into Category I and on proposed amendments to the biologics regulations should be submitted by March 13, 1986. Comments on the confidentiality of data submitted for review by the Panel should be submitted before January 13, 1986. FDA proposes that any final regulation based on this proposal become effective 60 days after the date the final regulation is published in the **Federal Register**. Labeling requirements, including the requirements in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57), would become effective 30 months after the date of publication of the final rule in the **Federal Register**.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven F. Falter, Center for Drugs and Biologics (HFN-364), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of February 13, 1973 (38 FR 4319), FDA issued § 601.25 (21 CFR 601.25) concerning procedures for the review of the safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. Under the panel assignments published in the **Federal Register** of June 19, 1974 (39 FR 21176), the biological products reviewed were assigned to one of the following categories: (a) Bacterial vaccines and bacterial antigens with "no U.S. standard of potency," (b) bacterial vaccines and toxoids with standards of potency, (c) viral vaccines and rickettsial vaccines, (d) allergenic extracts, (e) skin test antigens, and (f) blood and blood derivatives.

Under § 601.25, FDA assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the Commissioner which was to: (1) Evaluate the safety and effectiveness of the biological products, (2) review labeling of the biological products, and (3) identify the biological products under review that are safe, effective, and not misbranded. The advisory report includes recommendations classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel's statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by the Panel to be unsafe, ineffective, or misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. Those biological products in Category III for which continued licensing, manufacturing, and marketing during the period of further testing are recommended are designated as Category IIIA. Those biological products in Category III for which suspension of the product licenses pending submission of additional data are recommended are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

The definition above of Category IIIA was applied at the time of the Panel's review and served as a basis for the Panel's recommendations. In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA revised § 601.25 and created a new § 601.26 (21 CFR 601.26) to provide for the review by an advisory review panel of products currently recommended to be in Category IIIA. The purpose of the review will be to reclassify each Category IIIA product into either Category I or Category II as defined above, based on the available evidence for effectiveness. A more detailed description of the procedures for the review and reclassification of the products recommended for Category IIIA by the Panel appears later in this document in paragraph 1d of FDA's response to the Panel's report.

In this advisory report, some biological products are designated as Category IIIC, based on the Panel's conclusion that it was not possible to classify these products because of essentially administrative problems, rather than because of scientific questions. For example, some licenses are held for products which the manufacturer has not produced or marketed for many years. Other licenses are held for products for which there is no labeling, and which are manufactured only for combination with other biologically active components. The Panel has recommended that the licenses for products placed in Category IIIC be revoked, because the Panel was unable to determine the potential benefits and risks of the products in the event they were to be marketed. However, the Panel noted that in some cases it may be preferable for FDA and the manufacturer to take appropriate administrative actions to satisfactorily resolve information deficiencies, rather than to revoke the product license.

In the **Federal Register** of February 28, 1973 (38 FR 4359), FDA requested data and information regarding bacterial vaccines and toxoids with U.S.

standards of potency. Additional data and information regarding the safety and effectiveness of related immune globulins and sera were requested in the Federal Register of June 19, 1974 (38 FR 21176).

Some concern has been expressed that information submitted to FDA under § 601.25 will become public information. Data and information submitted in response to the February 28, 1973 and June 19, 1974 notices and falling within the provisions of 5 U.S.C. 552(b), 18 U.S.C. 1905, or 21 U.S.C. 331(j) have been handled as confidential. However, with the publication of this proposed implementation and the Panel's findings, such data and information will, under § 601.25(b)(2), be made publicly available after January 13, 1986, and may be reviewed at the office of the Dockets Management Branch, except to the extent that the person submitting the data and information demonstrates that it still falls within the confidentiality provisions of one or more of the above statutes. Accordingly, comments concerning confidentiality should be submitted by January 13, 1986. A letter dated October 21, 1985, was sent to each manufacturer having products under review by this Panel, informing them of the impending release of data and information and asking that the manufacturers promptly submit any comments concerning confidentiality.

The Panel appointed by FDA to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of bacterial vaccines, toxoids, related antitoxins, and immune globulins included the following individuals:

Panel Chairman, Gene H. Stollerman, M.D., Professor and Chairman, Department of Medicine, University of Tennessee College Memphis, TN 38163 (now Professor of Medicine, Boston University Medical Center);

Geoffery Edsall, M.D. (deceased), Professor Emeritus of Microbiology (Harvard School of Public Health and London School of Hygiene and Tropical Medicine);

Theodore C. Eickhoff, M.D., Professor of Medicine, Head, Division of Infectious Diseases, University of Colorado Medical Center, Denver, CO 80262;

John C. Feeley, Ph.D., Chief, Bacterial Immunology Branch (now Assistant Director for Laboratory Sciences, Bacterial Disease Division), Centers for Disease Control, Atlanta, GA 30333;

Hjordis M. Foy, M.D., Ph.D. Associate Professor (Since July 1, 1976, Professor), Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195;

Edward A. Mortimer, Jr., M.D., Chairman of the Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, NM 87131. (Since February 1, 1975, Professor and Chairman of the Department of Community Health and Professor of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106.)

Jay P. Sanford, M.D., Professor, Department of Internal Medicine, University of Texas, Southwestern Medical School at Dallas, Dallas, TX 75235. (Since June 1, 1975, Dean, School of Medicine, Uniformed Services University, Bethesda, MD 20014.)

The Panel was convened on July 12, 1973, in an organizational meeting. Working meetings were held on: July 12, September 24–25, November 9–10, December 13–14, 1973; February 13–14, April 9–10, June 13–14, September 12–13, November 7–8, 1974; January 13–14, February 24–25, May 15–16, June 19–20, September 11–12, November 20–21, 1975; January 12–13, March 27–28, May 17–18, July 22–23, October 23, December 14–15, 1976; March 24–25, December 12–13, 1977; and February 1–2, 1979.

Two nonvoting liaison representatives served on the Panel. Ms. Laryl Lee Delker, nominated by the Consumer Federation of America, served as the consumer representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D., substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Scientific Advisors and Consultants, FDA. Jack Gertzog, Deputy Director, Office of Scientific Advisors and Consultants, FDA, served as Executive Secretary of the Panel. Margaret Pittman, Ph.D., was selected by the Panel as a consultant.

Over 120 persons requested an opportunity or were otherwise invited to appear before the Panel and present their views on one or more of the vaccines and related matters. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Dockets Management Branch.

The Panel on Review of Bacterial Vaccines and Toxoids evaluated all data submitted for the following vaccines, toxoids, and other related products:

TABLE 1.—LIST OF PRODUCTS REVIEWED BY PANEL

Manufacturer	Product
Abbott Laboratories	Tetanus immune globulin (human).
Advance Biofacturers Corp.	Collagenase.
Armour Pharmaceutical Co.	Tetanus immune globulin (human).
Bureau of Laboratories, Michigan Department of Public Health.	Anthrax vaccine adsorbed, diphtheria antitoxin, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, diphtheria toxoid adsorbed, pertussis vaccine, pertussis vaccine adsorbed, tetanus immune globulin (human), tetanus toxoid adsorbed, typhoid vaccine.
Connaught Laboratories, Ltd.	BCG vaccine, botulism antitoxin, diphtheria toxoid, tetanus toxoid.
Cutter Laboratories, Inc	Pertussis immune globulin (human), plaque vaccine, tetanus immune glob-ulin (human), tetanus toxoid.
Dow Chemical Co. (The)	Diphtheria and tetanus toxoids adsorbed, diphtheria tetanus toxoids and pertussis vaccine adsorbed, diphtheria toxoid, diphtheria toxoid and pertussis vaccine adsorbed, pertussis vaccine, tetanus immune glob-ulin (human), tetanus toxoid tetanus toxoid, adsorbed.
Eli Lilly and Co.	Cholera vaccine, diphtheria and tetanus toxoids, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, pertussis vaccine, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine.
E.R. Squibb and Sons, Inc.	Tetanus immune globulin (human).
Glaxo Laboratories, Ltd	BCG vaccine.
Istituto Sieroterapico Vaccinogeno Toscano "Sclavo".	Diphtheria antitoxin, diphtheria toxoid, diphtheria toxoid adsorbed, tetanus antitoxin, tetanus toxoid, tetanus toxoid adsorbed.

TABLE 1.—LIST OF PRODUCTS REVIEWED BY PANEL—Continued

Manufacturer	Product
Lederle Laboratories, Division of American Cyanamid Co.	Botulism antitoxin, cholera vaccine, diphtheria antitoxin, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, gas gangrene polyvalent antitoxin, pertussis vaccine, streptokinase-streptodornase, tetanus antitoxin, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus and gas gangrene polyvalent antitoxin, tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed.
Massachusetts Public Health Biologic Laboratories.	Diphtheria antitoxin, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, diphtheria toxoid, tetanus antitoxin, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Cholera vaccine, diphtheria and tetanus toxoids and pertussis vaccine adsorbed, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, tetanus toxoid adsorbed, tetanus immune globulin (human), typhoid vaccine.
Merrell-National Laboratories, Division of Richardson-Merrell, Inc.	Cholera vaccine, diphtheria antitoxin, diphtheria and tetanus toxoids and Pertussis vaccine, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, Pertussis vaccine, tetanus antitoxin, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, tetanus toxoid adsorbed.
Metabolic, Inc.	Tetanus immune globulin (human).
Osterreichisches Institut Fur Haemoderivate G.m.b.H.	Tetanus immune globulin (human).
Parke, Davis and Co.	Diphtheria and tetanus toxoids, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed and poliomyelitis vaccine, diphtheria and tetanus toxoids and pertussis and poliomyelitis vaccine adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, diphtheria toxoid adsorbed, Pertussis vaccine, Pertussis vaccine adsorbed, tetanus antitoxin, tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed.
Swiss Serum and Vaccine Institute, Berne.	Tetanus antitoxin, tetanus toxoid adsorbed.
Texas Department of Health Resources.	Diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, Pertussis vaccine, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus toxoid, typhoid vaccine.
Travenol Laboratories, Inc., Hyland Division.	Pertussis immune globulin (human), tetanus immune globulin (human).
University of Illinois	BCG vaccine.
Wyeth Laboratories, Inc.	Cholera vaccine, diphtheria and tetanus toxoids adsorbed, diphtheria and tetanus toxoids and Pertussis vaccine adsorbed, diphtheria toxoid, diphtheria toxoid adsorbed, Pertussis vaccine, tetanus and diphtheria toxoids adsorbed (for adult use), tetanus immune globulin (human), tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine.

Only biological products that were licensed prior to July 1, 1972, are reviewed in this report.

The Advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of bacterial vaccines and toxoids has completed its review as follows:

Basis of Evaluation

1. *General background and history.* The diseases of man caused by bacteria and by some of their specific extracellular toxins from which useful vaccines have been produced represent extraordinarily diverse pathologic processes. The diseases range from tetanus to tuberculosis; the former is an accute illness caused by a single well-defined toxin and the letter is a chronic disease due to intricate bacterial-host cell interactions resulting in a wide variety of lesions. Moreover, the degree of protection offered by current immunization practices against these diseases range from virtually complete efficacy, as in the case of tetanus, to a very limited and temporary benefit, as in the case of choloera. A brief account of the history of immunization against these diseases may help both the lay and professional public to appreciate the background of our current achievements and dilemmas against which this Panel has been obliged to exercise its judgment in assesing the safety and efficacy of the products under its purview.

It is important for the public and its agencies to appreciate the tentative and envolving nature of the science of immuization, particulary to combat the notion that decisions made in the public interest at one point in time are necessarily valid and binding at another. The foundations of the modern science of bacteriology are more than a century old and were laid by Louis Pasteur and Robert Koch, who died within the momory of some persons still alive. Pasteur not only established the germ theory of disease, but, just 100 years ago (in 1877) discovered and applied the principles of active immunization by using living, attenuated cultures—"live vaccines." He argued that if Jenner could use cowpox (what Pasteur thought to be attenuated smallpox) as a vaccine, the same might be done with attenuated anthrax. This he succeeded in doing in preparing attenuated chicken cholera and anthrax vaccines for animals. Subsequently, "killed' bacterial vaccines were made by the end of the 19th century when A. E. Wright in England, among others, began immunizing against typhoid fever with heat-killed whole bacterial cells. Epidemics of cholera and plague, rampant in various parts of the world at the time, were quickly attacked with other vaccines many of which were similarly made from killed whole bacteria. In all three diseases, the vaccines seemed to afford some useful protection before advances could be made in worldwide sanitation and well before the instruction of antibiotics.

At the close of the 19th century, Koch was attempting to prevent and even to treat tuberculosis with tuberculin, the culture filtrate of tuburcule with bacilli. His failure to do so, plus the serious toxic and untoward effects that this treatment had on the disease, created reservations in the minds of both professionals and the public concerning the risks as well as the benefits of immunization attempts. Nonetheless, despite this setback, the first living bacterial vaccine to be used on a large scale in man came as a sequel to Koch's work when Calmette and Guerin introduced BCG vaccine into human immunization procedures in 1921.

To appreciate the speed of the development of the science of immunology, it is necessary to acknowledge not only the dramatic empirical discoveries of successful vaccines, but also the discovery of the immunologic processes upon which further progress in immunization was based. Two major forms of host defenses are referred to repeatedly in this report. They also have their origins in the medically tumultuous era of the late 19th century. Eli Metchnikoff, the Russion biologist who studied under Pasteur and eventually become a director of the Pasteur Institute, developed the concept of "phagocytosis." He gave the name of "phagocytes" (eating cells) to body cells in blood, blood vessels, lymph nodes, bone marrow, liver, and spleen which digest and destroy invading microorganisms as well as other foreign microparticles. This system of cellular immunity, responsible for the clearing of foreign agents from within the host, he considered to be the backbone of host

defense against infection. The "humoral theory" was introduced at the same time by G. H. F. Nutthall of Cambridge who studied the killing action of blood on bacteria (bactericidal effects). He showed these effects were due to chemical products of cells in blood serum and body fluids—substances called "antibodies" which could destroy or inactive some bacteria without help from phagocytes. By 1894, Richard Pfeiffer, one of Koch's pupils, demonstrated that such antibodies caused the disintegration of cholera vibrios. These he called "bacteriolysins."

The synthesis of humoral and cellular mechanisms of immunity was proposed by the Wright in 1903 when he demonstrated the prophagocytic effect of specific antibodies. Wright named antibodies "opsonins" or "bacteriotropins" which enhance the ability of phagocytic cells to recognize, ingest, and kill microorganisms. Although Wright's concepts of the interaction of antibodies and and cells applied well to antibacterial immunity against invasive bacterial diseases such as typhoid, pneumonia, streptococcal infections, and meningitis, it did not pertain as much to diseases produced by the action of toxins liberated by bacteria.

In diseases like diphtheria, tetanus, and botulism, neutralization of the soluble bacterial toxins (exotoxins) liberated during infection is of the utmost importance in the prevention of the diseases caused by these organisms. Thus, antibodies that neutralize such toxins are the basis of "antitoxic immunity," which constitutes an area of immunologic knowledge that is on a much firmer basis than the understanding of many forms of antibacterial immunity.

Again, in the last two decades of the 19th century, the principles of antitoxic immunity were established when Pasteur's associate, Pierre Roux, showed the dephtheria bacillus produced a powerful soluble toxin in the culture filtrate of the organism. Behring and Kitasato, disciples of Koch, by 1890 had prepared an antibody to the diphtheria toxin which they termed "antitoxin" and with such immune sera began the era of "passive immunization." Thus, antitoxin (serum prepared in horses against such toxins) could be used to prevent and treat certain diseases. The denaturation of the toxins with the addition of formalin rendered them harmless when injected into man and animals, but they still retained their ability to produce antitoxin antibodies. "Active" immunization against diphtheria and tetanus with these toxoids subsequently became routine in most countries of the world.

"Passive" immunization consists of the injection of antibodies made by another host, human or animal, into the person to be protected. Antibodies remain in that person for only a short time, however, until they are broken down, and thus provide only temporary benefit. Active immunization, on the other hand, consists of inducing the person to be protected to produce their own antibodies by giving small doses of the microorganism or toxin in a form that will not cause serious illness in the person. Once active immunity is induced, it tends to persist for long periods of time.

The important differences between passive and active immunization were clearly established in the 1890's by Jules Bordet and by Paul Ehrlich whose brilliant career not only included the standardization of toxins and antitoxins and the foundations of modern immunochemistry, but also led to the recognition of the presence in the blood and body tissues of "complement," the system of enzymes that are activated by antigen-antibody complexes and that result in the cellular and vascular events of inflammation leading to the destruction of bacteria and viruses and to the stimulation of the host cells which phagocytize and destroy organisms.

From Ehrlich's systematic, quantitative approach to the neutralization of toxins emerged the triumph over diphtheria and subsequently, even more brilliantly, over tetanus. By the First World War, the lives of many wounded men were saved by passive tetanus immunization and the control of tetanus during the Second World War with the toxiod could be regarded as a modern miracle of immunization.

Soon after the beginnings of immunology came the development of government supervising authorities in many countries to regulate standards of purity and potency to which preparations had to conform before they were released for public usage. The importance of international standards of vaccines was recognized by the Health Commission of the League of Nations which in 1929 appointed a permanent Commission on Biological Standardization. As a result, potency of vaccines were expressed in a more uniform notation which was accepted and understood throughout the world.

In the United States and Great Britain, the control of biological substances for sale became essentially the responsibility of the producing laboratory, but manufacturers worked under licenses issued by government agencies such as the current Bureau of Biologics, Food and Drug Administration, and Great Britain's Ministry of Health, respectively, and under standards of safety and potency defined by the regulations developed by these agencies. (Note: Because of a reorganization of FDA accomplished after the Panel submitted its report, the Bureau of Biologics is now the Office of Biologics Research and Review, Center for Drugs and Biologics (see 49 FR 10166; March 19, 1984).)

It has become generally understood that a successful and acceptable vaccine must be: (1) Safe and (2) effective. Safety means that the preparation used must not cause the disease against which it is directed and that the occurrence of reactions, both local and general, must be within acceptable limits. Efficacy implies a useful degree of clinical protection: In some infections, the best guide to immunity is the amount of circulating antibody in the blood against the causative agent. It is the clinical trial, however, which must provide the final critical assessment of the efficacy and safety of the new vaccine. The basic requirements of filed trials meeting modern critical criteria were well described by 1957 by W.C. Cockburn, and are elaborated upon in the Panel's generic statement on the requirements for a well-controlled field trial.

The World Health Organization, which was established in 1948, encouraged international cooperation in solving health problems and has been helpful in continuing with the work on establishing and promoting international standards for biological products which had begun with the work of the League of Nations.

The growing sophistication of the standardization of vaccines ultimately resulted in changes in Federal law and regulations whereby this Panel was established to help to determine whether currently licensed vaccines produced according to specified standards of potency are both safe and effective for human usage. Although the aims of the act are praiseworthy and the action timely, the judgment concerning safety and efficacy of bacterial vaccines and toxoids presents some complex and knotty overall problems.

2. *Overall problems*—a. *Determination of safety*—(1) *Risk/benefit assessment.* The concept of risks and benefits is a fundamental one in a consideration of vaccines, or any other therapeutic or preventive modality. Risks are considered to include the risk

of an adverse reaction to the vaccine; benefits, however, include not only the likelihood that a vaccine will protect against a disease, that is, its efficacy, but also that it will ameliorate the severity of the disease to be prevented. Greater risks of adverse effects might be tolerated for a vaccine that provided protection against a lethal disease than for a vaccine against a disease that is basically benign. Furthermore, "benefit" may extend not only to the recipient of the vaccine, but in some cases to society at large.

The risks versus the benefits of the vaccines covered in this report are, like other features of these vaccines, very diverse. Standards of safety must again be individualized for each kind of vaccine. For example, tetanus toxoid is among the safest of all vaccines and its benefits are enormous. Attempts to reduce its reactivity further must not, therefore, jeopardize its efficacy. Although the benefits of pertussis vaccine in infants have occasionally been questioned, the preponderance of expert judgment is definitely favorable. But this vaccine is highly reactive and very justifiable attempts to reduce its reactivity by purification are virtually thwarted by the dependence of the assessment of efficacy upon a mouse protection model which must be linked to clinical trials to confirm its validity. Despite the vaccine's hazards, therefore, attempts to modify it to improve its tolerance are difficult with present knowledge.

Risk/benefit assessments vary not only between one generic group of vaccines and another, but within a generic category, each product must be assessed individually for its special features that vary from the norm. In addition, some products were modified without updated evidence of their clinical efficacy. In some very uniform vaccines, such as tetanus toxoid, a relatively minor change in production to achieve greater purfication or a decreased concentration of toxoid to reduce reaction rates was examined by the Panel very critically because of the need to ensure that the vaccine performed at its expected high level of protection.

The concept of risk/benefit also includes the public's as well as the individual's protection. A vaccine that produces considerable discomfort and sometimes even severe general reactions is more acceptable if the protection it affords the individual also results in protection of the community by reducing contagion. Such is the case in vaccination against pertussis, a contagious disease particularly dangerous to very young infants but dramatically controlled by a rather reactogenic vaccine. In contrast, cholera vaccine exerts little or no effect on the prevalence or spread of the disease and acceptance of its reactions is limited.

(2) *Adjuvants.* In the course of its deliberations, the Panel was informed by the Bureau of Biologics of the results of studies of the effect of injection of aluminum adjuvants into special strains of white mice which have a very high natural incidence of fibrosarcoma of the skin. Such mice have been used in some screening studies for the oncogenicity of certain drugs. The experiments showed some enhancement in the rate of formation of fibrosarcomas in the mice that received aluminum adjuvants. The Panel asked for expert interpretation of the design and results of the mouse studies by scientists from the National Cancer Institute and Roswell Park Memorial Institute. These consultants concurred with the Panel in their opinion that the mouse findings were indeed reliable for the design of the experiments but that the significance of the findings for man could not be assessed from this model alone and that studies in other mammalian species should be made.

The Panel therefore surveyed data in man on fibrosarcomas in different populations from various cancer registries. These show that fibrosarcoma is a rare tumor, the incidence increasing sharply in old age. Cohorts were analyzed who were probably exposed to aluminum adjuvants, such as males born around 1920 who probably received immunizations during World War II, whereas the women generally did not. No increased rate of sarcoma in males in that cohort was detected. Because most Canadian vaccines do not contain aluminum adjuvants, mortality rates in Canada were compared with those in the United States for fibrosarcomas. Rates of connective tissue tumors were slightly higher among United States than Canadian males, but the rates for females were similar. The data did not disclose any major differences that would cause concern over the use of aluminum adjuvants whose benefits are considered to be of major value in the primary immunization of children with DTP vaccines. The Panel encouraged further studies on adjuvants, especially retrospective studies in humans, but did not consider that their recommendations for the safety and efficacy of DTP vaccines containing aluminum adjuvants should be modified at this time.

(3) *Liability and legal problems.* Almost any clinical investigation to improve well established and highly beneficial vaccines, or to assess more accurately their current reaction rates, is frustrated by the threat of malpractice suits and claims for damages against manufacturers. Physicians who administer vaccines as well as those who produce them feel threatened when reporting adverse reactions, even when the vaccine has been prepared and used in accordance with government regulations and recommendations. Moreover, some reactions are intrinsic to the process of human immunization and range from psychic trauma to fatal idiosyncratic reactions that are extremely rare and are an unavoidable hazard of introducing foreign substances into humans.

The United States has been backward in its failure to deal with the risks and responsibilities of immunization. Several European countries and Japan have established a public compensation system under which their governments have accepted responsibility for the recognized hazards of immunization. Some of these laws provide for compensation from public funds to patients suffering damage from vaccinations that are recommended by competent authorities. Damages have been paid as pensions.

The differences between the primary responsibility of the manufacturer and the ultimate responsibility of the State should be distinguished. The former should comply with the regulations of production and marketing procedures. If these obligations are fulfilled and the vaccine is administered correctly, responsibility for immunization accidents should rest with the official agencies recommending them. Unlike many other countries, the United States has not dealt adequately with this issue of immunization, and attempts to improve vaccines further will be hampered. Furthermore, collection of data to establish the efficacy of some of the current licensed products may also be hampered by this deficiency of public policy in the United States.

b. *Determination of efficacy*—(1) *The diverse immunologic actions of the vaccines.* The various vaccines that have been lumped together for this Panel's review are so diverse that standards of efficacy that apply to one may not apply to another at all. Progress in immunology is far greater in areas relevant to the effects of some vaccines compared to others. For diseases in which immunity depends upon specific antibodies which either neutralize toxin or which opsonize bacteria and lead to their prompt destruction within phagocytes, induction of such antibodies

correlates well with protection, and the measurement of such antibodies may reflect efficacy quite faithfully.

In many other kinds of antibacterial immunity, however, survival of organisms within cells after ingestion is a particular feature of the host-parasite contest. In these infections the role of cellular immunity is critical. Diseases such as tuberculosis and typhoid fever are illustrative of infections that may be considered intracellular as well as extracellular. Our knowledge of immunity in such diseases still awaits greater understanding of the cell-mediated defense process. The effects of vaccination therefore remain empirical in these diseases and can be established at present by field trials alone. In pertussis, for example, the relative roles of humoral and cellular immunity are not at all clear, and the antibodies that can be measured may or may not be protective.

Finally, protection against a disease such as cholera has been proven in recent studies to depend primarily upon the prevention of the attachment of the cholera vibrios to the surface of intestinal epithelial cells. The solution of this problem appears more feasible than the more complex antibacterial immunity of diseases like typhoid fever.

(2) *Establishing standards of efficacy.* It should be apparent that a standard of efficacy must be applied separately to each vaccine according to current expectations of its performance. For example, for the prevention of tetanus an almost perfect performance can be expected. Moreover, its efficacy can be quite accurately assessed by serum antitoxin levels. For diphtheria, the standard of efficacy is also high, but there is less certainty as to what level of antitoxic immunity constitutes adequate protection because strains of diphtheria may vary greatly in the amount of toxin they can produce, and absolute immunity based on a given level of antibody is less predictable.

A major dilemma repeatedly faced by the Panel was the decision whether to place a given product in Category I or Category IIIA. The law requires that each product be proven to be both safe and effective in man; for many products, licensed prior to the current, more stringent legislation, specific data related to efficacy are not available. Even in the absence of such data, however, the Panel has little doubt that the efficacy of tetanus and diphtheria toxoids are satisfactory because it is reasonable to infer that if they were not satisfactory, the remarkable reductions in tetanus and diphtheria associated with widespread use of these vaccines surely would not have occurred. Moreover, the techniques of production suggest that they should be efficacious.

But the charge to the Panel was to examine each licensed product from the standpoint of the scientific evidence that each is both safe and effective in humans. The various toxoids placed in Category IIIA by the Panel are believed to be entirely acceptable in terms of safety. The Panel believes that many are effective, but in the absence of recently obtained proof in humans for certain specific products, the Panel's charge to affirm the effectiveness of individual products could not allow a Category I assignment.

The feasibility of obtaining efficacy data is technically simple in the case of the toxoid vaccines (tetanus and diphtheria) because serum neutralizing anitbodies are readily measureable and these reflect efficacy accurately. Blood samples from relatively small numbers of healthy volunteers (see prototype model for study with 20 to 40 individuals) who receive immunization can therefore establish efficacy. Obtaining blood samples from healthy volunteers receiving licensed vaccines, particularly children and infants, is a problem currently complicated by recent regulations on informed consent. However, the difficulties which may be perceived in obtaining such data do not outweigh the importance to the public of assuring the efficacy of these universally administered vaccines in achieving primary immunization. For these reasons, the Panel recommends that products for which the human data requested are not available be assigned to Category IIIA.

In the case of pertussis, the situation is peculiar. Though the vaccine is a very effective one, it is quite crude, consisting either of killed whole cells or of a soluble product of the organism. The nature of immunity is unknown. The disease has almost disappeared in the United States, making field trials, at least in this country, impossible. The standard of efficacy is tied to a highly artificial mouse model of protection—one that bears essentially little similarity to the natural disease in man. Yet the last successful field trials conducted decades ago are tied to current products whose toxicity represents the major concern about the vaccine. Any move to make the vaccine safer by modifying it is fraught with the danger of altered efficacy which cannot be adequately assessed without an extensive field trial.

The plague and cholera vaccines place the Panel in the apparently inconsistent position of classifying them as effective without the extensive efficacy data that are available for other vaccines. These vaccines are of decidedly limited value. At the same time, the Panel demands of tetanus updated on antibody levels when relatively small changes in the vaccines have been introduced recently into the manufacturing process.The expectations of efficacy from the current plague and cholera vaccines are obviously quite different from those expected from tetanus.

Finally, standards for judging efficacy of currently available BCG vaccines are far from satisfactory. No reliable animal model or immunologic test has yet been discovered that accurately reflects human immunity; nobody can prove that the live vaccine strains have remained unchanged by repeated passage in the laboratories where they are maintained; and only new field trials that are in progress but are several years from completion can determine efficacy. Even then such efficacy would have to be related only to the strains used in the trial. Nonetheless, decisions have to be made based on past performances and to some degree upon the assumption that the strains of current vaccines are retaining their immunizing power. Lacking other alternatives, the decision for efficacy was made by the Panel with full knowledge of the assumptions that were made.

(3) *Extrapolation of data from the use of combined vaccines.* Practical considerations in the evaluation of efficacy for some products when data were unavailable made it desirable and sometimes necessary to extrapolate from data on the use of combined vaccines. This approach appears to be logical and valid, particularly for diphtheria, tetanus, and pertussis vaccines, because of the wide use of the combined diphtheria, tetanus, and pertussis vaccines and the endorsement of this immunization practice by all leading biomedical experts in this country. Accordingly, the Panel made use of the following extrapolation models whenever it seemed appropriate because of the availability of the data:

1. Diphtheria tetanus and pertussis (DTP) could provide efficacy data for pertussis (P) (but not for diphtheria (D) and tetanus (T) due to adjuvant effect of pertussis).

2. Tetanus and diphtheria (Td) could provide efficacy data for T and also possibly for diphtheria and tetanus (DT) and D if the small 2 Lf dose of DT in Td proved adequate. Caution would be necessary in extrapolating Td data in adults to children 6 years of age or younger.

3. DT could provide efficacy data for D, T, and for the T component of Td.

Combined product available	Would provide efficacy data for:
DTP	P
Td	DT [1] D [1] T
DT	D T Td (T-only).

[1] If response of 2 Lf Diphtheria toxoid were satisfactory, the larger amount in "D" products could be assumed satisfactory

(4) *Patient participation, informed consent, and clinical trials.* When sufficient data were not available from which to determine efficacy, the Panel had to consider the feasibilty and cost benefit of the required further clinical investigation. Such factors stimulating the Panel's desire for more data were: (i) Changes in the manufacturing process, the concentration of antigen, the purification of the product, or the additions of preservatives or adjuvants; (ii) the dependence of some manufacturers upon clinical data establishing the effectiveness of the same vaccine made by others; (iii) possible changes in the state of immunity of the population and secular changes in the epidemiology of the disease; (iv) the need for better products or immunization schedules to increase efficacy or decrease reactivity.

On the other hand, the Panel was mindful of the growing difficulties of obtaining participants and informed consent for clinical trials—even those as simple as obtaining a few samples of blood per patient by venipuncture. For primary immunization trials, the need to obtain consenting subjects who have no prior immunity imposes a further stringent limitation. If clinical trials were to require more than an assessment of humoral responses, the inability to evaluate protection against a challenge of natural disease in this country (such as in the case of tuberculosis or pertussis) made insistence upon such data unreasonable. The dilemmas of inadequate clinical data to judge efficacy versus limited access to such data led to productive discussions and workshops with manufacturers and the Bureau of Biologics to establish efficient and relatively standard protocols which would supply the required data from minimal numbers of participants and at minimal costs. The Panel's general recommendations contain suggestions arising from these conferences.

(5) *Animal models.* Animal models of the human diseases in which vaccines may be accurately and reliably assayed for safety and efficacy would solve many problems of clinical investigation and human trials. The Panel found this need particularly cogent in the case of pertussis and tuberculosis in which animal models were inadequate and field trials not feasible. In these instances recommendations that vaccines be classified in Category IIIA to obtain further proof of safety and efficacy will be greatly handicapped unless animal models are developed which correspond closely to the human disease counterpart.

(6) *Administrative problems.* Several administrative problems had to be solved by the Panel to carry out its charge and mission. Some licenses had been held on products which the manufacturers had not marketed for many years. Some of these products were intended to be used only when the vaccine was combined with others (for example, monovalent diphtheria toxoids). Some antiserums (equine diphtheria antiserum) and some toxins (diphtheria toxin for Schick testing) were considered useful for limited purposes only. They might be in limited supply, therefore, unless publicly subsidized. During the course of the Panel's review, licensed products were updated because of modifications, and license applications were amended to replace outdated products (for example, plague vaccine).

(7) *Related issues.* Careful attention was given to the opinions and policies of other governmental agencies and professional societies concerning the safety, efficacy, and recommended usage of the vaccines reviewed. The Panel was mindful that its decisions were concerned primarily with assessing evidence of safety and efficacy of the vaccines rather than determining either public health or clinical practice policy governing their usage. It was gratifying, however, that very few significant differences of opinion were encountered among recognized authorities. The most divergent opinions related to the issue of the efficacy of the BCG vaccines and reflected the need to establish whether or not prolonged storage and passage of the seed strains in laboratories had led to changes in their efficacy. Limited enthusiasm for the use of BCG by public health authorities in the United States as a means for the control of tuberculosis had to be weighed against: (i) Evidence of efficacy; (ii) alternative strategies for control; and (iii) the right of manufacturers to produce and physicians to use a vaccine, if effective, in some parts of the world and in some populations of the United States with unusual risks of exposure to tuberculosis. Althogh some would have preferred a "Category III" classification for BCG, requiring updated clinical data of efficacy, the feasibility of obtaining such data in the ensuing several years appeared remote and unnecessary at this time when weighed against the favorable evidence for BCG. The Panel was faced with having to make an "effective" versus "ineffective" judgment on the basis of the evidence at hand and the evidence, although incomplete, clearly called for a judgment of effectiveness.

3. *General recommendations*—a. *Support for widespread immunization programs.* Universal active immunization for the prevention of tetanus, diphtheria, and pertussis should be accomplished to take full advantage of the great effectiveness of these vaccines and to obviate the inherent risks, cost, and effort of passive immunization which is incompletely effective in the first two diseases and not effective in the third.

b. *Liability legislation for immunization.* Assessment of the safety of vaccines requires improved procedures for reporting adverse reactions. This in turn requires the development of a more enlightened public policy which includes acceptance by the U.S. Government of responsibility for the recognized and unavoidable hazards of immunization.

Legislation is urged that will provide compensation from public funds to individuals suffering damage from vaccinations that are recommended by competent authorities, carried out with vaccines that passed official safety and efficacy review, and that were administered by recommended techniques. Such legislation will not only greatly improve assessment of safety but will also enhance collection of the data necessary to establish efficacy by reducing the professional liability issues in clinical investigation of vaccines.

c. *Improved efficacy of clinical investigation.* The Bureau of Biologics should offer guidance to manufacturers with regard to recommended protocols which would help to provide adequate clinical data for assessing vaccine efficacy. Because of the increasing difficulties in obtaining informed consent to conduct studies on normal individuals, even studies requiring no more than serial venipunctures, it would be most efficient and economical to develop protocols that would provide required information with the fewest numbers of participants and specimens. These considerations are especially appropriate in studies involving children. Cooperation among manufacturers and the Bureau of Biologics should be promoted to adopt relatively standardized protocols that might set minimum limits to the numbers of individuals required to achieve

statistical strength of data and appropriately controlled conditions, laboratory methods, and population groups.

Currently there is a conflict between the public's need for precise data regarding the safety and efficacy of immunization programs and the rights of the individual, both in terms of experimental risk and privacy. Despite the need to protect the privacy of the individual, a mechanism should be developed that would provide means of access for authorized investigators to demographic and health data on individuals in order to conduct long-term followup studies of immunization procedures.

d. *Improved production procedures.* Some standards of purity, immunogenicity, and immune responses for well-established vaccines are based upon old-fashioned methods that should be updated by more sophisticated techniques made possible by advancing scientific knowledge. Efficacy and safety should be assessed and defined in terms of more modern standards of quantitative immunobiologic testing, chemical purification, and clinical evaluation. The motivation and impetus to accomplish this is unlikely to come spontaneously from pharmaceutical manufacturers unless review of vaccine licensure is conducted periodically. In addition, workshops should be promoted regularly by the Bureau of Biologics to encourage progress in methodology and to coordinate further efforts at standardization.

e. *Research priorities*—(1) *Animal models.* There is great need to develop animal models that accurately predict vaccine responses in man. Throughout the Panel's review, one of the most frequently recurring problems was the need to minimize our dependence on the laborious collection of expensive and often virtually unobtainable clinical data in order to determine efficacy. Manufacturers are not primarily responsible to implement the quest for animal models, and the development of such models will require public research support.

(2) *Laboratory tests and procedures.* Increased emphasis is needed on the development of laboratory tests and procedures that reflect vaccine efficacy with sufficient accuracy so as to minimize the need for field trials. Improved immunologic tests, the use of tissue culture assays, and relatively simple, reliable, and low-risk clinical procedures, such as skin tests, would simplify clinical investigation of vaccine efficacy.

(3) *Collaborative and cooperative studies.* Collaborative and cooperative studies should be encouraged particularly when such group efforts at collecting data may reduce the cost and effort and increase the availability of opportunities for clinical investigation, or may resolve quickly and efficiently such issues as dose schedules and the frequency and intervals of injections of vaccines within a generic group that are comparable in potency.

(4) *Areas of limited knowledge concerning effective vaccines.* Support is needed for research in areas where knowledge of the mechanisms of immunity is limited. It is possible that the judgment of a vaccine as safe and effective may actually discourage research by lowering the apparent priority for the need to improve the vaccine. In diseases such as pertussis, typhoid fever, and tuberculosis, the mechanisms by which immunity is produced and the specific antigens that are responsible for the induction of immunity and for reactogenicity are poorly understood. Further research efforts to reduce the toxicity of these vaccines and to improve their effectiveness will require specific public support.

(5) *Increased efficiency of effective vaccines.* Support should be available for clinical investigation in areas of vaccine research where it is likely that further progress can be made even where a high degree of vaccine efficacy already exists. An example would be the improvement of the already very safe and effective tetanus vaccines by reducing the number of injections required to achieve primary immunization.

(6) *Unmet needs.* Finally, rearch is needed to fulfill unmet needs in protection against bacterial infections. Streptococcal, staphylococcal, gonococcal, hemophilus, and pseudomonas infections, to name but a few, are potentially preventable by immunization. Morever, there are some products that are needed and can probably be prepared but are not available now, such as botulinus human immune globulin and diphtheria human immune globulin.

f. *Assurance of vaccine availability.* Close surveillance is necessary of certain vaccine products whose ongoing production in the United States may be discontinued or suspended for a commercial reasons despite current or potential needs. Diphtheria toxin for Schick testing and equine diphtheria antitoxin for the treatment and passive immunization of diphtheria are two examples. Continued interaction between the Bureau of Biologics and the Centers for Disease Control should be encouraged to ensure government stock piling of required products that are no longer produced commercially.

In addition, some products are produced solely by foreign firms. The Istituto Sieroterapico Vaccinogeno Toscano Sclavo pharmaceutical firm in Italy is a major source of diphtheria antitoxin, and the status of diphtheria antitoxin produced in the United States is uncertain. Connaught Laboratories of Canada is the only producer of trivalent botulinus antitoxin. Furthermore, a major vaccine produced by a single domestic firm represents an inherent danger, in that the public is dependent upon a limited source without well-defined mechanisms for the control of production and supply.

Public policy needs to be formulated more thoroughly in the entire area of production and supply of vaccines. Prospective planning and negotiation between public agencies and the pharmaceutical industry should be established as a process by which to ensure vaccine availability when the market alone is inadequate to accomplish this end. Consideration should be given to the establishment of a National Vaccine Commission which can address itself to the solution of these problems.

g. *Improved reporting of adverse reactions.* At present, there are virtually no standards set for what constitutes untoward reactions to vaccines except their most severe and dire complications; therefore, it is difficult to document the actual reactogenicity of some products. Standards for "threshold reactions" above which reports are required need to be established for each generic group of vaccines. The Study Commission on Drug Use, which is studying adverse drug reactions, should be urged to consider reactions to biological products as well.

h. *Improved labeling.* Review of the labeling of products submitted to the Panel identified a number of deficient areas in which substantial improvement should be made. A standard for adequate labeling along the lines outlined by the generic labeling statement of the Panel should be adopted so that the accuracy and readability of all labeling can be brought to an optimally useful level.

i. *Improved administrative procedures*—(1). *Periodic review of all licensed vaccines.* Periodic review of all licensed vaccines should be carried out to assure that the safety and efficacy of these products are kept current and that standards of production and assay are modernized.

(2) *Limited term for vaccine licenses.* By limiting the period for which

vaccines may be licensed, all products, old and new, will be assured regular review. Furthermore, new vaccines that have only limited evidence of efficacy or for which the clinical efficacy data needs to be extended by further experience (situations in which we now assign "Category IIIA," i.e., insufficient data but probably effective) should be provisionally licensed for only limited periods of time within which additional data can be generated.

(3) *Revocation of licenses for nonmarketed vaccines.* Some products that have not been marketed for many years are still licensed, and it is not known whether they would still qualify as safe and effective products if and when production is resumed. Some products have never been marketed in the form for which they were licensed. In the light of current efficacy review standards, it would be better policy to revoke such licenses and require reapplication when necessary.

(4) *Consistency of efficacy data.* Protocols for efficacy studies should be reasonably consistent throughout the industry for any generic product and should employ standard tests, standard procedures for conducting tests, and standard reference sera. It would be advantageous to develop industrywide, consistent, standardized guidelines for adducing required data. Such standardized procedures may need review and updating periodically, as new improved laboratory tests become available.

j. *International cooperation.* The Panel recommends that international coordination of vaccine standardization and assessment of safety and efficacy be encouraged through groups such as the World Health Organization, the International Association for Biological Standardization, and between ministries of health of various countries. In many instances the assessment of vaccine efficacy may be possible only in those countries where an opportunity for field trials may exist.

k. *Role of review panels.* Judging from the experience of the Panels during their reviews, their current roles as advisory groups should be extended so that they may continue to serve to help assess future safety and efficacy issues that arise with new or improved vaccines.

l. *Privacy of panel sessions.* The Panel has had little problem in performing its functions at open sessions and believes that closed sessions are necessary only to protect the rights of confidentiality to which license submissions are entitled. The Panel also has had no objection to having its sessions taped and recorded.

m. *Transcription policy.* The cost/benefit of verbatim transcription of the entire deliberations of the Panel, especially those that lead to a documented report, is, however, very limited. Verbatim transcription of the vast amount of tedious and noncontroversial detail covered in reviews is enormously wasteful, inhibits free, relaxed, and creative discussion and exposes Panel members to the risk of remarks and opinions that may be only tentative and that may be quoted out of context.

4. *Summary of unresolved problems.* In concluding its report, the Panel deems it important to call attention to some of the major unresolved problems that have made its advice and decisions most difficult and that will continue to hamper the assessment and the improvement of the safety and efficacy of vaccines.

a. Emphasis upon proof of efficacy and upon critical standards of the scientific quality of vaccine data may inhibit the motivation to modify and improve current vaccines and to introduce new ones. If rigid and critical standards are to be set and met, much effort should be put into finding efficient and effective ways to encourage and expedite the conduct of such research.

b. The complexity of the legal and administrative procedures deemed necessary to ensure the protection of the rights of individuals participating in clinical investigations impose serious restraints to the acquisition of vaccine efficacy data, because such studies are usually undertaken in normal individuals and often, in the case of universally administered vaccines, in relatively low risk groups. Public policy will have to be formulated to provide incentives to both clinical investigators and participants to engage in the carefully designed field trials and other controlled experiments that are now required. The U.S. public should share as a whole in the responsibility to participate in such studies. As previously noted in section 2.b.(2) of this preamble, the difficulties that may be perceived in obtaining such data do not outweigh the importance to the public of assuring the efficacy of these universally administered vaccines in achieving primary immunization.

c. Standards of efficacy will have to be evolved for products that are not amenable to clinical trial (e.g., botulism antitoxin).

d. Emphasis upon the individuals' rights of privacy of personal health data can conflict with the public's need for data on immunizations which requires access to health records. Specific exceptions will have to be written to the laws protecting confidentiality of public health information, which is now regarded as private.

e. Finally, the glaring absence of a coordinated national immunization policy that would efficiently implement and expedite vaccination procedure and vaccine development, production, and supply is now apparent. Such a policy should be formulated without further delay so that future decisions on vaccine safety and efficacy can be made with greater assurance of public acceptability and support.

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Labeling

Review of the labeling of products submitted to the Panel on Bacterial Vaccines and Toxoids identified a number of deficient areas in which, in the judgement of the Panel, substantial improvement should be made. The following generic comments on the subject of labeling highlight the view of the Panel on what constitutes adequate labeling, and provides a standard such that all labeling can be brought to an optimal level.

General Comments

Labeling should meet the following general criteria:

The labeling should be written in clear English. In many instances, current labeling is written with very complex sentence structure. There is very often marked ambiguity of meaning. In some instances, even Panel members charged with reviewing the subject were unable to determine the precise meaning of statements in the package insert; the physician who may be expected to give the labeling little more than a cursory reading therefore may often receive inadequate guidance.

Labeling should ordinarily contain information in the following format and order:

The labeling should be easily legible and printed in such a fashion as to attract, rather than to repel or discourage, the reader. Much of the present labeling is printed in type so small as to discourage all but the most determined reader.

The labeling should contain a summary of the essential scientific information the physician needs to use the bacterial vaccine or toxoid safely and effectively in the care of patients. It shoud be informative, accurate, and nonpromotional in tone.

Labeling should be reviewed and revised as necessary at intervals of no more than every 2 years. The date of last revision should be clearly identified in the label. Although the area of bacterial vaccines and toxoids has not been marked by rapid and dramatic advances resulting from medical research, immunization practices do evolve gradually with time and in the light of new data or circumstances. Many of the recommendations contained in the labeling of products currently on the market are out of step with current practice and recommendations. Bibliographic citations should similarly be revised and updated at intervals of no more than every 2 years.

Description
Clinical Pharmacology/Biological Activity
Indications and Usage
Contraindications
Warnings
Precautions
Adverse Reactions
Overdosage
Dosage and Administration
How Supplied

The Panel has reviewed and concurs with the proposed format changes as described in the statement on "Labeling of Prescription Drugs Used in Man" (21 CFR Part 200), previously circulated by the Food and Drug Administration. The following comments presume the adoption of these new standards, follow the same recommended format, and reflect the Panel's particular concerns in the labeling of bacterial vaccines and toxoids.

Description

This should be a concise statement of the method of preparation of the product, the characteristics of strain or species used, the scientific name of the bacterium, noting the specific strain if important, the process used, the potency standard that has been met, the antigenic content of the product, the stabilizers and preservatives included, and the suspending menstruum. Terms such as "purified" and "refined" are more promotional than scientifically meaningful. An accurate statement of the precise process that is used would be considerably more meaningful.

Clinical Pharmacology/Biological Activity

This section should contain a concise factual summary of the immunological response to the product in terms of immunity, antibodies, or other parameters. Specific points to be covered, when applicable, include: The proportion of individuals in which antibody will be produced, the number of doses required to produce satisfactory levels of antibody, techniques and reliability of antibody measurements, the time at which antibody is detectable, peak antibody levels to be expected, expected decay of antibody titers, and the degree and duration of protection to be expected. Concise summary description of data in support of the efficacy of the product in animals or in man should also be included.

Indications

The indications should be stated as specifically as possible. Liberal use should be made of the recommendations of official bodies such as the Public Health Service Advisory Committee on Immunization Practices, Center for Disease Control, the Infectious Disease Committee of the American Academy of Pediatrics, and the American Public Health Association. (Note: Subsequent to the Panel's completion of this report, the Advisory Committee on Immunization Practices was renamed as the Immunization Practices Advisory Committee and the Center for Disease Control was renamed as the Centers for Disease Control.) The specific recommendations of these advisory groups should, if appropriate, be reprinted in their entirety in the labeling. The number and frequency of injections of a given antigen(s) should be specifically stated. If products containing more or fewer antigens as combined products (e.g., DT, DTP) are preferred for a specific purpose, this should be so stated in this section. In such a case, the circumstances should also be defined when the product under consideration should be used rather than the preferred product. Where appropriate, labeling should also point out the generally accepted superiority of adsorbed vaccines and toxoids over comparable fluid products.

Contraindications

This section should state those situations in which the agent should not be used because the risk of use clearly outweighs any possible benefit. Such situations include administration of the agent to patients known to have a serious hypersensitivity to it and use of the agent in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it or not receiving the expected benefit from it. This section should list known hazards, and theoretical hazards, if mentioned, should be identified as such. The Panel encountered in its review a number of labels in which it appeared that producers were overly concerned about protecting themselves, rather than the patient.

Warnings

This section should state serious adverse reactions and potential safety hazards, limitations of use imposed by them, and steps which should be taken if they occur. This section should describe any unusual circumstances relating to the use of the product,

including particularly any circumstances under which use of the product may be hazardous or less effective. The specific circumstances and the specific hazards should be described fully.

Precautions

This section should contain the following subsections as appropriate for the product:

1. *General.* This subsection should list any special care that should be exercised to permit safe and effective use of the product by the physician.

2. *Clinical and laboratory tests.* This subsection should list those laboratory tests that may be needed to follow the patient's response or to identify possible adverse reactions.

3. *Special instructions to be given the patient.* This subsection should specify instructions for patients to achieve safe and effective use. Any patient's brochure or printed instructions to vaccines should be reprinted under this section heading.

4. *Clinically significant product interactions.* This subsection should provide specific practical guidance to the physician on avoiding and/or managing clinically significant drug interactions, such as might occur with simultaneous active-passive immunization.

5. *Pregnancy.* Recommendations concerning the use of the product during pregnancy should be detailed in this section.

Adverse Reactions

This section should contain not only a description of the nature of local and systemic adverse reactions that have been observed following use of the product as recommended, but also their relative frequency. Specific recommendations for management of adverse reactions should also be included in this section, as should recommendations for reporting of adverse reactions to the manufacturer and FDA.

Overdosage

This section should describe the signs, symptoms, and labotatory findings of accidental overdosage and the general principles of management. It should include specific information, if available, on the emergency treatment, antidotes, and the value of any recommended therapeutic measures.

Dosage and Administration

This section should state the usual recommended dose and frequency, and if appropriate, limits beyond which the product should not be administered. Precautions against inadvertent intravenous injections should be included. It should include the intervals recommended between doses, and modification of dosage needed in specific patient populations such as infants and children. Specific tables or nomograms should be included to clarify dosage schedules. This section should also contain specific directions on dilution, preparation, and administration of the product if needed, and storage conditions for stability of the product where important.

How Supplied

This section should state the available dosage forms, potencies, and units of issue of each product to which the labeling is applicable.

Generic Statement on Requirements for a Well-Controlled Field Trial

Some of the immunizing agents the Panel was required to evaluate had been tested for efficacy only in the first part of the 20th century, when the methodology for obtaining unbiased reliable results in field trials had not yet been fully worked out. Examples of such agents are diphtheria and tetanus toxoids. The respective diseases have declined in incidence, and opportunities for additional field testing for efficacy do not exist in this country.

In developing new immunizing agents, the products are generally first tested in animals for their toxicity and ability to elicit antibody response. When the animal model is suitable, the protection provided by immunization against challenge by the microorganism is also evaluated. Subequently the immune response in humans is measured, and the dose which induces a seemingly adequate immune response with an acceptable low rate of adverse reactions is sought.

The final and most important step is the field trial, when a large number of presumably nonimmune humans is inoculated, and the incidence of the disease among vaccinees and control subjects is compared.

In the past "historical" controls were frequently employed to test the effects of a new vaccine. By this no-longer-acceptable technique, the frequency of illness in a vaccinated group was compared with the frequency in a similar unvaccinated population at some time in the past. Unfortunately, a decline in disease frequency after vaccination cannot be interpreted as resulting from vaccination, because the changes may be due to natural disease cycles, to changing socioeconomic conditions, or to therapeutic measures, such as antibiotics.

Also no longer acceptable are comparisons of the frequencies of disease in those who do and do not volunteer for a vaccine study. The fallacy of this approach is that volunteers differ from nonvolunteers in many important aspects. For instance, the former may be more health conscious and inclined towards prevention; they may come from smaller families and living conditions may differ from those of nonvolunteers. Such behavioral and socioeconomic factors may affect the risk of exposure and the host's natural ability to resist infection. Modern scientific methodology requires that volunteers for a study be divided into groups by a randomization procedure, one group constituting the control group, which is given a placebo (inactive, dummy) substance. Randomization is necessary to ensure that the volunteers are distributed without bias, thereby increasing the chances that all variables, known and unknown, that might affect the results of the study are distributed evenly between vaccinated and control groups. Indeed, if the populations are heterogeneous in age, sex, race, or other important variables, it may be necessary to classify or "stratify" them into groups according to these characteristics with randomization within these groups. These rigidly designed experiments, with or without stratification, are called "controlled trials."

An additional requirement in a controlled trial is that the study be carried out double-blind if at all feasible. This implies that both the study subjects and the observers are unaware of the treatment assigned to the individual in order to ensure unbiased assessment of outcome.

Before subjects are enrolled in controlled trial, ethical considerations require that all the procedures in the studies are explained to them, and that the risks as well as possible benefits are adequately described. The right to withdraw from the study at any time without penalty is pointed out. The rights of the subjects are protected by special committees in all major research centers and by special committees at the Department of Health and Human Services. These committees review the applicable consent forms and the research. All government-sponsored research and virtually all other research involving human subjects requires review by institutional human subjects rights committees.

Whenever practical, in order to provide some benefit to the control group, a vaccine against an entirely

different disease, rather than an inactive placebo, is given to the control group.

Assignment to groups is carried out after the subjects have decided on participation, and after the study has been fully explained to them. Participation of children requires special consideration. Consent from parents as well as older children must be obtained.

In carrying out controlled field trials of new improved vaccines, ethical considerations do not allow a placebo assignment if an effective vaccine already exists. Thus, comparison can only be made between those given the new and the old product; enrollment of very large population groups may be necessary in order to distinguish small differences in efficacy.

Analysis of the results of a vaccination study is achieved by "breaking the code" identifying the allocation of individuals to vaccinated or control groups. The code is broken at the end of the study or after an outbreak of the disease has occurred. Under some circumstances it may be desirable for a statistician, who possesses the allocation code but is not participating directly in the study, to examine periodically the results as they accumulate. By this mechanism, called sequential analysis, the study can be interrupted as soon as it has become evident that one treatment or vaccine is superior to the other.

Field trials designed to measure efficacy directly have become increasingly difficult to conduct under conditions of decreasing incidence of natural disease. For this reason, serologic documentation of efficacy must increasingly be substituted in lieu of direct evidence of efficacy. The following protocol is provided to serve as an example of one type of clinical study which would provide reliable information on the efficacy of the product to be assayed as simply and as economically as possible and is illustrative of many of the concepts implicit in the Panel's position regarding well-controlled field trials as well as in FDA's regulations regarding such matters (see 21 CFR 314.111).

Sample Protocol for Assaying Efficacy of Tetanus Toxoid in Man

Objective. To determine by a study with the fewest number of subjects and fewest number of bleeds required whether a particular preparation of Tetanus Toxoid (alone or combined with Diphtheria Toxoid) produces an acceptable level of immunity in individuals not previously inoculated with Tetanus Toxoid. An acceptable level of immunity is defined as:

1. Over 80 percent of subjects having >0.01 International Unit of Tetanus Antitoxin per mL in a serum sample drawn 10–14 days after basic immunization (2 injections of adsorbed Toxoid or 3 of fluid Toxoid) have been given. OR

2. Over 80 percent having >0.1 International Unit per mL in serum sample drawn 10–14 days after a reinforcing injection given 6 to 12 months following basic immunization as defined above.

It is to be noted that 80 percent "success" by either criterion given above is a minimum tolerated level; the normal success rate, in many studies reported over the last 3 decades, is 95–100 percent.

Subjects. The study population should consist of healthy children of adults or either sex, and should have acceptable evidence of being primary responders to tetanus toxoid. In the case of infants less than 6 months of age, negative immunization history from a responsible parent or guardian would be considered acceptable. For older children and adults, the most valid evidence of primary response is the absence of serum antitoxin 7 days after the initial dose of toxoid. In neither instance is a preimmunization serum necessary. Data from older children and adult subjects screened for antitoxin negativity by a zero-day rather than a 7-day bleeding may be confounded by the inadvertent inclusion of individuals who are secondary rather than primary responders.

Numbers. Size of group should be so selected as to provide serological data on 40 acceptable subjects at end of study. Sixty is recommended as a minimum starting number if subjects can be carefully selected by good histories of no prior Tetanus Toxoid injections (about 10–20 percent will have had previous toxoid injections without their knowledge). However, larger samples, if possible, would be desirable and might provide more data. Another 10–20 percent may be expected to drop out of the study along the way.

Evaluation. On a 95 percent probability basis, US MIL–STD 105D (Canadian Standard CA–C–115; "Specification for Sampling Procedures and Tables for Inspection by Attributes," *British Standards Institution*, BS 6001, 1972), indicated that the following 2-sample sequence may be used to obtain an answer:

	Accept	Reject
1st sample of 20	1 failure	4 failures.
	for 2 or 3 failures, go to:	
2nd sample of 20 (Total of 40)	4 failures	5 failures.

Active Immunization Products

Generic Statement on Diphtheria Toxoid

Diphtheria is an infectious and communicable disease of man which usually involves the upper respiratory tract and sometimes produces skin infections. The causative agent is *Corynebacterium diphtheriae*, a gram-positive bacillus with metachromatic granules. Upper respiratory diphtheria is characteristically associated with the production of pseudomembrane in the nasal passages, pharynx, and/or larynx, and with the appearance of systemic symptoms due to adsorption of an exotoxin. Fifty years ago there were approximately 200 cases per 100,000 population in the United States each year (roughly 350,000 cases annually). This has decreased to a rate of about 0.1 per 100,000 population in recent years (200 to 400 cases annually). Approximately 10 percent of patients with diphtheria succumb. Death may be due to respiratory obstruction by the memberane or to remote effects of the toxin upon the myocardium or peripheral nervous system.

Because the morbidity and mortality of diphtheria are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used for nearly 80 years in the treatment of the disease and for its prevention in exposed, susceptible individuals. This approach to control of the disease is only partially successful because the disease is already well established by the time it is recognized, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin.

Further, antitoxin does noting to prevent spread of disease. Penicillin or other effective antibiotic agents will usually eradicate the organism, but because they have no effect against toxin, antibiotics are only an adjunct to therapy.

Since passive immunization with antitoxin and therapy with antimicrobial agents do not provide a satisfactory approach to the control of diphtheria, active immunization of humans against the toxin has been employed for many years (also see Generic Statement on Diphtheria Antitoxin). The reduction in morbidity and mortality from diphtheria in the United States during the past half century is largely attributable to widespread immunization against the toxin.

Description

Diphtheria toxoid is a cell-free

preparation of diphtheria toxin treated with formaldehyde so that when administered to humans it does not produce the known toxic effects of diphtheria toxin, but nonetheless produces a specific immune response to the toxin.

The rationale for this preparation is based on the fact that the pathogenicity of the *Corynebacterium diphtheriae* for man is almost entirely derived from the effects of its exotoxin. Rarely, apparently nontoxin producing strains of the organism produce disease. Also uncommon is disease produced by toxigenic strains in individuals immune to the toxin. In these rare instances, the significance of the disease is dependent upon local inflammatory response, and not upon systemic dissemination of toxic products.

Early in this century, attempts were made to devise means by which immunity to the toxin might be induced in man. The potency of the toxin is such that the miniscule amounts that can be safely administered to man fail to induce protection. Indeed, the disease itself sometimes fails to induce immunity in survivors. The first successful preparation for inducing immunity was a balanced combination of diphtheria equine antitoxin and the toxin. Disadvantages included reversion to toxicity when frozen, frequent sensitization to horse serum, and less than optimum induction of the immune state.

Attempts to detoxify the toxin without destroying its antigenicity repeatedly failed because of the instability of the toxoid, until it was shown that formaldehyde treatment of the toxin produced the desired result. Current toxoids are a result of this observation.

Combinations of the formaldehyde-inactivated toxoid with various aluminum compounds have resulted in preparations more antigenic than the fluid (plain) toxoid, and represent the most commonly used preparations in the United States. Such preparations are designated "adsorbed."

Production

A strain or *Corynebacterium diphtheriae* established as a potent toxin producer is grown in a liquid medium so constituted as to afford optimum conditions for toxin production. The medium must be free of blood products, horse or other animal serum, and any proteins known to be allergenic to man. Removal of bacterial cells and sterilization are accomplished by centrifugation and filtration. The resultant toxin is tested for potency according to the U.S. standards and is incubated with formaldehyde in established proportions to effect conversion to toxoid. Before or after conversion to toxoid, additional steps are usually taken to purify and concentrate the fluid antigen partially.

Treatment of the fluid toxoid with aluminum compounds is employed utilizing established techniques to produce the adsorbed product. A preservative (usually thimerosal but never phenol) is added.

The amounts of toxoid present in preparations are specified in flocculation units (Lf), measured by established techniques.

Use and Contraindications

This product, used for active immunization against diphtheria, is rarely indicated as a single toxoid, either in the fluid or adsorbed form. For primary immunization of children younger than 7 years of age, it should almost always be used in a combined product with tetanus toxoid and pertussis vaccine. Poliomyelitis vaccine consisting of inactivated poliovirus may be included as a fourth antigen, but live, oral, poliovirus vaccine consisting of attenuated virus is currently preferred for poliomyelitis immunization in the United States. The triple antigen products are preferred over monovalent diphtheria toxoid not only because of efficiency and economy but also because pertussis vaccine enhances the immunogenicity of the toxoids (adjuvant effect). Also, the adsorbed products are more antigenic than the fluid products and the antitoxic immunity is of longer duration.

Thus, it is strongly recommended that routine immunization of children under 7 years of age against diphtheria be accomplished by the use of combined adsorbed diptheria and tetanus toxoids and pertussis vaccine (DTP), according to schedules recommended by the Public Health Service Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics, and the American Public Health Association. These advisory bodies also recommended the use of adsorbed combined tetanus and diphtheria toxoids of the adult type (Td) for primary immunization of children older than 6 years and adults. However, the efficacy of Td as a primary immunizing agent against diptheria has not been firmly established. (See Special Problems, Number 1, diphtheria toxoid generic statement.)

In the unusual instances in which primary immunizatin with monovalent diphtheria toxoid is indicated, the adsorbed form is preferable. Primary immunization with adsorded toxoid comprises three doses, 2 given 4 to 8 weeks apart, and the third dose (reinforcing) 1 year later. Booster doses should probably be given 5 years after the primary three doses and again after an interval of approximately 10 years. (See Special Problems, Number 1, diphtheria toxoid generic statement.) In children older than 6 yeas and adults the booster doses should probably be given as one-fifth of the usual dose or as Td because of an increased likelihood of reactions. Monovalent diphtheria toxoid may be used for booster doses in the presence of an outbreak of diphtheria, but usually under these circumstances advantage should be taken of the opportunity to enhance tetanus immunity by the use of Td.

If the fluid toxoid is used, primary immunization should include 4 doses, 3 doses 4 to 8 weeks apart, and a fourth dose 1 year later. Booster doses should be given as with the adsorbed preparation.

The fluid toxoid may be administered subsutaneously or intramuscularly. The adsorbed toxoid is preferably administered intramuscularly.

Absolute contraindications to the use of diphtheria toxoid are virtually nonexistent. Apparent anaphylactic reactions to diphtheria toxoid have been rarely reported. A marked fibrile response to an injection should be cause for reducing the subsequent dose to one-tenth or one-fifth the former dose. Individuals receiving corticosteriods or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time. In the presence of a fibrile illness it is advisable not to administer diphtheria toxoid alone or in combination with pertussis vaccaine because of possible confusion as to the cause of further fever.

Inasmuch as clinical diphtheria may not induce adequate active immunity, immunizationof individuals who have recovered from diphtheria and who remain Schick-test positive should be undertaken employing a reduced initial dose because of possible sensitivity.

Safety

Fluid and adsorbed diphtheria toxoid must be tested to ensure sterility, the absence of free toxin, and the absence of blood group substances in significant

amount. All of these tests are well defined and described by the Bureau of Biologics. Experience with the administration of millions of doses has shown that life-threatening reactions to this toxiod are extremely rare. Transient local reactions and systemic symptoms, primarily fever, are frequent, expecially in individuals sensitized by prior exposure to the toxin or toxoid. These reactions are not life-endangering and usually persist only a day or two. The severity of these reactions is directly proportionate to the amount of toxoid administered.

Manufacturers are required to record all reported reactions.

Efficacy

Although controlled studies employing currently acceptable design methodology and statistical analysis have not been carried out, extensive experience in many countries has shown that the systematic use of this product for the immunizatin of infants and children has been associated with a striking reduction in the incidence of the disease. Similar but less extensive experience indicates comparable effectiveness in older age groups.

The potency of diphtheria toxoid prior to administration to humans is tested in guinea pigs, and standard procedures for such testing have been developed and are required of manufacturers by the Bureau of Biologics. In the case of the fluid toxoid, each lot must be tested by immunizing guinea pigs, followed by subsequent challenge with toxin to show protection. Unimmunized control animals must be employed to ensure the lethality of the toxin used to challenge the immunized animals. Adsorbed diphtheria toxoid is tested by immunizing guinea pigs and subsequently determining diphtheria antitoxin levels as prescribed.

Quantitative correlation, however, between the results of animal protection tests and primary immunogenicity in man has not been established, although it is assumed that there is a direct relationship. For primary immunization, direct testing of antitoxin response in man should be required, and should be repeated whenever significant changes in the manufacturing process are made. However, past experience indicates that all toxids which meet the requirements of the Office of Biologics Research and Review (OBRR) for potency in animals have proved effective as boosters in man. (See Special Problems, Number 3, Diphtheria Toxoid Generic Statement.)

Because field testing of disease prevention is currently not feasibile, testing for efficacy in man requires evaluation of the induction of serologic immunity. This may be achieved by serological tests, or by the performance of the Schick skin test which reflects serologic and clinical immunity with satisfactory accuracy. Three doses of the fluid toxoid, given 4 weeks apart, or 2 doses of the adsorbed preparation, separated by 4 weeks, should result in at least 80 percent conversion of Schick positive or seronegative subjects to the Schick negative state of to seropositivity (0.01 or more units of dophtheria antitoxin per mL of serum) by 1 month after the last dose. To avoid confounding by anamnestic responses, use of the Schick test technique for efficacy testing in man should be limited to young infants clearly receiving primary immunization. Similarily, infants should be used for serologic testing, or a blood sample should be drawn 7 days after the first dose and tested for evidence of an accelerated immune response which, if absent, would indicate primary immunization.

Special Problems

Diptheria toxoid, as an immunizing agent in man, presents several problems that warrant efforts toward solution.

1. Although the safety of different lots of diptheria toxoid products may be assured by animal testing, no aninal model or other laboratory technique for evaluation of effectiveness has been directly coorelated with primary immunogenicity in human with acceptable precision. Titers of antibodies as determined by neutralization of the toxin in experimental animals or in tissue culture systems are better related to immunity than is the presence of hemagylutinating antibodies in serum specimens. However, the presence of low neutralizing titers does not ensure protection against large amounts of toxin.

2. The nonspecific reactogenicity of diphtheria toxoid, probably due largely to extraneous proteins derived from the organisms, represents a complicating factor in the immunization of individuals who have become sensitized to these proteins. The Panel has noted that there are no purity requirements in terms of Lf content per milligram of nitrogen except for the Td product.

3. For several reasons, diphtheria toxoid, fluid or adsorbed, is not as effective an immunizing agent as might be anticipated. First, clinical diptheria may occur occasionally in immunized individuals—even those whose immunization is reported is reported as complete by recommended regimens. However, when it does occur in such individuals, it appears to be milder. Second, diptheria toxoid provides protection only against the toxin and not against the somatic components of Corynebacterium diphtheriae. Occasional local infections, respiratory or cutaneous, may occur in immune individuals and nontoxigenci strains may produce focal infections. Although both of these situations are encountered from time-to-time, they are not of major importance. Third, the permanence of immunity induced by the toxoid in the light of decreasing likelihood of exposure to the organism (the "streetcar booster") is open to question. In the absence of occasional exposure, it is possible that individuals immunixzed as children will not retain a degree of immunity that will provide adequate protection in later years. Fourth, the smaller amount of diphtheria toxoid present in tetanus and diphtheria toxoids combined for adult use (Td) has never shown conclusively to be an adequate primary immunizing agent. Furthermore, the intervals between booster doses of Td in adults sufficient to maintain diphtheria immunity have not be established. Fifth, commendable efforts by producers to reduce the nonspecific reactivity of the toxoid by increased purification may have resulted in diminished immunogenicity.

Finally, the absence of proof recently obtained in humans for certain diphtheria toxoids by simple serological tests or readily measureable antibodies could not allow a Category I assignment. (See section 2.b. (2) of the Introduction in this Report.)

Recommendations

The following recommendations for the production, use, and evaluation of diphtheria toxoid are made:

1. Of maximum importance is the development of an animal or laboratory testing system that correlates consistently and with acceptable precision with primary immunogenicity in humans. Public funding to support such research should be made available. Until such a model is established, current toxoids and new variations on such toxoids will require field testing in humans employing serologic methods. Such field testing is expensive and difficult to conduct both because of the problem of finding suitable nonimmune subjects and because of the current restraints on research using human beings. Further, the necessity for field testing of each toxoid produced by a new or varied technique would understandably inhibit manufacture rs in terms of innovation and improvement, and place a difficult burden upon the Bureau of Biologics in determining which alterations in production methods

represent sufficient departures to warrant field testing. Enhanced correlation of existing animal models with immunogenicity in man would obviate such repetitive, time-consuming, logistically difficult, and expensive field studies.

2. Efforts should be made to reduce nonspecific reactogenicity of the toxoid. Standards should be established for purity of the toxoid in terms of Lf content per milligram of nitrogen.

3. Public support for the development of a more immunogenic toxoid should be considered. Of much lower priority is development of an immunizing agent against components of the organism other than the toxoid.

Monitoring of the diphteria immune status of the population by Schick testing or serologic testing would seem to be of maximum importance to prevent the development of a large population at risk in the future. The value of the Schick test is well established. However, the preparation of Schick test material is an understandably unprofitable undertaking for manufacturers. Public support may be necessary for continued production of this material, which is infrequently used but occasionally invaluable.

4. It is recommended that the apparent immunogenic superiority of the adsorbed toxoid over the fluid preparation be strongly emphasized and be included in labeling of products.

5. Finally, for the diphtheria toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistence on effectiveness data and contraints on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction to this Report.]

Basis for Classification

Past experience indicates that all diphtheria toxoids that meet the Bureau of Biologics' requirements for potency in animal tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For these products, therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.

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SPECIFIC PRODUCT REVIEWS

Diphtheria Toxoid Absorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Manufactured by Connaught Laboratories Limited

1. *Description.* This product contains 40 to 50 Lf fluid diphtheria toxoid per mL. According to a revision of manufacturing procedures in 1973, the current product should contain 50 Lf per mL.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for active immunizations against diphtheria. Three doses of 1 cc (50 Lf) each at intervals of 4 weeks, beginning at 3 to 6 months of age. Reinforcing doses of 1 cc are given 1 year after the primary series and 4 years later. At school age an additional reinforcing dose of 0.1 to 0.2 mL may be given without being preceded by a reaction test.

b. *Contraindications.* Contraindications are not well outlined. Reaction tests are recommended in older children (over 8 years) and adults.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In studies (Ref. 1) carried out in 1964 to 1965, 68 children, ages 7 to 15 years, were evaluated for their diphtheria antitoxin levels after 3 injections of Connaught Laboratories DT—polio vaccine. Sera from 54 children had no preimmunization antibody, and were considered to be primary responders. Eighty-three percent had protective levels of diphtheria antibody 1 month after the third injection.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data relating specifically to this product are presented. The manufacturer states that adverse reactions have not been reported.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of the product is satisfactory.

d. *Labeling.* There is some inconsistency in labeling in the submission as to exact Lf content. Contraindications should be listed.

4. *Critique.* This product meets United States standards for animal safety and potency and appears safe in humans. Serologic data show adequate antibody response. The package insert should mention contraindications, and it should be stated that the preferred product for immunizations of infants is a combination product (DTP).

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Diphtheria Toxoid Fluid Manufactured by Dow Chemical Company

1. *Description.* This manufacturer maintains a license for fluid diphtheria toxoid, although it has apparently never marketed the product as a monovalent antigen, either in the fluid or adsorbed form. Instead, it is supplied in 2 adsorbed products, 1 in combination with tetanus toxoid and the other with tetanus toxoid and pertussis vaccine. Techniques for preparation of the toxoid

for ultimate combination meet or exceed Federal requirements.

2. *Labeling*—a. *Recommended use/indications.* Nonexistent because the product is not marketed.

b. *Contraindications.* Nonexistent because the product is not marketed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2). *Human.* No data relating directly to this product are available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2) *Human.* No data relating specifically to this product are available. There have been only 5 reports in a 10-year period of reactions to the adsorbed product combined with tetanus toxoid, and all 5 of these were insignificant.

c. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined for this unmarketed product.

4. *Critique.* The manufacturer maintains a license for diphtheria toxoid, fluids although it has never been marketed in the monovalent form. Inasmuch as the manufacturer does maintain a license for 2 combined forms of adsorbed diphtheria toxoid, the Panel believes that maintenance of this license is superfluous.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

No data have been provided by the manufacturer for diphtheria toxoid, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Diphtheria Toxoid Adsorbed Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

1. *Description.* A diphtheria toxoid purified by the metaphosphoric acid method, containing 15 Lf of toxoid per 0.5 mL dose, and 2 mg aluminum hydroxide per 0.5 mL dose[1] (80 percent of maximum permitted amount). It is preserved in thimerosal at a concentration of 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against diphtheria in children under 6, two 0.5 mL doses 6 to 8 weeks apart and a "booster" dose 1 year later. There is no discussion concerning choice of this product as aganist diphtheria toxoid or diphtheria and tetanus toxoid and pertussis vaccine. The container label should say "SHAKE WELL."

b. *Contraindications.* Acute or active infections and temporary immunosuppression; in situations involving prolonged immunosuppression an extra dose is recommended.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A "controlled study" (Ref. 2) is cited using this toxoid in combination with typhoid-paratyphoid A and B (TAB) for children all preiously immunized against diphtheria. Three to 4-fold increases in antitoxin titer were observed. Additional data submitted on DT and Td provided evidence of effectiveness.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The lack of complaints or claims against the product suggest that it is presumably not unduly reactive.

4. *Benefit/risk.* The benefit-to-risk assessment of this product is satisfactory.

5. *Critique.* Additional data were provided to the Panel subsequent to the original submission. The data were submitted as part of a license application to FDA for DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective.

6. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of the Report.

[1] The label submitted to the Panel is wrong. This product contains of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling has been corrected.

Diphtheria Toxoid Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is a fluid diphtheria toxoid, which is no longer issued. It contains 20 Lf of diphtheria toxoid per mL. No information on production details is provided. The diluting medium is sodium chloride, buffered with 0.05 M phosphate buffer The preservative is thimerosal in concentration 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* No labeling is included in the submission.

b. *Contraindications.* No labeling.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several published reports on the efficacy of the manufacturer's products are cited in the submission (Ref. 3). In the 1950's, this toxoid appeared efficacious in eliciting antitoxin response in persons who did not demonstrate measurable antitoxin in their blood.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Safety data are presented (Ref. 3) from a multitude of publications from the 1950's and 1960's, and suggest that the product is innocuous.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product appears to be satisfactory.

4. *Critique.* This fluid diphtheria toxoid has been shown to be safe, and the data from the literature support its efficacy when used as directed for primary immunization. No package insert is provided.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in this country in the form for which licensed.

Diphtheria Toxoid Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid, Fluid, Manufactured by Parke, Davis & Company

1. *Description.* This is a fluid diphtheria toxoid containing 68 Lf of diphtheria toxoid per 0.5 mL dose. The

final product contains 0.5 percent glycerin, 1:10,000 thimerosal as a preservative, and is suspended in isotonic sodium chloride. A strain of *Corynebacterium diphtheriae* PW8 of proven toxigenicity is used for toxin production. Formaldehyde is used as the toxoiding agent, and the toxoid is then further purified by ultrafiltration, ammonium sulfate precipitation and subsequent dialysis.

This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. *Labeling*—a. *Recommended use/indications.* No labeling was submitted.

b. *Contraindications.* No labeling was submitted.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal minimum requirements for diphtheria toxoid.

(2) *Human.* In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, a total of 61 prison inmates were given a variety of preparations containing Parke-Davis diphtheria toxoid singly or in combination with tetanus toxoid and poliomyelitis vaccine (Ref. 4). In most instances the doses administered probably elicited booster responses. It is not stated, however, where the products used were fluid or adsorbed toxoids. Furthermore, it was not clear whether the vaccines were experimental lots or the toxoids currently in use.

b. *Safety*—(1) *Animal.* This product meets Federal requirements for diphtheria toxoid.

(2) *Human.* No data were provided to substantiate the safety of this product.

c. *Benefit/risk ratio.* This cannot be determined in the absence of adequate data with regard to safety and efficacy.

4. *Critique.* This is a fluid diphtheria toxoid, currently licensed, but not marketed, which appears to meet animal efficacy and safety requirements. Satisfactory data have not been provided by which to assess either the safety or efficacy of this product in humans, whether used for primary or booster immunization.

No labeling has been submitted.

The Panel has a general concern about the present indications for the use of fluid diphtheria toxoid, in view of the greater and more durable immunity provided by adsorbed toxoids.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Adsorbed Manufactured by Parke, Davis & Company

1. *Description.* This is an aluminum phosphate adsorbed diphtheria toxoid, containing 15 Lf per 0.5 mL dose, and 2.5 mg of aluminum phosphate per 0.5 mL dose. It is suspended in 0.9 percent saline, and 1:10,000 thimerosal is included as a preservative. The manufacturing process, clarified in a supplemental submission, defines the strain of *Corynebacterium diphtheriae* to be used, and outlines a process of ultrafiltration, ammonium sulfate precipitation, and subsequent dialysis. This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be recommended for the active immunization of children from 6 months to 8 years of age, where a multiple antigen is not indicated. The labeling further states that this product may be used to immunize older children and adults, but with appropriate caution because of the possibility of reactions.

A complete immunizing treatment is said to consist of two 0.5 mL doses at intervals of 4 to 6 weeks. A recall dose 1 to 2 years after the initial course is recommended for full protection. The labeling was last revised in December 1964, and thus differs strikingly from current national recommendations.

b. *Contraindications.* No absolute contraindications are listed. Children with a negative Schick test are recommended not to receive diphtheria toxoid.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements for diphtheria toxoid.

(2) *Human.* In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, prison inmates were immunized with various combinations of Parke-Davis diphtheria toxoids (Ref. 4). In most instances, the serologic responses obtained apparently represented booster reactions. Furthermore, it is not clear whether the products used were fluid or adsorbed diphtheria toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements for diphtheria toxoid.

(2) *Human.* There is adequate documentation of the safety in humans of Parke-Davis adsorbed diphtheria toxoids, as contained in the submission.

(c) *Benefit/risk ratio.* This cannot be determined with precision, owing to the absence of satisfactory data documenting the efficacy of this product when used as a primary immunizing agent. However, it is likely that the benefit-to-risk assessment would be satisfactory when the toxoid is used as a booster immunizing agent.

4. *Critique.* Since this product is not currently on the market, the labeling is badly out-of-date, and requires substantial revision in order to conform with current national recommendations for use of diphtheria toxoids. Furthermore, the statement that children with a negative Schick test do not require diphtheria toxoid is inappropriate, inasmuch as a Schick-negative child may become positive as time goes on, and therefore should have appropriate boosters as recommended in standard immunization schedules.

The Panel finds there is adequate documentation for the safety of this product, for that period of time when this product was previously on the market, as well as adequate documentation of its efficacy in humans when used as a booster immunization. Satisfactory data for the efficacy of adsorbed toxoid in humans, when used for primary immunization, have not been provided.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product has not been marketed for a number of years in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid, Fluid, Manufactured by Texas Department of Health Resources

1. *Description.* This is a fluid diphtheria toxoid which is purified and concentrated by the ammonium sulfate fractionation method. It is diluted in buffered saline and preserved in 1:10,000 thimerosal. It contains 120 Lf of diphtheria toxoid per mL.

2. *Labeling*—a. *Recommended use/indications.* The manufacturer recommends this product for use in infants and young children only when there is a contraindication to the administration of preparations of diphtheria toxoid combined with tetanus toxoid and pertussis vaccine. When necessary to administer the preparation to individuals less than 7 years of age, 3 injections of 1.0 mL subcutaneously are recommended at 3 to 4 week intervals. For the primary immunization of individuals greater than 7 years of age in is recommended that adult-type tetanus

and diphtheria toxoids be administered. There is no recommendation for reinforcing doses nor is a schedule for primary immunization of individuals 7 years of age or older provided.

b. *Contraindications.* It is a recommended that individuals 7 years of age and older should receive no more than 0.05 mL by injection without testing for sensitivity. Other contraindications are not specified.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data directly related to this product are not available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No serious reaction has been reported related to the many thousand doses of the product distributed over the 10-year period.

c. *Benefit/risk ratio.* Although the risk from this preparation is low and the benefit is probably high, in the absence of human data no precise statement can be made regarding primary immunization. However, the benefit-to-risk assessment is satisfactory when the toxoid is used as a booster immunizing agent.

4. *Critique.* The Panel has a general concern about whether there are present indications for the use of fluid diphtheria toxoid, in the light of greater and more prolonged immunity provided by the adsorbed preparations. Furthermore, although this preparation is presumbly highly potent (120 Lf per dose), direct evidence of its superiority to, or comparability with adsorbed preparations as immunizing agents in humans is not available. Finally, the recommendations for its use are not consonant with those of advisory bodies in the United States.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued provided that labeling is revised in accordance with the Panel's comments regarding labeling.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the manufacturer's license for this product be maintained for a period not to exceed 3 years, during which time the manufacturer will be expected to provide satisfactory evidence of efficacy in humans under conditions of primary immunization. Labeling should be revised in accordance with the recommendations of this Report.

Diphtheria Toxoid Manufactured by Wyeth Laboratories, Inc.

The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Adsorbed Manufactured by Wyeth Laboratories, Inc.

The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

References

(1) BER Volume 2124.
(2) BER Volume 2111.
(3) BER Volume 2053.
(4) BER Volume 2003.

Generic Statement on Tetanus Toxoid

Tetanus is an acute disease of the nervous system caused by infection with the tetanus bacillus, *Clostridium tetani*, which produces an extremely potent neurotoxin that is lethal to man in miniscule amounts (approximately 7 millionths of a milligram). The tetanus bacillus also produces lesser reactive substances. The disease is of major importance, killing perhaps 1 million people worldwide annually, many of whom are newborns. The tetanus bacillus is probably primarily a resident of the intestinal tract of various animals, but spores are widely distributed in soil and dirt, and when carried into devitalized injured human tissue that is low in oxygen, the spore form of the bacillus can germinate, multiply, liberate toxin and hence cause the disease. The disease can be prevented by immunization with tetanus toxoid. Immunization is indicated for everyone, since natural immunity, if it exists at all, is exceedingly rare in man; not even the disease itself produces immunity in those who recover from it.

Because the morbidity and mortality of tetanus are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used for many decades in the treatment of the disease and for its prevention in exposed susceptible individuals. More recently the use of antitoxin prepared from horse serum has been largely replaced by the use of tetanus immune globulin (TIG) prepared from human serum. This approach to control of the disease is only partially successful because the disease may already be established by the time of treatment, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin or TIG. Penicillin or alternative effective antibiotic agents may eradicate the organism, but because they have no effect against toxin, antibiotics are only an adjunct to therapy. For these reasons, passive immunization with antitoxin or immune globulin and therapy with antimicrobial agents have been an unsatisfactory approach to treatment of the disease, and active immunization of humans against the toxin had been employed for many years.

Nature of Product

Tetanus toxoid is a formaldehyde detoxified bacteria-free filtrate of an anaerobic culture of a specially selected strain of *Clostridium tetani;* sometimes the culture is lysed before filtration to liberate more toxin. Toxin yields are comparable to those obtained with *Corynebacterium diphtheriae* and indeed the two toxins are, as protein molecules, remarkably similar despite the great differences in their pharmacologic action.

Production

Tetanus toxoid is produced with high yields in a simple liquid anaerobic medium, is detoxified with formaldehyde, is partially purified and thus freed of extraneous bacterial proteins, and in final dilution is administered in a dose similar to or slightly less (in terms of flocculation or Lf units) than that for diphtheria toxoid. The medium must contain no substance derived from horses, no know allergens, and no more than a specified trace of blood-grouping substances. Although tetanus toxoid has been widely and successfully used in the plain ("fluid") form, the superiority of aluminum salt-adsorbed tetanus toxoid has been clearly demonstrated, and this form of the toxoid is the most widely used.

Purification of tetanus toxoid is usually accomplished by methanol precipitation, by ammonium sulphate or metaphosphate purification, or less often by ultrafiltration. It is diluted to a concentration that will pass official requirements and a preservative (usually thimerosal) is added. It is subjected to the standard tests for sterility, safety, and potency required by the U.S. regulations.

The antigenicity in man of tetanus toxoid can vary considerably from preparation to preparation; this variation is partly due to variations in

the quality and content of toxoid (about 2 to 10 Lf) or of aluminum ion in the adjuvant. The protective level is assumed to be approximately 0.01 unit per mL of tetanus antitoxin toxoid. The geometric mean antibody titer response to various preparations in man after a single dose of either fluid or adsorbed toxoid is extremely variable, from less than 0.001 unit to 0.05 unit. However, with 2 doses of adsorbed toxoid, or 3 doses of fluid toxoid, this variation is greatly reduced and titers usually exceed the protective level.

Use and Contraindications

This product is often used singly as well as in combination with diphtheria toxoid (DT or Td) or with diphtheria toxoid and pertussis vaccine (DTP). The most commonly used product is DTP, which is routinely recommended for use in children 6 years and under in age; for older children and adults it is recommended that tetanus and diphtheria toxoids (combined) for adult use (Td) be employed for booster purposes. Tetanus toxoid is used singly by physicians who consider that the diphtheria component is either unnecessary, or likely to cause an untoward reaction in the patient. The fluid toxoid is given in 3 doses at least a month apart, with a fourth reinforcing dose, generally about 8 to 12 months later. The adsorbed form is given in 2 doses at least a month apart, with a reinforcing dose as in the case of fluid toxoid. Routine booster injections are recommended at 10 year intervals. In the case of wounds, boosters are recommended if the interval since the last booster is more than 5 years, and in the opinion of some, if the interval is more than 1 year.

In areas where neonatal tetanus is a problem, it can be virtually eliminated by administering either (1) two or more properly spaced doses of adsorbed toxoid to all women of child-bearing age, or (2) two or more doses of adsorbed toxoid during pregnancy, at least a month apart, with the second dose at least 2 and preferably 3 weeks before delivery.

Safety

Problems of adverse reactions to tetanus toxoid have been rare, especially since the elimination, over 30 years ago, of the highly allergenic Witte peptone from the production medium. Most of the local and febrile reactons that are seen appear to be related to more frequent inoculations than are necessary. In general, however, tetanus toxoid has an almost unique record for safety, no deaths having been associated with the administration of 2.5 million doses in a series reported from Denmark, where a thorough followup study was possible.

Manufacturers are required to record reported reactions.

Efficacy

When used as recommended, tetanus toxoid has provided protection to over 95 percent of those inoculated as judged by the induction of serum titers of at least 0.01 antitoxin unit per mL. Indeed, during World War II, only 4 properly immunized U.S. Army personnel developed tetanus among 2,500,000 persons wounded or injured. Other apparent failures have been reported, but in almost all instances they were associated with incomplete immunization or a false history of immunization.

Special Problems

Continued efforts should be made to establish, for routine lot-to-lot control, the usefulness of the quantitative technique of the evaluation of tetanus toxoids against the International Standards. This technique has been accepted by the European Pharmacopoeia. Direct human testing of any new or altered product should be required until such time as these efforts are completed. The Panel accepts the Bureau of Biologics' potency requirements in animals as evidence of adequate immunogenicity for use as a booster in man.

Historically, the antitoxin resonse to the initial 2 doses of adsorbed toxoid has been excellent. However, recent changes in manufacturing procedures may have resulted in lowering of the immunizing potency of tetanus toxoid in some products; hence, there is a need for reevaluating the primary antigenicity of current preparations in man.

Considerable confusion exists concerning the interchangeability of fluid and adsorbed toxoid. However, studies have shown the greater efficacy of adsorbed toxoid, not only in the magnitude but in the duration of the immune response. This superiority is particularly marked in combined active-passive immunization.

The incidence of reactions, though not of major importance, might be reduced by purification of the toxoid and by eliminating excessive booster doses in highly immunized persons.

Recommendations

There is a need for further studies on the World Health Organization-sponsored quantitative potency test in animals to establish the conditions under which the results are reproducible and to relate these results more closely to those obtained in immunization of man.

Efforts should be encouraged to enhance the immunogenicity of tetanus toxoid without increasing its reactogenicity so that fewer injections are required for primary immunization. Furthermore, it is essential to validate the immunogenicity in man of toxoids in current use that have not already been so tested. An illustrative protocol for such tests has been developed.

It is recommended that the immunogenic superiority of the adsorbed toxoid over the fluid preparation, especially with regard to the duration of protection, be emphasized and be included in labeling of products.

A minimum standard of purity should be established for tetanus toxoid.

Finally, for the tetanus toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistance on effectiveness data and constraints on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction in this Report.)

Basis for Classification

Past experience indicates that all tetanus toxoids that meet the Bureau of Biologics' requirements for potency in animal tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore, direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For those products, therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.

References

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(3) Newell, K.W., D.R. LeBlanc, G. Edsall, L. Levine, H. Christensen , M.H. Montouri, and N. Ramirez, "The

Serological Assessment of a Tetanus Toxoid Field Trial," *Bulletin of the World Health Organization*, 45:773–785, 1971.

(4) VanRamshorst, J.D., H. Cohen, L. Levine, G. Edsall, "The Relation Between Animal Potency Tests and the Human Response to Adsorbed Tetanus Toxoids," *Journal of Biological Standardization*, 1:215–220, 1973.

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(6) Edsall, G., M.A. Belsey, D.R. LeBlanc, and L. Levine, "Host Factors in the Response to Immunization," *Progress in Drug Research*, 19:263–273, 1975.

(7) Vaccinum Tetanicum Adsorbatum, supplement to Volume III, pp. 174–178, European Pharmacopoeia 1977, 57 Maisonnuve, S.A., Saint Ruffine, France.

SPECIFIC PRODUCT REVIEWS

Tetanus Toxoid Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* This preparation comprises tetanus toxiod, adsorbed onto aluminum phosphate, and contains 5 to 10 Lf per 0.5 mL.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for use in the initiation and maintenance of immunity to tetanus in adults. It is specifically recommended that infants and young children be immunized with a combined preparation containing diphtheria toxoid and pertussis vaccine and that adolescent children receive primary immunization with tetanus and diphtheria toxoids of the adult type. The recommended course for primary immunization with this product comprises 2 injections of 0.5 mL intramuscularly 4 to 6 weeks apart, followed by a reinforcing dose 6 to 12 months later. A further reinforcing dose of 0.2 mL every 10 years is advised. The package insert contains no mention of reinforcing doses with injury.

b. *Contraindications.* Acute respiratory or other infections are given as reasons for deferral of immunization, and a warning about the possibility of an unsatisfactory immune response in individuals receiving immunosuppressive drugs is provided. It is stated that individuals not previously immunized will not be protected by tetanus toxoid at the time of injury and recommends instead that tetanus immune globulin and toxoid, given simultaneously at different sites, be given at the time of injury followed by later completion of active immunization against tetanus. A warning about rare anaphylactic responses is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* As evidence for efficacy, the general literature regarding the effectiveness of tetanus toxoid is cited in the submission to the Panel (Ref. 1). Also, the current paucity of tetanus in the United States and Michigan, as well, is noted. It is concluded that the absence of tetanus in Michigan is due, at least in part, to the millions of doses of tetanus toxoid distributed from this manufacturer in Michigan during the years 1962 through 1972. Serologic evidence of the immunogenicity of this product includes the results of a study of 81 children who received 3 injections of a preparation containing diphtheria toxoid, pertussis vaccine, and inactivated poliomyelitis vaccine combined with tetanus toxoid. All children achieved satisfactory titers of tetanus antitoxin. Evidence of efficacy of this preparation for reinforcement of immunity against tetanus is provided in a study of 31 individuals, all with a history of prior tetanus immunization, who were given a single 0.2 mL reinforcing dose. All achieved excellent rises in antitoxin titers.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Evidence of human safety is provided by a review of the total number of doses given and the reported reactions over a 10-year period. Among a few million doses there were four reactions resembling immediate anaphylactic shock. The remaining reactions were minor and local.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product for primary immunization is probably satisfactory, although the lack of data regarding its efficacy in humans as a primary immunizing agent prevents precise evaluation. Its benefit-to-risk assessement for booster immunization is satisfactory.

4. *Critique.* This extensively used product appears to be quite safe and well-established as efficacious when used for reinforcement of immunity in previously immunized individuals. However, the Panel does not believe that the data relating to the efficacy of tetanus toxoid as a primary immunizing agent when combined with diphtheria toxoid, pertussis vaccine, and poliomyelitis vaccine can be extrapolated to substantiate the efficacy of this product when used without such combination.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxiod, Fluid Manufactured by Connaught Laboratories, Limited

1. *Description.* This is a fluid tetanus toxoid containing 12 Lf of toxoid per mL. The toxin is prepared in a casein hydrolysate medium, inactivated by formalin, and diluted in saline containing 15 parts per million of Tween 80.

2. *Labeling*—a. *Recommended use/indications.* The recently revised package insert submitted by the manufacturer contains a satisfactory description of the preparation. For primary immunization, 4 subcutaneous injections of 1 mL are recommended, the first 3 being 4 to 8 weeks apart and the fourth dose 6 to 12 months later. Further reinforcing doses are recommended at 5 year intervals. A reinforcing dose with injury is not recommended if less than 1 year has elapsed since the last dose. If the last administration of tetanus toxoid was more than 5 years previously, both a reinforcing dose and tetanus antitoxin are recommended.

b. *Contraindications.* The manufacturer warns that turbid or cloudy tetanus toxoid should not be used, and a warning about anaphylactic reactions is included. No other contraindication is listed

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Evidence for efficacy of this product was provided in a 1964–1965 study (Ref. 2) in which 67 children, age 7 to 15 years, were tested for tetanus antibody after a course of 3 injections of

Connaught DT—polio vaccine. Forty-four children had no preimmunization tetanus antibody and were considered primary responders. All of the 44 sera showed a level of 0.125 antitoxin units per mL or greater 1 month after the third injection. Furthermore, an antibody survey in Ontario, where this toxoid is used almost exclusively for tetanus immunization, showed that approximately 98 percent of children less than 18 years of age exhibited satisfactory antibody titers of 0.01 unit per ml of serum or more.

The human efficacy data demonstrate somewhat lower titers following immunization than those achieved with adsorbed preparations.

b. *Safety*—(1) *Animal.* This product meets Federal requriements.

(2) *Human.* of 1,422 injections of tetanus toxoid to employees at Connaught Laboratories, 30 were associated with reactions, all of which were local (Ref. 2). Evidence is also provided by intradermal testing that Sephadex purification of this toxoid markedly reduces local reactions. Only 1 allergic reaction has been reported from several million injections of this toxoid in the last 5 years.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is very satisfactory.

4. *Critique.* This fluid tetanus toxoid has been shown to be both safe and efficacious. Although it is questionable whether any fluid toxoid is as immunogenic as adsorbed preparations, both in terms of antibody titers achieved and duration of immunity, when used as recommended its efficacy considerably exceeds the protective threshold. The package insert deviates from the usual U.S. recommendations for immunization, particularly in the recommendation that tetanus antitoxin be employed along with a booster if more than 5 years has elapsed since the last dose. The use of tetanus antitoxin under these circumstances is superfluous, assuming that primary immunization has been completed. Further, the package insert contains no comment about the effects of immunosuppressive drugs on the immune response to this product.

5. *Recommendations.* Although the Panel feels some preference for absorbed over fluid toxoids, the Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the package insert should be revised in accordance with currently accepted guidelines. The package insert should also include a recommendation that for the primary immunization of children a combined product containing diphtheria toxoid and pertussis vaccine, as well as tetanus toxoid, is preferred.

Tetanus Toxoid Manufactured by Cutter Laboratories, Inc.

1. *Description.* Purified tetanus toxoid in sodium chloride, buffered with sodium succinate and containing 1:10,000 thimerosal in a dose of 60 Lf per mL.

2. *Labeling*—a. *Recommended use/indications.* This product is used only for hyperimmunization of adults who volunteer to serve as donors in the preparation of human hyperimmune tetanus globulin. It is administered in a dose of 0.5 mL (30 Lf) given by intramuscular or deep subcutaneous route. It is used only by Cutter Laboratories and not marketed. A donor may receive either no more than 3 injections in a single year followed by a single injection the following year, or no more than 1 booster injection per year for 3 years.

b. *Contraindications.* Any acute respiratory disease or any active infection is reason for deferring an injection. It should be noted here, also, that persons with a history of adverse reactions to tetanus toxoid should be excluded. This is now mentioned under "Adverse Reactions" in the package insert.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal Requirements.

(2) *Human.* The company summarizes their experience as follows (Ref. 3): Cutter Laboratories, tetanus toxoid, 60 Lf per mL, after total donations of many thousand units of plasma, has been shown to be 90 percent effective in producing adequate plasma tetanus antibody titer (10 International Units or more). Also, after many thousand booster injections and a followup of 22,672 donors, tetanus toxoid, 60 Lf per mL, has been shown to be safe for hyperimmunization of adult plasama donors for plasma used in the production of tetanus immune globulin (human).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Mild side effects were reprted (Ref. 3) a total of 10 times following 22,672 booster injections of tetanus toxoid, 30 Lf, giving a low order of incidence: 0.04 percent. Side effects include five cases of rash and hives, three of mild fever, and one each of swelling of glands and transient dizziness.

c. *Benefit/risk ratio.* This product is designed for hyperimmunization of volunteer subjects. Traditional benefit-to-risk assessment are inappropriate considerations. The risk is low; benefit to mankind is high.

4. *Critique.* This product is used only to produce hyperimmunization of adult tetanus plasma donors. Cutter Laboratories report a very low rate of adverse effects of the relatively high dose of tetanus toxoid (30 Lf) in persons who already have received their basic series of immunization. Prior to the actual booster immunizations each donor reads and signs the tetanus information and donor's consent and release form.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the package insert should be revised in accordance with currently accepted guidelines and recommendations of this Report.

Tetanus Toxoid, Fluid, Manufactured by Dow Chemical Company

1. *Description.* Tetanus toxoid, fluid, is a preparation of tetanus toxoid detoxified with formalin, purified and concentrated by alcohol fractionation, and containing 8 Lf per 0.5 mL human dose. It is preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The fluid product is recommended primarily for booster use after exposure to tetanus in previously immunized individuals. It is stated that multiple antigen vaccines (i.e., DTP) are preferred for children under 6 years of age.

b. *Contraindications.* Immunization should be deferred if respiratory disease or other active infections exist and in patients under immunosuppressive treatment. Fractional doses are recommended in cerebral injury, asthma, allergies, and histories of severe febrile reactions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this specific product were provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on this product were provided. Data from adverse reactions reported to the company and retrieved from their complaint files show no unusual number of reactions. The validity of such data is always open to question, but the rate of reported untoward reactions is somewhat higher with the fluid product than with the adsorbed product. Most of the reactions were local in nature;

allergic or anaphylactoid reactions were noted in a very few cases.

c. *Benefit/risk ratio.* Assuming that the product can be demonstrated efficacious for primary immunizaiton, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunizaiton.

d. *Labeling.* Fluid toxoid is recommended for booster doses following injury in the labeling for both fluid and adsorbed toxoids. The more rapid response to fluid toxoid alluded to is of very dubious significance. The recommendation that boosters be given if the previous dose was received more than 1 year previously is obsolete and encourages excessive booster doses. In addition, fluid toxoid in combination with tetanus immune globulin (TIG) is recommended if more than 10 years have elapsed since the last booster dose. This should be changed to adsorbed toxoid, which is more effectve in combination with TIG. The Public Health Service Advisory Committee on Immunization Practices recommendations on wound management should be followed.

The recommendation to defer immunization when polio is present in the community is also obsolete.

4. *Critique.* In view of the product's ability to meet the potency test in animals specified by minimum requirements, it is adequate for booster immunization use in humans. However, no data are available for the product to demonstrate its efficacy for primary immunization. In addition, in the opinion of some, there is no real need for the fluid product. The alleged superiority of fluid products for booster doses following injury is of dubious significance.

While specific data on reactions were not provided, safety is not considered a significant issue. Complaint file data indicate no unusual or unexpected problems.

5. *Recommendations.* The Panel recommeds that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not exceed 3 years during which time the manufacturer shall be expectect to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Dow Chemical Company

1. *Description.* Tetanus toxoid adsorbed is an alum-precipitated preparation prepared by the same method as the fluid product but containing 12 to 16 Lf per 0.5 mL human dose versus 8 Lf for the fluid product. The adsorbed product contains 2.5 mg alum per dose. It is preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The adsorbed product is recommended over the fluid product for primary immunization, although is stated the fluid product may be used. It is stated the multiple antigen vaccines (i.e., DTP) are preferred for children under 6 years of age.

b. *Contraindications.* Immunization should be deferred if respiratory disease or other active infections exist and in patients under immunosuppressive treatment. Fractional doses are recommended in cerebral injury, asthma, allergies, and histories of severe febrile reactions. Cautions are inserted that aluminum adjuvants may cause fat necrosis or draining cysts if not properly injected.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this specific product were provided.

b. *Safety*—(1). *Animal.* This product meets Federal requirements.

(2). *Human.* No specific data on this product were provided. Data from adverse reactions reported to the company and retrieved from their complaint files show no unusual number of reactions. The validity of such data is always open to question, but the rate of reported untoward reactions is somewhat lower with the adsorbed product than with the fluid product. Most of the reactions were local in nature; allergic or anaphylactoid reactions were noted in a very few cases.

c. *Benefit/risk ratio.* Assuming that the product can be demonstrated efficacious for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. *Labeling.* The package insert states that fluid toxoid is recommended for booster doses following injury. The more rapid response to fluid toxoid alluded to is of very dubious significance. The recommendation that boosters be given if the previous dose was received more than 1 year previously is obsolete and encourages excessive booster doses. In addition, fluid toxoid in combinations with tetanus immune globulin (TIG) is recommended if more than 10 years have elapsed since the last booster dose. This should be changed to adsorbed toxoid, which is more effective in combination with TIG. The Public Health Service Advisory Committee on Immunization Practices recommendations on wound management should be followed.

The recommendation to defer immunization when polio is present in the community is also obsolete.

4. *Critique.* In view of the product's ability to meet the potency test in animals specified by minimum requirements, it is adequate for booster immunization use in humans. However, no data are available for the product to demonstrate its efficacy for primary immunization. The alleged superiority of fluid products over adsorbed products for booster doses following injury is of dubious significance.

While specific data on reactions were not provided, safety is not considered to be a significant issue. Complaint file data indicate no unusual or unexpected problems.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Eli Lilly and Company

1. *Description.* Each 0.5 mL of this product contains about 7.5 Lf of purified tetanus toxoid in 0.3 M glycine, preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, four 0.5 mL doses over 1 year are recommended; emergency boosters and active-passive primary immunization are also listed as indications.

b. *Contraindications.* Acute respiratory disease or other active infection are contraindications for use. In individuals who have shown sensitivity reactions to previous injections of tetanus toxoid, a small test dose should be given first. Epinephrine should be available to combat severe systemic reactions if they develop.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2). *Human.* No data were presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Few complaints for many million doses are reported and suggest that no major problem exists.

c. *Benefit/risk ratio.* There is some reason to question the benefit gained from use of this fluid product for primary immunization in light of the limited available data on efficacy. The benefit-to-risk assessment is satisfactory for booster immunization.

4. *Critique.* This package insert does not point out the general preference for adsorbed rather than fluid toxoid, nor does it indicate the superiority of adsorbed toxoid in active-passive immunization. No data are presented to indicate whether this specific product is effective in man.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Eli Lilly and Company

1. *Description.* A sterile suspension of tetanus toxoid precipitated with aluminum potassium sulfate to a final concentration of 2.25 mg per mL (1.125 mg per dose), and suspended in 0.3 M glycine. About 7.5 Lf of toxoid are present per dose; 0.01 percent thimerosal is added as a preservative. The toxoid is purified by the Pillemer process which is said to remove practically all of the inert proteins.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, the package insert recommends two 0.5 mL doses 4 to 6 weeks apart and a third dose 1 year later. No special reference is made to the reinforcing dose, but normal booster recommendations are up-to-date.

b. *Contraindications.* Acute respiratory diseases or other active infections are contraindicated. In individuals with preceding history of reactions to tetanus toxoid, small doses should be given. Epinephrine should be at hand.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data were presented by the manufacturer. One study by Snyder (Ref. 4) reports rather poor first-dose response to this product, so that some uncertainty exists as to whether it is sufficiently antigenic. It should be noted that this product contained relatively little aluminum ion.

b. *Safety*—(1) *Animal.* this product meets Federal requirements.

(2) *Human.* No controlled observations presented. The complaint file discloses a few complaints for several million doses sold. Most of these were apparently local reactions, pain or febrile reactions. One "systemic" reaction was recorded.

c. *Benefit/risk ratio.* Provided evidence is furnished to indicate that this product is effective for primary immunization, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

4. *Critique.* The 1 mL label, included with the manufacturer's submission, is almost unreadable. Other labeling supplied by the manufacturer is clear and informative. Comment(s) on the need for careful resuspension of the precipitate appears in the circular for the prepackaged product but not the standard product. This submission presents less information than is needed on the response of normal individuals to 2 and 3 doses of this product when used as recommended. The labeling should stress the importance of the third dose as part of the primary immunizing series.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Plain, Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

1. *Description.* This product contains 40 to 50 Lf tetanus toxoid per mL.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for primary immunization for tetanus. The dose is 0.5 mL intramuscularly or subcutaneously in 3 doses 4 to 6 weeks apart for primary immunization and a fourth dose approximately 1 year later. A booster dose every 10 years is recommended. For wound management, a booster dose is not recommended unless more than 5 years have lapsed since the patient's third or last booster dose.

b. *Contraindications.* Immunizations are deferred in any acute or active infection and in persons receiving immunodepressants.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims on efficacy are based on published reports cited in the manufacturer's submission to the Panel (Ref. 5) in which the Sclavo product was used and produced satisfactory antitoxin response. However, published data on efficacy when the product is used for primary immunization are lacking. Separate unpublished data showing antibody response when the adsorbed product is used for primary immunization in children show marginal results, with a relatively large proportion of children not reaching an antitoxin level of 0.01 International Units after 2 injections. The product was proven effective as a booster, however.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission states that few complaints of adverse reactions have been reported, without any further analysis of such data.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory for primary immunization if the product is shown to be effective and is satisfactory for booster immunization.

d. *Labeling.* Instructions regarding booster doses following wounds could be improved by including the table from the Public Health Service Advisory Committee on Immunization Practices recommendations.

4. *Critique.* This product meets the U.S. standards for animal safety and

potency and appears to be safe in humans. Additional serologic data establishing its efficacy for use in primary immunization are needed. The efficacy of the product as a booster is established. In the package insert, recommendations regarding booster doses should follow U.S. guideines.

Possibility and description of adverse reactions should be mentioned. The manufacturer's data submission does not describe or elaborate on reported adverse reactions.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

1. *Description.* This product contains 10 Lf tetanus toxoid and 2 mg [1] aluminum hydroxide per 0.5 mL dose. According to the package insert, this product is highly purified, but methods of production and purification are not described.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for primary immunization for tetanus. The dose is 0.5 mL intramuscularly in 2 doses 6 to 8 weeks apart for primary immunization and a third dose approximately 1 year later. A booster dose every 10 years is recommended. For wound management, a booster dose is not recommended unless more than 5 years have elapsed since the patient's third or last booster dose.

b. *Contraindications.* Immunizations are deferred in any acute or active infection and in persons receiving immunodepressants.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims of efficacy are based on published reports cited in the manufacturer's submission to the Panel (Ref. 6) in which the Sclavo product was used in special clinical settings and produced satisfactory antitoxin responses. However, published data on efficacy when the product is used for primary immunization are lacking. Separate unpublished data showing antibody response when the adsorbed tetanus toxoid was used for primary immunization in Italian children showed marginal results, with a relatively large proportion of children not reaching an antitoxin level of 0.01 International Unit after 2 injections. The product was proved effective as a booster, however.

In 1977, completed studies of this manufacturer's DT and Td among children and adults, conducted in Mexico, show satisfactory antitoxin response for tetanus as well as diphtheria. These studies were included in the manufacturer's license application to FDA.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission states that few complaints of adverse reactions have been obtained, without any further analysis of such data.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

d. *Labeling.* Instructions regarding booster doses following wounds could be improved by including the table from the Public Health Service Advisory Committee on Immunization Practices recommendations.

4. *Critique.* This product meets the U.S. standards for animal safety and potency and appears to be safe in humans. Additional data were provided to the Panel subsequent to the original submission. The data were submitted in support of DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective. In the package insert, recommendations regarding booster doses should follow the U.S. guidelines.

The possibility and description of adverse reactions should be included in the package insert. The manufacturer's data submission does not describe or elaborate on reported adverse reactions.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Tetanus Toxoid Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product is a fluid tetanus toxoid prepared from toxin produced by the method of Mueller and Miller, detoxified with formaldehyde, "refined" by the Pillemer method, diluted in phosphate buffer and 0.3 M glycine to a final concentration of 5 Lf per dose, and preserved with 0.1 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, the dose is three 0.5 mL injections intramuscularly at 3 to 4 week intervals and a fourth dose 1 year later. The labeling notes the immunogenic superiority of adsorbed toxoids and the lack of any significant advantage of fluid toxoid as regards speed of booster response. Wound booster recommendations appear to be based on current Public Health Service Advisory Committee on Immunization Practices recommendations.

b. *Contraindications.* Acute respiratory disease or other active infection; immunosuppressive or cytotoxic therapy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Reports of the Investigational New Drug 262 study included in the manufacturer's submission to the Panel (Ref. 7) suggest very poor primary response to preparation D (a fluid toxoid containing 6 Lf per dose but described as "the current commercial product"). Of 10 subjects, 2 were "protected," 4 had minimal antibody levels, and 3 had no measurable response. In a second study, only 2 of 6 subjects given this toxoid were primary responders; both of them had only marginal protection at 90 days. The protocol fails to state whether a third injection of the fluid toxoid was given, however, and then antibody responses suggest that it was not given.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Twenty-eight minor complaints and apparently no major ones in 3 years are recorded, with several million doses distributed. This suggests a low degree of reactivity. Reactions in the studies noted above were nil (in six subjects).

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product would be satisfactory if the product is shown to be affective for primary immunization

[1] The labeling submitted to the advisory Panel is wrong. This product contains 1 mg of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling has been corrected.

and is satisfactory for booster immunization.

4. *Critique.* The Panel found this to be an exceptionally informative submission, which brings to light the problem of whether or not the responses to "basic" immunization (i.e., 3 doses of fluid or 2 of adsorbed toxin) with recent preparations are less good than had been expected. When "full primary" immunizations (i.e., 4 doses of fluid or 3 doses of adsorbed tetanus toxoid) had been achieved, evidence of immunogenicity was satisfactory. However, this might result in 6 to 12 months of suboptimal protection.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Tetanus toxoid is prepared from toxin produced by the method of Mueller and Miller, detoxified with formaldehyde, "refined" by the Pillemer method, diluted in sodium chloride solution, and adsorbed with not more than 0.8 mg of aluminum phosphate per does. The final concentration of toxoid is 5 Lf per dose and 0.01 percent thimerosal is present as a preservative.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, two 0.5 mL injections intramuscularly at 4 to 6 week intervals and a third dose 1 year later. The labeling notes the immunogenic superiority of adsorbed toxoids and the lack of any significant advantage of fluid toxoid as regards speed of booster response. Wound booster recommendations appear to be based on recent Public Health Service Advisory Committee on Immunization Practices recommendations.

b. *Contraindications.* Acute respiratory disease or other active infection; immunosuppressive or cytotoxic therapy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Reports of the Investigational New Drug 262 study included in the manufacturer's submission to the Panel (Ref. 8) suggests unexpectedly poor primary responses to two preparations, one with about half the aluminum content, the other with about four times the aluminum content of the standard Lederle Laboratories Division commercial product. With the low adsorbent preparation, two of eight primary responders had subprotective levels 30 days after the dual injection. With the higher (maximum permitted) adsorbent content, two of eight primary responders again failed to reach protective levels after 2 doses.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Fourteen complaints were recorded in 4½ years during which a few million doses of adsorbed toxoid were distributed. Details are lacking but "convulsions" are mentioned in the condensed statement.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory if the product is shown to be effective for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* The Panel found this to be an exceptionally informative submission, which brings to light the problem of whether or not the responses to "basic" immunization (i.e., 3 doses of fluid or 2 or adsorbed toxoid) with recent tetanus toxoid preparations are less good than had been expected.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is a fluid tetanus toxoid containing 10 Lf per mL of tetanus toxoid, preserved with 1:10,000 thimerosal, and diluted in phosphate buffered saline at a pH of 7.0. The toxoiding agent is formaldehyde, and the purification process is carried out by ammonium sulfate precipitation followed by dialysis against distilled water.

The dose is not specified, for the manufacturer has not produced this material for some years, but desires to retain a license for possible future production.

2. *Labeling*—a. *Recommended use/indications.* No labeling was submitted by the manufacturer.

b. *Contraindications.* No labeling was submitted by the manufacturer.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements. In addition, the efficacy of this product in animals is well documented, due largely to a series of investigations identified in the manufacturer's submission of data to the Panel (Ref. 9) which used products from the Massachusetts Public Health Biologic Laboratories.

(2) *Human.* The efficacy of this product in humans, measured serologically, is well documented, both when used as a primary immunizing agent and when used as a tetanus booster. It appears, however, that the adsorbed tetanus toxoid from this same manufacturer induces a thirtyfold higher secondary response than does fluid toxoid, on the basis of a comparison of group geometric mean serum antitoxin titers sampled 56 days after an active-passive tetanus immunization study.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The references cited adequately document the safety of this product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The Panel has a general concern about the indications for use of a fluid tetanus toxoid, in the light of the documented superiority of adsorbed tetanus toxoid, not only in the magnitude but in the duration of the immune response. Furthermore, the Panel is unable to assess this product adequately in the absence of appropriate labeling, recommendations for use, and contraindications.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product has not been produced for a number of years and is not marketed in the form for which licensed and consequently there are insufficient data

on labeling, safety, and effectiveness for a contempory batch of this product.

Were appropriate labeling to be submitted, the Panel would recommend that the manufacturer retain full licensure for this product.

Tetanus Toxoid, Adsorbed Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is an adsorbed tetanus toxoid, containing 10 Lf units per mL of tetanus toxoid, 4 mg per mL of aluminum phosphate, preserved in 1:10,000 thimerosal, and containing sodium chloride and sodium acetate as diluent. The toxoiding agent is formaldehyde, and purification is carried out by ammonium sulfate precipitation and subsequent dialysis against distilled water. The recommended dose, 0.5 mL, contains 5 Lf of tetanus toxoid.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for the routine immunization of individuals against tetanus, and for routine and emergency recall injections. For primary immunization, 2 doses of 0.5 mL are recommended at least 4 weeks apart with a reinforcing dose 6 to 12 months later and routine booster doses approximately every 10 years. It is recommended that combination toxoids with diphtheria are preferable for immunization; no mention of DPT appears in the labeling. The recommendations for use appear to be identical to those of the Public Health Service and the Advisory Committee on Immunization Practices.

b. *Contraindications.* No absolute contraindications are listed. The labeling does state that the material should not be given as elective immunization when the patient has an acute infectious illness.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements. In addition, the efficacy of this product in animals is well documented, due largely to a series of investigations identified in the manufacturer's submission of data to the Panel (Ref. 10) which used products prepared by this manufacturer.

(2) *Human.* The efficacy of this product in humans, measured serologically, is satisfactorily documented, both as regards its effectiveness as a booster and as a primary immunizing agent.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The safety of this product in humans is adequately documented.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The manufacturer's submission contains satisfactory evidence of both safety and efficacy as well as appropriate and satisfactory labeling.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Tetanus Toxoid, Fluid, Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This is a fluid tetanus toxoid containing 20 Lf of toxoid per mL. The toxin is prepared in a special semisynthetic culture medium which is not further described. It is also purified by methods which are not described. The diluting medium is an aqueous solution of 0.3 M glycine, and the preservative is thimerosal in a final concentration of 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* The labeling states that tetanus toxoid fluid is recommended for all adults and children. Three doses of 0.5 cc (10 Lf) are injected intramuscularly or subcutaneously at an interval of 3 to 4 weeks followed by a reinforcing dose of 0.5 cc after approximately 1 year. A routine booster dose of 0.5 cc is recommended at intervals not greater than 10 years. A booster dose is also recommended immediately upon the occurrence of a wound that potentially may be contaminated unless a booster does has been given within 1 year.

The recommendation that fluid tetanus toxoid is the preferred preparation for wound booster is of dubious clinical significance. No mention of this is made in the labeling for the adsorbed product. The labeling for the fluid product could be improved by incorporating the table from the Public Health Service Advisory Committee on Immunization Practices recommendations used in the adsorbed product package insert as a convenient booster dose guide for injury.

b. *Contraindications.* Infants with a history of febrile convulsions should be given fractional doses of tetanus toxoid. Also, if unusual reaction occurs following the first injection, the volume of the second injection may have to be reduced. Any febrile respiratory illness or other active infection is reason for delaying use of tetanus toxoid, unless withholding involves greater risk.

The advice that heat-sterilized individual needles should be used as a precaution seems outdated in view of current practices. Similarly the caution in performing immunizations during polio epidemics seems unnecessary at the present time because of the rarity of such events.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data for this specific product are given. Claims for efficacy are based on references in the submission (Ref. 11) to published reports pertinent to tetanus toxoids in general.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims for safety include reference to literature on safety of tetanus toxoid. Data from complaint files suggest a low rate of reports of adverse reactions, especially to the adsorbed product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory if the product is sufficiently immunogenic in man, but because this product has not been marketed for several years, no benefit-to-risk assessment can be made.

4. *Critique.* This is a product that has not been marketed in this form for several years.

The package insert deviates from the usual U.S. recommendations for immunization, and is in need of updating.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Tetanus Toxoid Adsorbed Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This is an adsorbed tetanus toxoid containing 20 Lf of toxid and 2.0 mg aluminum sulfate per mL. The toxin is prepared in a special semisynthetic culture medium which is not further described. It is also purified by methods which are not described. The diluting medium is an aqueous solution of 0.3 M glycine and the preservative is thimerosal in a final concentration of 1:10,000.

2. *Labeling—a. Recommended use/indications.* Tetanus toxoid adsorbed is recommended for primary immunization for tetanus. Two doses (10 Lf) are injected intramuscularly at an interval of 3 to 4 weeks followed by a reinforcing dose of 0.5 cc after approximately 1 year. A routine booster dose of 0.5 cc is recommended at intervals not greater

than 10 years. A booster dose is also recommended immediately upon the occurrence of a wound that potentially may be contaminated unless a booster dose has been given within 1 year.

b. *Contraindications.* Infants with a history of febrile convulsions should be given fractional doses of tetanus toxoid. Also, if unusual reactions occur following the first injection, the volume of the second injection may have to be reduced. Any febrile respiratory illness or other active infection is reason for delaying use of tetanus toxoid, unless withholding involves greater risk.

The advice that heat-sterilized individual needles should be used as a precaution seems outdated in view of current practice. Similarly, the caution in performing immunizations during polio epidemics seems unnecessary at the present time because of the rarity of such events.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data for this specific product were provided with the initial submission. Some additional data were provided by Merck Sharp & Dohme (Ref. 11), but were considered insufficient to demonstrate its effectiveness for primary immunization. Claims for efficacy are based on published reports pertinent to tetanus toxoids in general.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims for safety include reference to literature on safety of tetanus toxoid. Data from complaint files suggest a low rate of reports of adverse reactions.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory if the product is shown to be effective for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* In combination with other data available to the Bureau of Biologics about these licensed products and well-known published information on tetanus toxoid, it would seem that safety and efficacy for booster immunization are well established.

The package insert deviates from the usual U.S. recommendations for immunization, and is in need of updating.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This is fluid tetanus toxoid containing 4 Lf per 0.5 mL, the recommended dose. the preservative is thimerosal, 1:10,000. The culture medium employed is not specified in the material submitted; formaldehyde is used as the toxoiding agent, and subsequent purification includes ammonium sulfate precipitation and subsequent dialysis.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary immunization of infants and children. Three injections of 0.5 mL, 3 to 4 weeks apart are recommended, with a fourth dose approximately 1 year later and booster doses every 10 years thereafter. Booster doses with injury are recommended if more than 5 years have elapsed since the last booster. Mention is made in the labeling of the preferability of the absorbed tetanus toxoid. The recommendations for use appear to be identical to those of the Public Health Service Advisory Committee on Immunization Practices.

b. *Contraindications.* No absolute contraindications are listed. The labeling suggests that immunization be deferred during the course of any acute illness, and the elective immunization of patients over the age of 6 be deferred during an outbreak of poliomyelitis.

3. *Analysis*—a. *Efficacy—(1) Animal.* This product meets Federal requirements.

(2) *Human.* A substantial body of literature is included in the manufacturer's submission (Ref. 12) which attests to the general efficacy of tetanus toxoid. None of the evidence supplied, however, relates specifically to tetanus toxoid as produced by Merrell-National Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission notes that only six reports of adverse reactions were received in a 5-year period during which many millions of doses were distributed. One of these reactions was anahylactic in nature, another was associated with upper extremely paralysis, and the other four were apparently mild reactions.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product for primary immunization cannot be established with certainty, owing to the lack of adequate evidence of efficacy. The benefit-to-risk assessment of this product is satisfactory for booster immunization.

4. *Critique.* The Panel can accept the evidence for safety of this product, as well as evidence for its efficacy in booster immunization, the latter based on the meeting of current Federal minimum requirements for efficacy in animals. Evidence supporting the efficacy of this product as a primary immunizing agent in humans, however, is lacking.

Futhermore, the Panel has some reservation about the need for fluid tetanus toxoid preparations, in the light of the documented superiority of adsorbed products, both in the terms of magnitude and duration of the immune response.

Reference to the avoidance of immunization during outbreaks of polimomyelitis are probably no longer necessary.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued.

The Panel recommends that this product be placed in Category IIIA as regards to its use in primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunizaiton. In addition, the labeling, although presently satisfactory, will require periodic revision as indicated in the Generic Statement on Labeling.

Tetanus Toxoid Adsorbed Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This is a purified tetanus toxoid precipitated with 0.75 percent alum (aluminium potassium sulfate), in an isotonic sodium chloride solution. The toxoiding agent is formaldehyde. The purification process includes ammonium sulfate precipitation and subsequent dialysis. The final product is preserved in 1:10,000 thimerosal. The recommended dose, 0.5 mL, contains 5 Lf units of tetanus toxoid.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus in children and adults. The recommended schedule for primary immunization in both children and

adults is 2 injections 4 to 6 weeks apart, followed by a third 0.5 mL dose approximately 1 year after the second injection. A booster dose of 0.5 mL is recommended every 10 years thereafter to maintain adequate protection. If an injury other than a clean minor wound occurs more than 5 years after the last dose, a recall or booster dose is recommended. The superiority of adsorbed tetanus toxoid over fluid tetanus toxoid preparations is indicated in the labeling.

b. *Contraindications.* No absolute contraindications are listed. The labeling suggests that immunization be deferred during the course of an acute illness, and that elective immunization of patients over the age of 6 months be deferred during an outbreak of poliomyelitis.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A substantial volume of literature in the submission (Ref. 13) attests to the general efficacy of tetanus toxoid. There are no data on efficacy, however, relating specifically to tetanus toxoid produced by Merrell-National Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The data provided are identical to those submitted for this manufacturer's fluid tetanus toxoid.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product for primary immunization cannot be precisely estimated, owing to the lack of data supporting the efficacy of this product when used as a primary immunizing agent. The benefit-to-risk assessment of this product for booster immunization is satisfactory.

4. *Critique.* The Panel accepts the evidence for the safety of this product, as well as evidence supporting its efficacy for booster immunization, the latter based on meeting current Federal minimum requirements in animal tests. Specific data in support of the efficacy of this product in humans when used as a primary immunizing agent are lacking.

References to the avoidance of immunization during outbreaks of poliomyelitis are probably no longer necessary.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued.

The Panel recommends that this product be placed in Category IIIA as regards its use in primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. In addition, the labeling, although presently satisfactory, will require periodic revision as indicated in the Generic Statement on Labeling.

Tetanus Toxoid, Fluid, Manufactured by Parke, Davis & Co.

1. *Description.* This toxid contains 5 Lf tetanus toxid refined by ultrafiltration per 0.5 mL dose with 0.01 percent thimerosal as preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The labeling notes that the American Academy of Pediatrics and the Public Health Service Advisory Committee on Immunization Practices recommended use of adsorbed rather than fluid toxoid (but, nevertheless, the labeling recommends this fluid toxoid). Contrary to general practice, it recommends the use of fluid toxoid with TIG. It fails to note the usual precautions about the reduced efficacy in immunosuppressed individuals.

b. *Contraindications.* Acute febrile illness is a contraindication. The usual precautions regarding steril equipment, availability of epinephrine, and avoidance of injection into blood vessels are mentioned.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are presented for this specific product. Some published data (Ref. 13) suggest that the primary immune response to a virtually identical, but experimental, fluid preparation is rather short-lived. No data are provided on response after reinforcing inoculation.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The large number of doses distributed, and the very small number of complaints received, together with the apparently satisfactory experience of MacLennan (Ref. 13), suggest that this product is safe in man.

c. *Benefit/risk ratio.* There is some reason to question the benefit gained from use of this fluid product, in light of the limited available data on efficacy for primary immunization. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. *Critique.* The labeling needs careful revision and updating as noted above. The lack of a buffer in this product is surprising. Available data are insufficient to classify this product when used for primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this prodict be placed in Category IIIA as regards its use for primary immunization and that the apprpriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* Contains 5 Lf tetanus toxid refined by ultrafiltration per 0.5 mL dose with 0.01 percent thimerosal as preservative. The toxoid is adsorbed on 2.5 mg aluminum phosphate per dose.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus.

b. *Contraindications.* Acute febrile illness; standard precautions regarding sterile equipment, availability of epinephrine, and avoidance of intravenous injection are mentioned. The possible reduced efficacy of the product in immunosuppressed individuals is not mentioned.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data were presented for this specific product. Published studies on a similar experimental product (Ref. 13) indicate a good immune response in man, but later studies on a different group (Ref. 14) showed an unexpectedly poor response to the first 2 doses.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The large number of doses distributed, and the very small number of complaints received, together with the apparently satisfactory experience of MacLennan (Ref. 13), suggest that this product is safe in man.

c. *Benefit/risk ratio.* Provided the efficacy of this preparation for primary immunization is clearly established, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

4. *Critique.* This is one of the few currently used tetanus toxoids for which even limited data for primary

immunization in man are available. Six out of six patients have shown a vigorous primary response by hemagglutinations titer to 2 doses. However, the data are less than required. Hence, further evaluation in man is necessary in order to achieve statistical significance. Post-exposure booster recommendations are now obsolete. The labeling needs some expansion, revision, and updating.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exeed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Swiss Serum and Vaccine Institute Berne

1. *Description.* This is an aluminum phosphate adsorbed preparation of tetanus toxoid containing 20 Lf per mL. It contains aluminum phosphate, 2 mg per mL, and is preserved with 0.01 percent thimerosal. The product is said to be purified, but neither the method of purification nor detoxification is described.

2. *Labeling*—a. *Recommended use/indications.* The product is recommended for active immunization against tetanus. The recommended schedule consists of 2 injections of 0.5 mL each at an interval of 4 weeks and a third injection of 0.5 mL 6 to 12 months later. Booster doses are recommended every 10 years, or in the case of injury, provided the patient has not had an injection within the previous year.

b. *Contraindications.* This product should not be given during acute illnesses. This product should be administered to children with a history of convulsions only under medical supervision.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several published studies are cited in the manufacturer's submission to the Panel (Ref. 15) which show that the product induces an adequate antitoxin response when given as a booster. The data show that these responses are satisfactory when given simultaneously with tetanus immune globulin. The data do not clearly demonstrate the efficacy of the product as a primary immunizing agent.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Reaction rates given for an industrial population studied are low and within expected limits.

c. *Benefit/risk ratio.* Assuming that the product is found to be an effective primary immunizing agent, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

d. *Labeling.* This package insert is in need of revision to bring it up-to-date with current recommendations. A booster dose is recommended in the case of injury if more than 1 year has elapsed since the last injection. This obsolete recommendation invites excessive booster doses; the latest Public Health Service Advisory Committee on Immunization Practices recommendations should be incorporated to clarify this problem and the related need to use tetanus immune globulin in some patients.

The statement concerning administration of the product to children prone to convulsions only "under medical supervision" seems superfluous. The product should always be so administered.

4. *Critique.* This product has been demonstrated to be adequate for booster immunization. Adequate data are not available to demonstrate its efficacy as a primary immunizing agent.

The safety of the product has been adequately demonstrated, and no unusual frequency of untoward local reactions have been noted.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Texas Department of Health Resources

1. *Description.* This is a fluid tetanus toxoid prepared by detoxification of tetanus toxin with formaldehyde (and "heat"), purified by ammonium sulfate fractionation, diluted to 40 Lf per dose, and preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The basic immunization schedule consists of three 1 mL doses at 3 to 4 week intervals with a fourth dose 1 year later. Routine boosters are recommended at 5-year intervals.

b. *Contraindications.* None listed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No human data on antitoxin response to primary or booster immunization are presented. "Periodic blood antitoxin" levels are mentioned but no data were provided. A chart labeled "Tetanus Mortality and Immunization in Texas" (Ref. 16) submitted as evidence of efficacy is unsatisfactory and could be interpreted as suggesting that the decline in incidence slowed down with the introduction of toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled studies of reaction rates have been performed. It is stated that no adverse reactions were reported in the past 10 years. The high Lf content of this product is a matter of some concern in this regard.

c. *Benefit/risk ratio.* Assuming that evidence can be presented that the product is effective for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. *Labeling.* The package insert is in need of professional review and revision to bring it up-to-date with current recommendations. For exposure to risk of tetanus, a booster is recommended if a year has elapsed since the last injection. This obsolete recommendation invites excessive boosters; the latest Public Health Service Advisory Committee on Immunization Practices recommendations should be incorporated to clarify this problem and the related need to use tetanus immune globulin in certain patients. The labeling should put special emphasis on the need for the reinforcing dose at 1 year. Since this is a fluid product, the labeling should also note the published evidence questioning the advisability of using fluid toxoid simultaneously with

passively administered tetanus immune globulin.

4. *Critique.* In view of the product's ability to meet the minimum requirements including the potency test in animals, it is adequate for booster use in humans. However, no data are available to demonstrate its efficacy as a primary immunizing agent.

Two matters are of fundamental concern: (a) The Lf content of this product may be excessively high, inviting excessive reactions or possibly even suggesting poor antigenic quality; (b) in the opinion of some, there is no need for a fluid product in view of the superiority of adsorbed products.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy and rate of adverse reactions of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This is a fluid preparation of tetanus toxoid containing 5 Lf of tetanus toxoid per 0.5 mL with 1:10,000 thimerosal as a preservative. Sodium chloride is the diluent.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for active immunization against tetanus but is is specified that the adsorbed preparation is preferred both for basic immunization and recall doses. Otherwise the recommended use/indications are identical to those of the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics. For primary immunization, 3 doses at 4-week intervals followed by a reinforcing dose 6 to 12 months later, all at 0.5 mL, are recommended. Routine reinforcing doses at 10-year intervals are recommended, and recommendations for reinforcing doses with injury follow those of public advisory groups. The package insert describes techniques for administration in detail. Fractional doses are recommended for children with cerebral damage, neurological disorders, or a history of febrile convulsions. Included are warnings about the transmission of serum hepatitis as a result of improper techniques, the possibility of inadequate immunization of individuals receiving immuno-suppresive drugs, the need to determine whether there was an untoward reaction to a prior dose, and the possibility of rare allergic reactions.

b. *Contraindications.* An acute respiratory or other infection is specified as a contraindication to routine immunization, but is not included as a contraindication to a recall dose following injury. No other specific contraindication is listed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data regarding the efficacy of this specific product in humans are provided.

b. *Safety*—(1) *Animal.* Although no data were provided with the submission, the product meets Federal requirements.

(2) *Human.* No data regarding safety in humans are provided.

c. *Benefit/risk ratio.* Presumably this product has a satisfactory benefit-to-risk assessment for primary immunization although specific data with which to determine this with precision are not available. The benefit-to-risk assessment is satisfactory for booster immunization.

4. *Critique.* It is likely that this product is efficacious and quite safe, although specific data are not available. The Panel does have some doubts about the need for fluid tetanus toxoid preparations in the light of the apparent superiority of adsorbed products.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This is an aluminum phosphate adsorbed tetanus toxoid containing 5 Lf of tetanus toxoid per 0.5 mL. It is preserved in 1:10,000 thimerosal and diluted in saline.

2. *Labeling*—a. *Recommended use/indications.* For primary immunization, 2 injections of 0.5 mL at 4-week intervals followed by a reinforcing dose 6 to 12 months later are recommended. Routine reinforcing doses are recommended at 10 year intervals. The current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Disease of the American Academy of Pediatrics are included. However, it is not stated to what populations this specific preparation should be administered. There is no mention of the preferability of combined preparations containing diphtheria toxoids and pertussis vaccine for routine administration.

Techniques for administration are very well described. Fractional doses are recommended for children with cerebral damage, neurological disorders, or history of febrile convulsions. Warning about the transmission of serum hepatitis with improper techniques, the possibility of inadequate immunization of individuals on immunosuppressive drugs, the need to determine whether there was an undue reaction to a prior injection, and rare allergic reactions are included.

b. *Contraindications.* An acute respiratory or other infection is specified as a contraindication except when the reinforcing dose is required following injury. No other absolute contraindication is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A review of the general efficacy of tetanus toxoid, adsorbed, is provided (Ref. 17), but there is no information relating to this specific product.

b. *Safety*—(1) *Animal.* Although no data were provided with the submission, this product meets Federal requirements.

(2) *Human.* The excellent safety record of tetanus toxoid in general is provided in the manufacturer's submission, but information relative to this specific product is not included.

c. *Benefit/risk ratio.* Although this product has been in use for many years and there is no reason to believe that the benefit-to-risk assessment is not satisfactory for primary immunizataion, no specific data are available. The benefit-to-risk assessment for booster immunization is satisfactory.

4. *Critique.* From the description of the methods employed in preparing this product and from the statement that

required animal testing for efficacy is undertaken, it would seem that this product is both safe and efficacious for booster immunization. However, specific data regarding safety in animals and both safety and efficacy in humans are not provided. The package insert does not specify populations to which this specific product should be given, and preference for combined preparations containing diphtheria toxoid and pertussis vaccine is not expressed.

5. *Recommendations.* The Panel recommends that his product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

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Generic Statement

Diphtheria and Tetanus Toxoids (DT) for Pediatric Use

See Generic Statements for monovalent diphtheria and tetanus toxoids.

Description

The combination of diphtheria and tetanus toxoids for pediatric use (DT) is intended for the immunization of children against diphtheria and tetanus under circumstances in which the use of these two toxoids combined with pertussis vaccine is undesirable or contraindicated. Current licensed products include both fluid and adsorbed forms of DT.

Production

The manufacturing process basically comprises the production, detoxification, purification, and titration of the two toxoids independently. By Federal regulation, the individual toxoids for the adsorbed forms must be adsorbed prior to combination. Both the tetanus and diphtheria toxoids components must be tested for detoxification prior to combination. After combination, both components must be tested for antigenic potency in animals. Currently, there is striking variation among the licensed products in terms of the flocculation titers (Lf) for diphtheria and tetanus toxoids per dose. The ranges of Lf for diphtheria toxoids for the fluid product are 25 to 125 and 7.5 to 25 for the adsorbed product. The Lf range of tetanus toxoid is 5 to 10 for the adsorbed product and 5 to 40 for the fluid product.

Use and Contraindications

This product should be used for primary immunization and for booster doses for children 6 years of age or less in instances in which pertussis immunization is contraindicated. Thus, its major use would be for completion of immunization and for booster doses for children who have responded to the triple combination of diphtheria and tetanus toxoids and pertussis vaccine (DTP) with a significant reaction believed or suspected to be a consequence of the pertussis component. Under such circumstances completion of the primary immunization schedule with adsorbed DT is preferred and should comprise a series of 3 doses (considering the doses of DTP already given as part of the series) with the first 2 given 4 to 8 weeks apart and the third 1 year later. A booster dose of TD should be given at school entry, and subsequent booster doses should be given approximately every 10 years, employing tetanus and diphtheria toxoids combined for adult use (Td). Recommendations for immunization with fluid DT are identical except that the primary series should comprise 4 doses, with the first 3 being given 4 to 8 weeks apart and the fourth a year later. Circumstances may occur, such as outbreaks of diphtheria, in which it would be advantageous for individuals older than 6 years of age to receive a larger amount of diphtheria toxoid than is present in the Td (adult type). Diphtheria and tetanus toxoid may be considered for use under these circumstances.

The only contraindication to the administration of DT is a prior severe hypersensitivity reaction. It is also not recommended for use in individuals 7 years of age or older. It is advisable not to administer the product during a febrile illness because of possible confusion as to the cause of persistent fever if such should occur. Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time.

Safety

Both components of this combined product are tested for safety in animals and for sterility according to Federal requirements as with the monovalent toxoids.

Efficacy

Minimum requirements specify that the diphtheria toxoid component of the combined product may be tested for potency in guinea pigs either before or after combination, and that the tetanus toxoid component be tested for potency after combination. The Bureau of Biologics releases this combined product based on potency data as determined after combination. Neither the diphtheria nor the tetanus component exerts a significant adjuvant or suppressant effect upon the immunogenicity of the other.

Labeling

The labeling for some of the products is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics in that these groups recommend that Td (for adult use) be used for children over 6 years of age. Accordingly, the labeling should be modified for DT (for pediatric use) to recommend that these products be used for children "six years of age and under," rather than for children "under six" as is the case with some of the labeling.

Special Problems

The same problems that exist in terms of the immunogenicity of these toxoids administered in the monovalent form exist in the combined form.

Recommendations

The recommendations made for the individual toxoid components apply to the combined product. It is also recommended that requirements be updated to stipulate testing for potency after combination of the individual products.

Basis for Classification

The basis for classification of this combined product is the same as the basis for classification of the individual toxoid components.

References

(1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4–5, 1972.

(2) "Diphtheria—Tetanus—Pertussis," *in* "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication No. (Center for Disease Control), 76–8221:25–30, 1977.

(3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," *Morbidity and Mortality Weekly Report*, Suppl. August 1977, Health, Education, and Welfare Publication No. (Center for Disease Control), 77–8241.

SPECIFIC PRODUCT REVIEWS

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* This is a combined preparation containing 10 to 20 Lf of diphtheria toxoid and 5 to 10 Lf of tetanus toxiod per 0.5 mL. The toxoids are adsorbed on aluminum phosphate and preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the active immunization of children less than 6 years of age. The recommended dosage comprises two 0.5 mL intramuscular injections 4 to 6 weeks apart followed by a reinforcing dose 6 to 12 months later. A further reinforcing dose of 0.5 mL is advised at 5 years of age. The preferability of primary immunization with a trivalent preparation containing pertussis vaccine is not mentioned. If a dose has not been administered within the previous year, the manufacturer recommends a reinforcing dose of this preparation under any one of five circumstances: Exposure to diphtheria; injury with risk of contracting tetanus; unusual prevalence or risk of exposure to diphtheria; change of environment; and disasters which result in crowding or dislocation.

b. *Contraindications.* It is recommended that tetanus and diphtheria toxoids, adsorbed, for adult use, be used to produce and maintain active immunity against tetanus and diphtheria in individuals 6 or more years of age because of reactivity of this product. A warning that previously unimmunized individuals will not be protected by this product in case of exposure to diphtheria or tetanus is included. It is also stated that this preparation is useless in the treatment of diphtheria or tetanus. Any acute respiratory disease or other active infection is considered a contraindication. Deferral of immunization is recommended in individuals receiving short-term immunosuppressive therapy and, in instances of long-term immunosuppressive therapy, an extra dose is recommended 1 or more months after therapy is discontinued.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The only data available concerning primary immunization of humans related to this product comprise studies with a quadruple vaccine containing pertussis and poliomyelitis vaccines as well (Ref. 1). The adjuvant effect of pertussis vaccine is such that these cannot be accepted as evidence for efficacy of this preparation. There are, however, good data that indicate that this preparation is efficacious when used for reinforcement of immunization in previously immunized children.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* During the 10 years, 1962 to 1972, a few million doses of this preparation were distributed; only three reactions, all local, were reported. However, administration of this preparation to institutionalized adults yielded high rates of severe reactions.

c. *Benefit/risk ratio.* The risk of untoward reactions to this preparation, when used as recommended in children, is negligible. Efficacy of this preparation when used for booster immunization to diphtheria and tetanus is satisfactory. When used for primary immunization, its efficacy is probably satisfactory but data are not available to permit a definitive conclusion.

4. *Critique.* This is a widely used adsorbed combined preparation of diphtheria and tetanus toxoids employed for the primary immunization of children and reinforcement of immunity to tetanus and diphtheria in children. Unfortunately conclusive data documenting efficacy as a primary immunizing agent are not available.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required. The manufacturer should specify the preferability of the trivalent preparation containing diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, for the primary immunization of infants and children.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Dow Chemical Company

1. *Description.* This product contains 14 to 17 Lf of diphtheria toxoid, 7 to 10 Lf of tetanus toxoid, and not more than 5 mg of potassium alum per dose in 0.3 N glycine, with 1:10,000 thimerosal. The toxoids are fractionated by the alcohol method.

2. *Labeling*—a. *Recommended use/indications.* Two intramuscular injections of 0.5 mL each 4 to 6 weeks apart, with a reinforcing dose of 0.5 mL about 1 year later, are recommended for immunization of infants and children under 6 years, when pertussis immunization is not indicated. In older children, its use is permissible if they are first screened by Schick or Moloney tests, but the adult type preparation is preferred. Booster doses are recommended following exposure to diphtheria. The labeling recommends three primary doses for immunization of infants (without explanation).

b. *Contraindications.* Detailed precautions concerning anaphylactoid reactions are outlined. Immunization should be deferred in the presence of acute infections or immunosuppressive treatment or the presence of a polio outbreak. Fractional doses of single antigens should be used in children with allergies, brain injury, or a history of severe reactions, etc. Various other precautions are included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on the specific product are presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this specific product are presented.

c. *Benefit/risk ratio.* In the absence of data, assessment of the effectiveness of this product for primary immunization is not possible. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. *Critique.* This is a fairly typical combination of diphtheria and tetanus toxoids for pediatric use. The toxoids are fractionated by a well-established method, but the alum content appears somewhat low. The contraindications given are surprisingly detailed and the recommendations for three primary injections in infants are not explained. The data presented on efficacy and safety are derived from published papers on other products, but not on this specific product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Manufactured by Eli Lilly and Company

1. *Description.* This is an alcohol fractionated toxoid (Pillemer method) and contains 7.5 Lf tetanus toxoid and 25 Lf diphtheria toxoid per 0.5 mL dose. It is preserved with 1:10,000 thimerosal and is diluted in 0.3 molar glycine solution.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization of children under 6 against diphtheria and/or tetanus in circumstances where use of DTP may be contraindicated. The package circular recommends that three 0.5 mL doses by given subcutaneously at intervals of 4 to 6 weeks for primary immunization and that a reinforcing dose of 0.5 mL be given to children under 6 years of age about 1 year after the primary series. A booster dose is recommended at the time of entry into school (about 5 years of age).

b. *Contraindications.* These include active infections, possible exposure to polio, a history of central nervous system damage, or convulsions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on primary or secondary responses to this specific product were provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data from detailed studies on this specific product were provided. Data from the manufacturer's complaint files indicated only a low rate of consumer complaints concerning reactions, all of which were mild.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. *Labeling.* The labeling is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics in that the latter groups recommend that Td be used for children over 6. Accordingly, the labeling should be modified to recommend that the product be used for children "six and under" (rather than "for children under six").

The labeling should also be modified to reflect the well-documented advantages of the adsorbed product over the fluid product.

4. *Critique.* This submission is lacking in human data to demonstrate the ability of this product to elicit satisfactory primary or booster antitoxin responses in children of the age group concerned. In conjunction with a study of this type, detailed observations on reactogenicity should also be made.

In addition, the continued need for the fluid product is indeed questionable in view of the superiority of adsorbed toxoids as immunizing agents. Nonetheless, some physicians prefer the fluid product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Eli Lilly and Company

1. *Description.* This is an alcohol fractionated toxoid (Pillemer method) and contains 7.5 Lf tetanus toxoid and 25 Lf diphtheria toxoid per 0.5 mL dose. The adsorbed (alum precipitated) product is stated to contain 7.25 mg or less of alum per mL. It is preserved with 1:10,000 thimerosal and is diluted in 0.3 molar glycine solution.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization of children under 6 against diphtheria and/or tetanus in circumstances where use of DTP may be contraindicated. The package circular recommends that two 0.5 mL doses be given intramuscularly at an interval of 4 to 6 weeks for primary immunization and that a reinforcing dose of 0.5 mL be given 1 year later. A booster dose of 0.5 mL is recommended at the time of entry into school (about 5 years of age).

b. *Contraindications.* These include active infections, possible exposure to polio, a history of central nervous system damage, or convulsions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on primary or secondary responses to this specific product were provided.

b. *Safety—Animals.* This product meets Federal requirements.

(2) *Human.* No data from detailed studies on this specific product are provided. Data from the manufacturer's complaint files indicated only a low rate of consumer complaints concerning reactions, all of which were mild.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. *Labeling.* The labeling is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the

American Academy of Pediatrics in that the latter groups recommend that Td be used for children over 6. Accordingly, the labeling should be modified to recommend that the product be used for children "six and under" (rather than "for children under six").

The labeling should also be modified to reflect the well-documented advantages of the adsorbed product over the fluid product.

4. *Critique.* This submission is lacking in human data to demonstrate the ability of this product to elicit satisfactory primary or booster antitoxin responses in children for the age group concerned. In conjunction with a study of this type, detailed observations on reactogenicity should also be made.

In addition, the continued need for the fluid product is indeed questionable in view of the superiority of adsorbed toxoids as immunizing agents. Nonetheless, some physicians prefer the fluid product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product is a combined diphtheria and tetanus toxoid contained in physiological saline, 0.85 percent, with 0.01 percent thimerosol added as preservative. Formaldehyde is used as the toxoiding agent with both toxins, which are then purified by the Pillemer Alcohol Fractionation Method, diluted with phosphate buffer, with aluminum phosphate being added to a final concentration of 2.0 mg per mL. Each 0.5 mL dose contains 12.5 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid, in addition to 1 mg of aluminum phosphate.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for use as a primary immunizing agent against tetanus and diphtheria in infants and children less than 6 years of age. The package insert does not clarify the differences between this product and DPT, nor the difference between this product and the adult Td preparation.

b. *Contraindications.* Acute respiratory disease or other active infection is suggested as a reason to defer immunization.

3. *Analysis*—a. *Efficacy—(1) Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data supporting the human efficacy of diphtheria and tetanus toxoids is cited (Ref. 2), but no information is provided relative to the use of this specific product as produced by Lederle Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled data are presented on the safety of this product in humans. The submission notes that many hundred thousands of doses were distributed through the years 1970 to 1972, whereas during the period 1969 through June 1973, seven complaints were received by the manufacturer. These included local reactions, redness, and induration at the site of injection.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be satisfactorily assessed, owing to the lack of data in support of the efficacy of this product when used for primary immunization in humans. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* The major defect in this submission is the absence of data to support the immunogenicity of this product when used for primary immunization in infants and children 6 years of age and under.

The labeling strongly suggests that a primary immunizing series is 2 intramuscular doses of 0.5 mL each. The "reinforcing dose" recommended 1 year after completion of the primary immunization is, in fact, part of the primary immunizing series. The labeling should clarify this point, and emphasize that immunization should not be considered complete until the third dose has been given.

The labeling fails to clarify when this preparation should be used in lieu of triple antigen (DPT) and fails further to establish the difference between the DT preparation for use in children 6 years of age and under and the adult Td preparations.

The advertising submitted by Lederle Laboratories was apparently last revised in December 1963, and differs strikingly from current recommendations.

5. *Recommendations.* The panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This product contains 15 Lf per mL diphtheria toxoid and 15 Lf per mL tetanus toxoid, adsorbed on 4.0 mg per mL aluminum phosphate, preserved with thimerosal in dilution 1:10,000 in a diluent of 0.01 M sodium acetate and 0.1 M sodium chloride, pH 6.0 ± 0.1. In the production of tetanus toxoid, the modified Mueller medium is used.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for primary or booster immunization against diphtheria and tetanus of children 6 years of age or less when immunizing preparations containing pertussis vaccine would be considered undesirable. Two intramuscular doses of 0.5 mL are given 4 to 6 weeks apart, followed by a reinforcing dose approximately 1 year later.

b. *Contraindications.* These include acute infectious illnesses.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* References to the literature of several animal studies are given in the manufacturer's data submission to the Panel (Ref. 3). This product meets Federal requirements.

(2) *Human.* Serologic studies have shown combination vaccines including the pertussis component to be efficacious. Likewise, diphtheria and tetanus toxoids have been shown to be efficacious in adults not only for booster purposes but also for primary immunizations. Studies of tetanus and diphtheria toxoids in children are lacking. However, since these toxoids have been shown effective for primary

immunization in adults where they are given in a lower dosage than in children, it may be assumed the product is effective in children.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Most studies in the literature concern adult preparation or combinations including pertussis antigen. In such preparations the rates concerning safety appear adequate.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

4. *Critique.* A large number of studies (Ref. 3) have been conducted with the Massachusetts' product, as shown in the list of references. Thus, the tetanus and diphtheria toxoids have been shown to be efficacious in primary immunizations in adults using lower doses than those used in children.

Likewise, many studies of reactions to the toxoids have been conducted.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Diphtheria and Tetanus Toxoids Manufactured by Parke, Davis & Co.

1. *Description.* This is a mixture of diphtheria and tetanus toxoids in 0.85 percent saline solution, containing 2 percent glycerine, purified by filtration, and containing 125 Lf of diphtheria toxoid and 5 Lf of tentanus toxoid per dose. The preservative is thimerosal 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for prevention of diphtheria and tetanus in children under 6 years (or over 6 if screened with Moloney test). The dose is three injections of 0.5 mL each, intramuscularly or subcutaneously, 3 to 4 weeks apart, and a reinforcing dose about 1 year later. It is recommended for use where a fluid product is preferred. Routine boosters are given preferably at the time of school entrance. For subsequent boosters, the adult type of tetanus and diphtheria toxoids is recommended. Emergency boosters are advised for exposure to diphtheria. For boosters after tetanus-prone injuries, the adult type preparation is recommended.

b. *Contraindications.* Acute febrile illness or treatment with steroids are reasons for postponing inoculation.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No relevant data were presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Ten year old protocols are presented, which are presumably applicable, but this cannot be clearly determined without knowing when the present "purification" procedure was adopted. Temperature rises in protocol 275–1 appear to be abnormally high, i.e., 26 out of 30 subjects show 1° F or higher rises at 24 hours. The manufacturer's covering memorandums of March 11, 1964 (Ref. 4) regarding the investigator's data in protocol 275–1 defines temperature rise so as to allow a final temperature of 0.4° above normal, which gives only 4 rises in 30 subjects. Thus the data are difficult to interpret.

c. *Benefit/risk ratio.* Appears to be similar to that for other combined diphtheria and tetanus toxoids, except that the content of diphtheria toxoid is extraordinarily high. The product is fluid and, therefore, less efficient, and the reaction rate seems high according to the record.

4. *Critique.* This is a fluid combined diphtheria and tetanus toxoid for pediatric use, purified by a somewhat ambiguous method. It contains an excessive quantity of diphtheria toxoid, causing what appears to be more than the expected number of febrile reactions in adult volunteers, and there are not sufficient data to evaluate either its efficacy or safety for primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This is an adsorbed combined diphtheria and tetanus toxoid which contains 15 Lf of purified diphtheria toxoid and 5 Lf of purified tetanus toxoid, adsorbed on 2.5 mg of aluminum phosphate per dose. The product contains 0.9 percent sodium chloride and 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the primary immunization of children under 6 years of age when a triple vaccine is contraindicated or not recommended. The recommneded schedule is 2 doses of 0.5 mL 4 to 6 weeks apart with a reinforcing dose of 0.5 mL about 1 year later. Recommendations concerning subsequent boosters conform with those of the American Academy of Pediatrics and the Public Health Service Advisory Committee on Immunization Practices. The recommendations regarding "wound boosters" are obsolete, as are the references; the package insert is dated 1970.

b. *Contraindications.* Acute febrile illnesses and courses of immunodepressant—including steroid—therapy are indications for postponing immunization. In addition, the insert recommends a Moloney test and an analogous test with tetanus toxoid before administering this preparation to children over 6 years of age. There is no mention of the use of adult-type tetanus-diphtheria toxoid for boosters.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Brief tabular summaries (Ref. 4) indicate that the product tested in 1961 to 1962 was satisfactory as a booster antigen, with what appears to be a relatively high reaction rate, primarily local (subjects were adults). No primary response data were presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The moderate-to-high reactivity mentioned above was observed in adults; hence, the acceptability of the product for children cannot be assessed.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be satisfactorily assessed, owing to the lack of data in support of the efficacy of this product when used for primary immunization in humans. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory. There was a higher rate of reactions in adults.

4. *Critique.* This product appears to be a typical combined diphtheria and tetanus toxoid product. However, data on the efficacy and tolerance of this product for primary immunization in the age group for which it is indicated are lacking.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the

appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Texas Department of Health Resources

1. *Description.* This product contains 30 Lf of diphtheria toxoid and 20 Lf of tetanus toxoid per mL, adsorbed onto aluminum hydroxide, the content of the latter not to exceed 1.2 mg per mL in the final product. It contains 1:10,000 thimerosal, and the diluent is sodium acetate and buffered saline.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for immunization of children under the age of 6, or in children for whom there is a contraindication for combinations with pertussis vaccine. The dosage for primary immunization is 2 doses of 0.5 mL intramuscular injections at 4 to 6 weeks intervals followed by a third reinforcing dose 12 months later.

The skin should be cleansed with tincture of iodine and alcohol prior to immunizaion.

b. *Contraindications.* These include active respiratory disease or other active infections.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* One indirect data are provided (Ref. 5) demonstrating decreased incidence of tetanus and diphtheria in Texas relative to increased distribution of doses of vaccines for these agents.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The producer states that over the past 10 years many hundred thousand doses of the vaccine were distributed without any serious reactions being reported.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. *Labeling.* The recommended use is in general agreement with the Advisory Committee on Immunization Practices recommendations. It would be desirable to have the Lf content stated on the label, particularly as it is relatively high.

The recommendations for use of Td adult type for booster purposes is correct but easily misunderstood, since the name of the 2 products are almost identical: "tetanus and diphtheria toxoid, adsorbed (Td)" and "diphtheria and tetanus toxoid, adsorbed." Some of the labeling included in the manufacturer's data submission is illegible.

5. *Critique.* The manufacturer claims the product was patterned after that of the State of Massachusetts and thus controlled studies were not deemed necessary. However, the Lf content is considerably higher (15 Lf for tetanus toxoids, and 10 Lf for diphtheria) than what was used in Massachusetts at the time of this review (according to their submission, 7.5 Lf each of diphtheria and tetanus toxoid for the Massachusetts Public Health Biologic Laboratories' product). Furthermore, the Texas Department of Health Resources uses, aluminum hydroxide, whereas the Massachusetts Public Health Biologic Laboratories uses aluminum phosphate as adjuvant. Labeling regarding the product to be used for boosters is somewhat confusing. There are no human serological studies reported on this product, and the data on lack of reactions appear to be inconclusive.

6. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufacturer by Wyeth Laboratories, Inc.

1. *Description.* This submission by Wyeth Laboratories includes an excellent summary description of the prepration of the two toxoids. The final product is a combined antigen product including in each 0.5 mL dose 10 Lf of diphtheria toxoid, 5 Lf of tetanus tooid, and 0.34 mg of aluminum as aluminum phosphate. Sodium chloride is used to adjust tonicity of the final product.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary immunization and booster doses of infants and children through 6 years of age. The labeling clearly points out that in most instances a triple antigen (DTP) would be the preferred product. The labeling further differentiates very clearly between this preparation and the adult Td adsorbed preparation.

b. *Contraindications.* Acute active infection is listed as a relative contraindication, except in situations requiring emergency recall or booster doses. An outbreak of poliomyelitis is suggested as a reason to defer elective immunization.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data supporting the human efficacy of diphtheria and tetanus toxoids is cited (Ref. 6), but no data are provided regarding this particular product as currently produced by Wyeth Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data regarding the safety of tetanus and diphtheria toxoids is cited, but no data are provided with regard to this specific product as currently produced by Wyeth Laboratories.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization cannot be precisely determined, owing to the lack of human data supporting its safety and efficacy. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* The labeling is clearly written, in conformity with current national recommendations, and clearly outlines the preferability of a triple antigen product. References to outbreaks of poliomyelitis as reason for deferral of elective immunization with adjuvant containing vaccines are probably no longer necessary.

The major defect in the submission is the lack of human data supporting the safety and efficacy of this product when used in primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards the use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently

accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop evidence regarding the efficacy of this product when used for primary immunization.

References

(1) BER Volume 2068.
(2) BER Volume 2028.
(3) BER Volume 2051.
(4) BER Volume 2003.
(5) BER Volume 2098.
(6) BER Volume 2015.

Generic Statement for Tetanus and Diphtheria Toxoids (Td) for Adult Use

See Generic Statement for Monovalent Diphtheria and Tetanus Toxoids.

Description

Tetanus and diphtheria toxoids for adult use (Td) comprises a combination of tetanus and diphtheria toxoids in which the diphtheria component is significantly reduced compared to DT. The diphtheria component is reduced to avoid adverse reactions, such as fever and other systemic manifestations, in individuals who may have had repeated prior exposure to diphtheria antigens and have thus become sensitized to one or more of these antigens. All presently licensed products are adsorbed.

Production

Production of Td follows the same manufacturing procedures as for the individual toxoids and DT, with two major exceptions. The diphtheria toxoid component is reduced to a maximum of 2 flocculation units (Lf) per dose. Also, the purity of the diphtheria toxoid component for this product must be at least 1,500 Lf per mg of nitrogen. The Lf of the diphtheria component of currently licensed products ranges between 1.38 and 2 per dose.

Use and Contraindications

Tetanus and diphtheria toxoids for adult use is designed for two specific purposes. First, it is intended for use as a booster against tetanus and diphtheria in individuals older than 6 years of age, for the reason that it is not recommended to administer pertussis vaccine after this age, and because of possible prior sensitization to the diphtheria toxoid component. In addition to its use as a routine booster, it is recommended for recall booster doses for the prevention of tetanus at the time of injury, at which time it would generally be useful to include enhancement of immunity to diphtheria.

The second purpose for which this combined product is recommended is that of the primary immunization of individuals older than 6 years. The usual recommendations are for the administration of 2 doses of Td at least a month apart, followed by a reinforcing dose approximately 1 year later and booster doses every 10 years thereafter, with appropriate intervening booster doses as recommended by national advisory committees, if injury or diphtheria exposure occurs. Contraindications are the same as for DT.

Safety

In accordance with Federal requirements, both components of Td must be tested for detoxification prior to combination. These requirements are the same as for the individual components and for DT.

Efficacy

The diphtheria component must be tested for potency in animals prior to combination and both toxoids are tested for potency in animals after combination by specified techniques.

The immunogenicity of both components for man is satisfactory for boosters, but the adequacy of the reduced diphtheria component for primary immunization has not been established for all products. Neither the diphtheria nor the tetanus component exerts a significant adjuvant or suppressant effect upon the immunogenicity of the other.

Special Problems

In addition to the problems of individual components (see Generic Statements on Individual Components), a major question is that of the immunogenicity of the smaller amount of diphtheria toxoid as a primary immunizing agent.

Recommendations

Because the same problems associated with the monovalent tetanus and diphtheria toxoids and DT apply to Td, the same recommendations apply with the exception of the issue of purity of the diphtheria toxoid.

In the absence of an animal or other laboratory model that can be interpreted with precision in terms of human immunogenicity, it is imperative that Td be studied in humans to ascertain its effectiveness as a primary immunizing agent against diphtheria.

Basis for Classification

The basis for classification of this combined product is the same as the basis for classification of the individual toxoid components.

References

(1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4–5, 1972.

(2) "Diphtheria—Tetanus—Pertussis," *in* "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication No. (Center for Disease Control) 76–8221:25–30, 1977.

(3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," *Morbidity and Mortality Weekly Report*, Suppl., Health, Education, and Welfare Publication No. (Center for Disease Control) 77–8241: 1977.

SPECIFIC PRODUCT REVIEWS

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Eli Lilly Company

1. *Description.* This product contains 7.5 Lf of tetanus toxoid, plus 1.5 Lf diphtheria toxoid per dose in alum at a concentration of 2.55 mg per mL with 0.3 M glycine and thimerosal 1:10,000. The toxin is produced by growth of the organism in casein hydrolysate, and the toxoid is purified by the Pillemer process.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary immunization of adults and children 6 years of age or older against diphtheria and tetanus, two 0.5 mL injections are given 4 to 6 weeks apart and another 0.5 mL dose about 1 year later. Routine boosters are recommended every 10 years.

b. *Contraindications.* Children under 6; acute respiratory disease or other active infections (defer immunization). The labeling includes a cautionary statement regarding use of steroids and after exposure to infections, including tetanus.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2). *Human.* No data were submitted to show evidence of immunogenicity for this product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A total of nine local and seven systemic reactions have been reported over a 5-year period, during which time many millions of doses were sold. This implies that the product does not have any unusual reactivity.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* The major problem apparent in review of this product is the lack of evidence for immunogenicity for this specific product when used in primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This is an alcohol-fractionated combined antigen preparation containing 5 Lf tetanus toxoid and 2 Lf diphtheria toxoid per 0.5 mL dose. It contains 2.5 mg per mL aluminum phosphate adjuvant and 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* The product is recommended for active simultaneous primary immunization of adults and children over 6 years of age against tetanus and diphtheria and for subsequent booster immunization.

b. *Contraindications.* Acute respiratory diseases or other active infections. Should not be used under 6 years of age.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data demonstrating the clinical potency of this specific product were presented. For this manufacturer's product (and similar products from other manufacturers), the suitability of the small 1 to 2 Lf dose of diphtheria toxoid for initiating primary immunization in very young children (beginning at age 7) is undocumented. Claims for efficacy are dependent on experience recorded in the literature for other products.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data from detailed studies were presented. However, general experience with this type of product is satisfactory, and the manufacturer has recorded a very low level of complaints from consumers.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. *Labeling.* The statement (under "Precautions") which reads "It should NOT (except in extreme emergency when no monovalent toxoid or antitoxin is available) be used as a therapeutic agent," is ambiguous and should be corrected.

Since Td is the product specifically recommended for "wound booster" doses by the Public Health Service Advisory Committee on Immunization Practices (and other groups), some discussion of its proper use for this purpose alone or in combination with tetanus immune globulin (where appropriate) in tetanus prone wounds is needed.

4. *Critique.* The submission (Ref. 1) is lacking in data to support the use of this product in primary immunization, although it would be unquestionably adequate for booster use. It is especially important to document the suitability of the low dose of diphtheria toxoid for primary immunization of young children (7 and older).

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This product contains 4 Lf per mL each of diphtheria and tetanus toxoid, 4.0 mg per mL aluminum phosphate, thimerosal 1:30,000 with 0.01 M sodium acetate and 0.1 M sodium chloride as diluent, pH 6.0. Tetanus toxoid is grown on a modified Mueller medium.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for immunization of persons over 6 years of age. A total of 3 intramuscular injections of 0.5 mL each are recommended. Preferably there should be a 12-month interval between the second and third doses.

The product is also used for booster purposes, preferably at 10-year intervals. The recommendations are in general agreement with those of the Public Health Service Advisory Committee on Immunization Practices.

b. *Contraindications.* Acute respiratory diseases, and poliomyelitis epidemics. The concern with poliomyelitis epidemics may be deleted in the label in view of the rarity of such occurrence.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* References to studies in animals of tetanus toxoid with the Massachusetts Public Health Biologic Laboratories' products are given in the manufacturer's data submission to the Panel (Ref. 2). This product meets Federal requirements.

(2) *Human.* The Massachusetts Public Health Biologic Laboratories' products have been tested in the field and data from the 1950's suggest that the recommended doses are highly efficacious as boosters. Also, their efficacy in adults for primary immunization have been established in the paper by Ipsen (Ref. 3).

b. *Safety*— (1) *Animal.* This product meets Federal requirements.

(2) *Human.* References in the submission to studies of reactions to toxoids made by Massachusetts Public Health Biologic Laboratories (Ref. 1) show acceptable low rates of reactions in the recommended doses.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

d. *Labeling.* The labeling is adequate and up-to-date.

4. *Critique.* Sufficient evidence has been published to demonstrate efficacy and safety in adult use, in the past, both for primary and booster immunizations. Although this product was last tested more than a decade ago and the immune status of the general population may have changed since then with regard to naturally acquired immunity, it may not be possible to obtain more current information on primary immune

responses to Td in adults in the near future.

5. *Recommendations.* The Panel voted after considerable discussion to assign this product to Category I on the basis of the older data with all due recognition of the possible limitations of the applicability of these data to the present day.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This product contains 20 Lf of tetanus toxoid, 4 Lf of diphtheria toxoid, and 2.4 mg of potassium alum per mL in 0.3 M glycine, with thimerosal 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* No packaging insert is provided, no information is given regarding use, no actual labeling is provided (the photo of a label is illegible), and no useful information on the product is submitted.

b. *Contraindications.* No information provided.

3. *Analysis.* No data furnished.

4. *Critique.* No information furnished (Ref. 4) is totally inadequate for an evaluation of this product.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This product contains up to 4 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid per mL, adsorbed onto aluminum potassium sulfate and preserved with thimerosal in physiologic saline.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for the primary immunization of adults and children of 6 years of age or older. The dose is 0.5 mL given intramuscularly. For primary immunization 2 injections 4 to 6 weeks apart and a third dose 1 year later are recommended. A reinforcing dose every 10 years is recommended. The package insert contains no comment regarding reinforcing doses with injury.

b. *Contraindications.* These include acute illness and an outbreak of poliomyelitis in the community. It is noted that immunosuppressive therapy may interfere with response.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No information directly related to this product is available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Over a 5-year period many million doses of this product have been distributed with a total of eight reactions, most of which appear to be minor. The only one of significance includes "paralysis," otherwise undefined.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* This widely distributed product meets the U.S. standards for animal safety and efficacy and appears to be safe in humans. There is no information regarding its efficacy in humans, other than by analogy with other products. The package insert should include acceptable recommendations about emergency boosters. The inclusion of a community outbreak of poliomyelitis as a contraindication is probably unnecessary at the present time.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Texas Department of Health Resources.

1. *Description.* This is a combined product containing, per 0.5 mL dose, 10 Lf of tetanus toxoid and 2 Lf of diphtheria toxoid, adsorbed onto aluminum hydroxide, with 0.01 percent thimerosal as the preservative.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for the primary immunization of children over 6 years of age and adults. The recommended course for primary immunization is 2 doses of 0.5 mL, intramuscularly at 4- to 6-week intervals with a third dose approximately a year later. Subsequent reinforcing doses are recommended at 10-year intervals. There is no recommendation for a reinforcing dose on occasion of risk from diphtheria or tetanus.

b. *Contraindications.* It is recommended that immunization of individuals with acute respiratory disease or other active infection be deferred. It is stated that the product should not be used for treatment of active tetanus and that the product will not protect against tetanus when given at the time of injury unless the individual has been actively immunized previously. It is also stated that an optimum immune response cannot be expected in individuals receiving immunosuppressive drugs.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several million doses were distributed in a 10-year period with no serious reactions reported.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product when used for reinforcement of previously established immunity is satisfactory. For primary immunization the risk appears to be low; data relating to the efficacy of this agent for primary immunization are not available and accordingly the benefit-to-risk assessment cannot be established with precision.

4. *Critique.* This combined, adsorbed diphtheria and tetanus toxoid preparation for the immunization of older children and adults would appear to be quite satisfactory for purposes of reinforcement of preexisting immunity. However, there are inadequate data regarding its efficacy for the primary immunization of such individuals.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to

develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* The Wyeth Laboratories' submission includes an excellent summary description of the preparation of the two toxoids. The final product is a combined antigen product, including in each 0.5 mL dose, 5 Lf of tetanus toxoid, 1.38 Lf of diphtheria toxoid, and 0.34 mg of aluminum as aluminum phosphate. Sodium chloride is added to the final product as necessary to establish isotonicity.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary and booster immunization of children over the age of 6 and adults against diphtheria and tetanus. The recommended number of doses and intervals between doses are consistent with recommendations of the Public Health Service Advisory Committee on Immunization Practices. The package insert emphasizes that this product should not be used for basic immunization or booster dosing in infants and children under 6 years of age.

b. *Contraindications.* Acute active infections are listed as a relative contraindication, except in the event that emergency booster dosing is required. An outbreak of poliomyelitis is said to be reason to defer elective immunization.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A recent report by McCloskey (Ref. 5) provides satisfactory evidence of the efficacy of Wyeth Laboratories' diphtheria and tetanus toxoids, adsorbed (for adult use), when used as a booster dose. He boosted 123 adult hospital workers with Td toxoid, containing 1 Lf of diphtheria toxoid, and found no diphtheria antibody response in 21 percent of this group 1 month later. Their preimmunization titers for diphtheria antibody were less than 0.01 unit per mL, and all of those who failed to respond had either never been immunized against diphtheria or had been immunized more than 10 years prior to inclusion in this study. This data provided reasonable evidence of satisfactory human immunogenicity for the diphtheria component when used as a booster dose. No data were provided for the efficacy of this product when used in primary immunization.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Adequate evidence is presented in the report of Sisk and Lewis (Ref. 6) of the safety of Td toxoid, as prepared by Wyeth Laboratories, when used as a booster dose. No evidence of safety is provided for the use of this product in primary immunization.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization cannot be assessed with certainty, owing to the absence of acceptable data regarding its efficacy. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. *Critique.* The labeling is generally satisfactory. The labeling is well written, the recommendations for use are consistent with advisory bodies such as the Public Health Service Advisory Committee on Immunization Practices, and the indications for use of this product are clearly delineated. It is probably unnecessary to continue to refer to outbreaks of poliomyelitis as reasons for deferral of elective immunization.

The major defect in the submission is the lack of human data on the safety and immunogenicity of this product when used as a primary immunizing agent.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards the use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop evidence regarding the efficacy of this product when used for primary immunization.

References

(1) BER Volume 2029.
(2) BER Volume 2054.
(3) Ipsen, J., Jr., "Immunization of Adults Against Diphtheria and Tetanus," *The New England Journal of Medicine*, 251:459–466, 1954.
(4) BER Volume 2010.
(5) BER Volume 2017.
(6) Sisk, C.W., and C.E. Lewis, "Reactions to Tetanus-Diphtheria Toxoid (Adult)," *Archives of Environmental Health*, 11:34–36, 1965.

Generic Statement

Pertussis Vaccine

Pertussis, or whooping cough, is a bacterial infection caused by *Bordetella pertussis* (formerly *Haemophilus pertussis*) and is characterized by severe and paroxysmal coughing which persists for some weeks. The disease affects primarily infants and young children, and its morbidity and mortality rates are inversely related to age. Infants do not acquire adequate immunity from their mothers and are therefore highly susceptible to infection. The infection is localized in the respiratory tract, especially on the epithelial surfaces of the bronchial tree. The paroxysms of coughing ("whoop") are believed to be caused either by the tenacious nature of the secretions or conceivably by an effect of the disease process on the nervous system. Immediate complications include encephalopathy and convulsions, pulmonary atelectasis, and secondary infections such as pneumonia and otitis media. Developmental retardation and bronchiectasis may occur as permanent sequelae.

Pertussis responds poorly to treatment with antimicrobial drugs. Erythromycin and ampicillin, the two most commonly used antibiotics, are effective only if given in the earliest stages, although secondary complications caused by bacteria other than *Bordetella pertussis* usually respond satisfactorily.

In the United States, morbidity and mortality due to pertussis rapidly declined after increased utilization of pertussis vaccine in the 1940's and its official standardization in 1949, although the disease persists as a significant contributor to infant mortality in developing countries. Indeed, the crude mortality rate from pertussis in this country decreased by 1967 to one two-hundred fiftieth of the 1930 rate; in 1973 only five deaths due to pertussis were reported. However, not all of this remarkable decline can be attributed to widespread use of the vaccine, for the reason that some decline in morbidity and morality from pertussis was observed in the United States and other Western countries, prior to the institution of immunization. Nonetheless, the inference that part of the decrease is due to the vaccine is supported by an increase of pertussis in England where vaccine of low potency had been used. In addition, the disease has increased in countries, including Denmark, England, and Japan, where the use of vaccine was decreased because of the fear of severe reaction.

Despite these favorable mortality trends, pertussis is far from eradicated in the United States. The disease is ubiquitous although its incidence is low. The exact rates, however, are unknown for several reasons. Cases are frequently

unreported or not recognized. Since verification of infection by isolation of the organism requires cultural methods not routinely used in many diagnostic laboratories, the infection may go undiagnosed. Further, serologic testing is not feasible for routine diagnosis. Infection in immunized persons may cause bronchitis but without typical whooping. Therefore, reports of pertussis obtained by the Center for Disease Control probably represent only a fraction of all pertussis infections occurring in the country.

The results of early studies of pertussis vaccines in the 1920's were encouraging, but far from satisfactory. Subsequent technical improvements in vaccine production included the use of freshly isolated and more immunogenic strains for vaccine production and later the testing of the potency of the vaccine by intracerebral challenge of vaccinated mice, a test that appears to correlate satisfactorily with the immunogenicity of the whole bacterial vaccine in children. Further, agglutination titers in the blood of vaccinated humans were found to correlate reasonably well with protection against disease. However, it should be noted that immunity achieved in man following the natural disease or immunization is not always absolute or permanent. Pertussis occasionally occurs in older children and adults with a history of prior immunization or infection.

Careful evaluation of several vaccines was conducted in Great Britain by the British Medical Research Council in the late 1940's and 1950's. Efficacy was estimated from home exposure rates, and the results showed that the most effective vaccines protected 90 percent or more of children from clinical disease. Vaccines lower in mouse potency were less effective. Other studies have also correlated the laboratory-assayed potency with clinical efficacy.

Description

Current pertussis vaccine are aqueous preparations of either killed whole *Bordetella pertussis* bacteria of a fraction of *Bordetella pertussis* bacteria. The vaccines may be fluid or adsorbed, and may be combined with other antigens.

In contrast to some other immunizing agents, such as diphtheria and tetanus toxoids, pertussis vaccine is a relatively crude preparation that contains the majority of the bacterial constituents, most of which are probably not relevant to the induction of immunity to the disease. The reason for this vaccine being impure is that the antigenic component of the bacterium responsible for clinical immunity has not yet been positively identified. There is one combined product presently licensed (a modified DTP) that contains a partially fractionated pertussis component and the relative efficacy of this product, compared to the whole bacterial pertussis vaccine, has not been determined in controlled field trials.

Production

Pertussis vaccine is made from cultures of one or more strains of phase I *Bordetella pertussis* that yield the required potency. The composition of the culture media must meet Federal regulations.

The bacteria are killed and detoxified by heating, addition of a chemical agent, and appropriate aging, or an acceptable combination of these. The bacterial content must meet requirements specified in terms of the U.S. Opacity Standard. Vaccine potency is determined by comparing the results of the mouse protection test with that of the U.S. standard pertussis vaccine. A preservative, usually thimerosal, is added.

Federal regulations require that each lot of pertussis vaccine be tested in mice for immunogenicity prior to release. In this test, mice immunized with the vaccine lot are challenged intracerebrally with live organisms, and the results compared with those in mice similarly immunized with the U.S. Standard Pertussis Vaccine. The essential procedures for the test and its interpretation are specified in the Code of Federal Regulations (21 CFR Part 620).

The test provides a means of estimating the mouse potency of the vaccine lot. It must have a mouse potency of 12 protective units per total human immunizing dose (3 doses), except that for the vaccine in the combined product containing poliomyelitis vaccine the potency may be no less than 14 units.

Use and Contraindications

Currently, in the United States it is recommended that routine immunization begin at 2 or 3 months of age. Although monovalent pertussis vaccine is available, the trivalent product, with tetanus and diphtheria toxoids (DTP), is preferable. Earlier immunization may be undertaken if the disease is unusually prevalent in the community, but the immune response of very young infants is less satisfactory than that of older infants. The usual primary immunization schedule comprises the intramuscular administration of DTP on four occasions: 3 doses containing 4 protective units of pertussis vaccine each at 4- to 8-week intervals with a fourth dose approximately 1 year after the third injection. A booster dose, preferably at the time of school entrance, is recommended. Administration of pertussis vaccine is generally not recommended after the age of 6 years because of the possibility of increased rates of adverse reactions and the fact that the disease is less severe in those 6 years or older, and because it has not usually appeared necessary for continuing protection. Rarely, in the presence of a community outbreak of pertussis, a booster dose of pertussis vaccine has been administered to older children and adults at risk, sometimes as a half dose (2 protective units).

An acute febrile illness is usually reason to defer immunization in order to avoid confusion as to the cause of subsequent fever and because of the possibility of an additive effect. The occurrence of an apparent severe reaction to the administration of any preparation containing pertussis vaccine requires consideration of modifying the subsequent dosage schedule. Significant reactions that have been attributed to pertussis vaccine have included high fever (greater than 39.5° C), a transient shock-like episode, excessive screaming, somnolence, convulsions, encephalopathy, and, extremely rarely, thrombocytopenia. Such reactions almost always appear within 24 to 48 hours after injection, but have been thought to occur after an interval as long as 7 days. Shock, convulsions, encephalopathy, excessive screaming, and thrombocytopenia, if believed by the physician to be due to the pertussis antigen, represent absolute contraindications to further administration of this vaccine. In the case of young children receiving combined preparations, immunization with the components of the preparation other than pertussis should be continued, usually as diphtheria and tetanus toxoids combined (DT). High fever and somnolence do not represent absolute contraindications to continuing immunization against pertussis, but the physician should exert caution and may wish to consider fractional doses for subsequent injections.

Safety

Federal regulations require manufacturers to test each lot of vaccine for toxicity in mice prior to release. In this test, evidence of toxicity comprises failure of mice to achieve specified weight gain when injected intraperitoneally with one-half the single human dose. Different strains of mice may vary in their rates of weight

gain and specifications for suitable test strains may be necessary. In addition to the toxicity test, each lot of vaccine must under go a general safety test using animals and a sterility test. These tests are described in Title 21, Part 600, Code of Federal Regulations. In addition, it is expected that manufacturers keep records of all reactions in humans reported to them, and that these records be available to the Bureau of Biologics on request.

In spite of these precautions, untoward reactions to pertussis vaccine in humans occur. Low-grade fever and local tenderness appear frequently after injection. The severe of disturbing untoward reactions, including shock, convulsions, encephalopathy, persistent high-pitched screaming, and thrombocytopenia, are rare complications, the rates of which are difficult to define precisely, at least in part because they are dften not reported. However, as morbidity and mortality from pertsussis have declined, these reactions have drawn considerable attention. The frequency of fatal reactions has been estimated to be 1 or 2 cases per 10 million injections in the United States. As with the neurologic complications of the disease, the mechanism of the untoward reaction is not understood. A responsible component in pertussis vaccine has not been identified, nor has any characteristic of vaccine recipients that predisposses to such reactions been found, although some observers have suggested that children with a history of convulsions are at higher risk. Observations in this and other countries indicate that vaccine, of excessively high potency may be more reactive.

Pertussis vaccine adsorbed onto aluminum compounds elicit fewer adverse reactions and are thought to provide better and longer protection. The adsorbed vaccines are comparable to plain vaccines in the mouse weight-gain test and are approximately twice as immunogenic per bacterial content in the mouse potency assay. Pertussis vaccines potentiate the antitoxin response to diphtheria and tetanus toxoids, and thus it is advantageous to provide primary immunization to infants with a combination of pertussis vaccine and these toxoids (see Generic Discussion of DTP).

Efficacy

Studies reported by the British Medical Research Council in the 1950's showed good correlation of the mouse protection test results with clinical protection. Based on these results and those of other studies, the mouse potency test has been accepted as an indication of efficacy in lieu of field studies. In addition to the mouse protection test, agglutination titers in the sera of those vaccinated in the British studies were found to correlate fairly well with efficacy. Agglutination titers of 1:320 or better were associated with protection in field studies. One notable exception was observed with a partially purified soluble antigen. This vaccine was found to be highly efficacious in terms of clinical protection but did not cause an aggultinin response except to the specific serologic strain that was used in the soluble antigen production. In other instances, it was observed that protection may sometimes exist in the presence of low agglutinin titers, but in general the presence of agglutinins seems to reflect immunity, though indirectly. Therefore, the agglutination test may be used to evaluate vaccine potency when the incidence of the disease is too low for meaningful field studies of clinical protection, a situation that exists in the United States at the present time.

Later in the 1960's low efficacy of British vaccines was reported. Subsequent analysis attributed these failures to use of a standard vaccine that contained 2 instead of 4 protective units per single dose.

Protection from disease is directly related to interval since vaccination. The extent to which vaccination modifies the disease, rather than prevents infection, is unknown.

Although the immunogenicity of pertussis vaccine is less, and the reactivity higher than most other commonly used vaccines, all evidence supports the belief that the benefits of universal pertussis immunization considerably outweigh the adverse effects. The morbidity, mortality, and neurological complications of immunizations are significantly less than those of the disease.

Special Problems

Although clearly of great value, pertussis vaccines do not exhibit the effectiveness and safety that have been achieved with certain other immunizing agents. Specific problems that deserve investigative pursuit may be grouped in three categories.

1. The pathogenesis of the disease and the biology of the organism are poorly understood. As a consequence, knowledge of the immune response and the mechanisms of complications of both the disease and immunization is limited.

It is not known what components of the organism are responsible for the clinical and pathologic features of the disease and its complications, or how they act. It is not known what component of the organism produces immunity, whether it is a single antigen, if it relates to the components that produce the disease characteristics, or whether it is identical to the mouse-protective antigen. Further, the biologic attributes of the organism that produce the neurologic complications of the disease have not been identified, nor is it clear that they are the same as those responsible for the neurologic sequelae of immunization.

Current pertussis vaccines are complex mixtures of reactive cellular substances. Some progress toward identification of the mouse-protective antigen has been made over the past 10 years. This component appears to be associated with the fimbriae and parts of the cell envelope. Whether the histamine-sensitizing and the lymphocytosis-promoting factors can be separated from the protective antigen is unclear.

Until better definition of the components of the organism and their relation to disease and immunity are established, the effect of attempts to improve immunogenicity and reduce reactivity of pertussis vaccines by purification or extraction can only be evaluated by costly and logistically difficult field studies in humans.

2. The current epidemiology of pertussis and that of vaccine-induced complications are not defined with satisfactory precision.

As noted previously, reported cases of pertussis probably represent only a fraction of those occurring. Without adequate surveillance of disease rates, the effectiveness of current vaccines and immunization programs cannot be monitored.

Although there is evidence of worldwide shifts in the major antigenic characteristics of pertussis strains causing clinical disease, it is not known whether these shifts have diminished the effectiveness of pertussis vaccine. Changes in the distribution of serotype antigens in disease isolates from populations undergoing immunization have been demonstrated in several different geographic areas. These shifts in serotypes have prompted changes in pertussis strains used for vaccines in certain countries. However, experimental evidence indicates the serotypes are not necessarily protective moieties and the vaccine potency has not been related to these bacterial antigens. Studies that suggest an increase in pertussis in immunized children because of shifts in the wild organism cannot be interpreted because the protective unitage of the vaccines

was not taken into account. However, there is no firm evidence, as of now, that it is important to modify pertussis vaccines so that the immunizing strains reflect the strains prevalent in the community. This problem cannot be evaluated without better surveillance.

Experience with modern pertussis immunization is not of sufficient duration to predict whether childhood immunization may in some instances postpone natural infection until a later age. The disease itself does not always assure life-long immunity. Further, it is possible that in the past, when the disease was more widespread, periodic exposure to pertussis provided reinforcement of immunity throughout life; if such naturally occurring boosters did contribute to the protection of older children and adults, low prevalence of the disease in recent years may be reflected by the appearance of a susceptible older population. Thus, the possible need to immunize adults, as well as children, may have to be considered in the future. This will require weighing the risks of widespread immunization of older children and adults against the fact that the disease in these age groups is milder than in young infants. Current data related to this question are inadequate for rational decisionmaking.

On the other hand, the usefulness of the currently recommended booster dose at school entrance has never been fully documented. Presumably, by keeping school children free from pertussis, transmission to younger siblings in the home is prevented. Whether this final booster offers additional protection from disease and/or such transmission is unproved.

The rates of severe untoward reactions to pertussis vaccines are not defined. Furthermore, the ultimate significance, if any, in terms of permanent sequelae, of vaccine-induced somnolence, excessive screaming, and high fever is unknown, and without such knowledge satisfactory recommendations for further immunization cannot be made if any of these reactions occurs. Physicians are expected to report complications of immunization to manufacturers in the United States, but compliance with this expectation is less than optimum. Many physicians are not cognizant of the importance of reporting untoward reactions or may be unaware of their clinical features. Further, both physicians and manufacturers may be held liable for damages in suits brought by patients who may suffer adverse effects from established vaccines. All these factors undoubtedly discourage reporting; without maximum reporting or some other form of surveillance, definition of the rates and significance of untoward reactions to current and future vaccines cannot be ascertained.

3. Laboratory procedures and technical requirements for the production and evaluation of pertussis vaccine exhibit certain problems that require solution.

The results of the weight-gain test in mice, used to determine toxicity of the pertussis vaccine, show variability between laboratories and therefore either the test requires more precise standardization or another method for determining toxicity is needed. This is a problem for both the test vaccine and the control reference vaccine. At present the only test shown to have any relation to clinical reactivity in man is the mouse weight-gain test.

Section 620.4(g) (21 CFR 620.4(g)) states that pertussis vaccine shall have a potency of "12 units per total human immunizing dose." Certain statistical variations in estimates of actual potency that provide some assurance that the product probably does contain 12 units per total human immunizing dose are permitted based on the number of assays performed. This is in recognition of inherent variability in this type of assay. Identification and improved control of the factors influencing the variability of this test is needed.

Further, definition of the total immunizing dose in the regulations as 12 units (3 doses of 4 units each) is now at variance with current practice and the recommendations of national advisory committees in that 4 doses of 4 units each are now advised and employed (see section on Use and Contraindications).

During the first studies of efficacy, agglutination tests were carried out by tube dilution, which required rather large amounts of sera. The microtests in general use today need to be standardized, since there is a tendency for each laboratory to use its own adaptation of the test, making comparisons among results from different laboratories almost impossible. However, agglutination antibodies may only be indirectly associated with protection, and may not constitute the protection-specific antibody. A more specific test should be substituted if and when it becomes available.

Recommendations

1. The Panel strongly recommends that adequate public support be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization. Without such basic studies a more effective and safer pertussis vaccine cannot be developed.

2. Surveillance of pertussis in well-defined populations should be undertaken. Such surveillance would have three purposes: first, to determine the incidence of the disease in the United States, including distribution by age and vaccine status; second, to evaluate the possibility that a change in serotypes of *Bordetella pertussis* in a community causes outbreaks of pertussis in individuals previously immunized with serotypes formerly present; and, third, to determine whether the current infrequency of the disease in the United States may ultimately result in a population of older children and adults whose immunity has waned because of a lack of repeated exposure to the organism.

The Panel is convinced that currently employed surveillance systems to identify adverse reactions to pertussis vaccine are inadequate and recommends that definitive steps be taken by the appropriate subdivisions of the Public Health Service to improve them. Several alternatives are available. Perhaps the same channels as those proposed for reporting of adverse drug reactions can be utilized. Special field stations with sufficient populations under surveillance may have to be established and funded.

3. Specific recommendations of the Panel regarding the production, use, and evaluation of pertussis vaccines include the following:

The weight-gain test in mice used to determine toxicity of pertussis vaccine needs revision to include specifications regarding mouse strain(s) to be used as a reference standard. Studies should be undertaken to develop other assays predictive of human reactivity. Obviously, better definition of the organisms' biological characteristics (Recommendations, No. 1) would facilitate prediction and prevention of reactivity in man.

The agglutination test used to determine vaccine response in humans should be standardized. It is recommended that a reference serum be used for comparison. A reference laboratory should be available at the Bureau of Biologics. The interval between immunization and obtaining serum for testing of the serologic response must be specified. An acceptable titer obtained by a standardized method should be defined; titer rises or geometric means titers are not adequate to evaluate

immunogenicity. (See discussion on Efficacy, Pertussis Generic Statement.)

Regulations concerning the maximum human dose should be updated to reflect current recommendations and practices. It should be required that pertussis vaccine have a potency of 4 protective units per single human dose. The upper estimate of a single dose should not exceed 8 protective units.

The vaccine label should warn that if shock, encephalopathic symptoms, convulsions, or thrombocytopenia follow a vaccine injection, no additional injections with pertussis antigens should be given (immunizations can be continued with DT). The label should also include a cautionary statement about fever, excessive screaming, and somnolence.

Any fractionated vaccine that differs from the original whole cell vaccine should be field tested until better laboratory methods for evaluating immunogenicity in man are developed. Field testing should include agglutination testing and, if possible, evaluation of clinical efficacy in man.

4. Petussis vaccine is one of the immunizing agents for which it is strongly urged that legislation be enacted to provide reasonable Federal compensation to the few individuals injured and disabled by participating in a meritorious public health program. Such legislation would protect manufacturers and physicians against liability in situations in which the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccine.

Basis for Classification

Because field trials are not now feasible, at least in this country, the standard of efficacy upon which major reliance has to be placed is a mouse protection test, the results of which were correlated closely with the original field tests upon which evidence of efficacy for pertussis vaccine is based. Agglutination titers provide general but not absolute correlative support. Therefore, vaccines prepared in accordance with the specifications of those found effective in field trials and meeting standards for mouse protection are considered eligible for assignment to Category I especially when supported by adequate agglutination titers.

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SPECIFIC PRODUCT REVIEWS

Pertussis Vaccine Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* Pertussis vaccine adsorbed is a suspension of killed *Bordetella pertussis* organisms in 0.85 percent saline solution mixed with a suspension of aluminum phosphate (no more than 1.5 mg per single dose), and preserved with thimerosal, 0.01 percent. The number of organisms is equal to 8 to 16 opacity units per 0.5 mL. Formaldehyde is added "if needed" to a concentration of not more than 0.01 percent. Each 0.5 mL contains 4 protective units.

2. *Labeling*—a. *Recommended use/indications.* This product may be used alone for active immunization if it is desired to begin after 3 months or for booster during outbreaks. Routine

immunization should be carried out with DTP. Three intramuscular injections each 0.5 mL, 4 to 6 weeks apart, boosters at 2 to 5 years of age. Not recommended above the age of 5 years.

b. *Contraindications.* (1) Respiratory or other acute infections; (2) cerebral damage; (3) severe febrile reactions; (4) encephalitic reaction to vaccine; and (5) persons on corticosteroid treatment.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A study reported in *The British Medical Journal* (Ref. 1) used this product. Table 1 in the study states a "plain suspension" was used, while this product is adsorbed. Vaccine used in the study had $10,000 \times 10^6$ organisms per mL. Dosage was 1, 2, 3 mL at monthly intervals for total of $60,000 \times 10^6$ organisms. Children 6 to 18 months were immunized. Vaccine lot D 231 was tested in 630 subjects with 655 controls; vaccine lot A 236 was tested in 1,056 subjects with 993 controls. The following table is a summary of the data presented in the study.

TABLE 1

Vaccine	Attack rate/1,000 child months		Percent attack rate in home exposure		Percent attack rate in other exposures	
	Vac.	Univac.	Vac.	Univac.	Vac.	Univac.
D 231	0.97	7.04	7.3	79.5	4.6	36.7
A 236	0.60	6.48	6.9	90.0	3.8	34.8

Comparison of attack rates in the two groups indicates that the vaccine provided approximately 80 to 85 percent protection against pertussis.

b. *Safety.* One child in five was visited 24 to 72 hours after each injection. No severe local or general reactions were observed although a number developed temperature rises within 24 hours.

No specific data are provided for the present product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment is favorable.

4. *Critique.* The human efficacy data would appear to prove the value of this product, but the studies were based upon a differing dosage schedule of a plain, not adsorbed, vaccine (with a greater dosage of antigen). Extrapolation of the British Medical Research Council data to the present product may not be entirely justified but provides some of the best available data.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Pertussis Vaccine Manufactured by Dow Chemical Company

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data for the manufacturer regarding the monovalent pertussis vaccine, and in the absense of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine, Fluid, Manufactured by Eli Lilly and Company

1. *Description.* Pertussis vaccine, fluid, is an unwashed suspension of killed *Bordetella pertussis* cells grown in modified Cohen-Wheeler medium. The methods of killing and detoxification are not given. The product is preserved with 1:10,000 merthiolate, and the total human immunizing dose (1.5 mL) contains the equivalent of 12 antigenic units of the U.S. standard pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against pertussis. The package circular recommends that three 0.5 mL doses be administered subcutaneously at intervals of 3 to 4 weeks for primary immunization. A booster or "optimun stimulating" dose of 0.25 to 0.5 mL is recommended for administration approximately 1 year after primary immunization.

b. *Contraindications.* Elective immunization should be postponed in the presence of acute infections. Postvaccinal neurologic disorders contraindicate further injections. Personal or family history of central nervous system damage or convulsions is an indication for fractional dosages. It is noted that corticosteroids may interfere with the immune response.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific studies on this product are presented or cited. Claims for efficacy appear to be based largely on demonstrated correlation of potency in mice and protective efficacy in children (Ref. 2).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on this product were presented. The manufacturer's submission indicated no consumer complaints over a 5-year period.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

d. *Labeling.* No mention is made of the desirability of using DTP for immunization of most infants.

Although postvaccinal neurological disorders including convulsions are listed as a contraindication to further use, the labeling goes on to recommend fractional dosage. This is contradictory.

The reference to avoiding use of the vaccine when polio is present in the community is outdated and should be deleted.

4. *Critique.* It should be noted that this is a whole-cell pertussis vaccine, and, as such, differs significantly from that used in this manufacturer's DTP, in which a "solubilized" bacterial fraction is employed.

While no specific studies on this product are presented or cited, claims for efficacy are justifiably based largely on the demonstrated correlation of potency as determined by the intracerebral mouse protection test and protective efficacy in children.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and

effectiveness for this product. Labeling should be revised in accordance with the recommendations of this Report.

Pertussis Vaccine, Fluid, Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine, Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* The manufacturer did not provide a description of the monovalent pertussis vaccine for which a license is maintained. Instead a submission for pertussis vaccine combined with diphtheria and tetanus toxoids is provided, and includes details of the production of the pertussis component. The manufacturer has released no monovalent pertussis vaccine for 12 or more years.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This pertussis vaccine prepared for the combined product meets Federal requirements.

(2) *Human.* The evidence for efficacy in humans comprises a study from 1950 in which 75 infants were immunized with this pertussis vaccine combined with diphtheria and tetanus toxoids (Ref. 3). In this study, satisfactory pertussis immunization was achieved as determined serologically.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* When employed in combination with diphtheria and tetanus toxoids no serious reaction occurred in 100 infants immunized.

c. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined for this product in the monovalent form.

4. *Critique.* This vaccine has not been marketed for more than 12 years and no specific data related to this product in the monovalent form were provided. Except for rare instances of community outbreaks of pertussis in which it might be desirable to administer monovalent pertussis vaccine, these products do not enjoy wide usage.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine Manufactured by Parke, Davis & Co.

1. *Description.* A sterile saline suspension of centrifuged and resuspended "selected" strains of Phase 1 *Bordetella pertussis* is grown on semi-synthetic liquid medium. The organisms are inactivated by incubation in the presence of formaldehyde. Thimerosal 0.01 percent is added as a preservative. Total dose contains 12 units of pertussis vaccine. The product is currently not marketed.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for "rapid primary immunization" of infants and children against pertussis—to be followed ordinarily by immunization with DTP in order to complete immunization against the other antigens in this combination; 3 doses of 0.5 mL each are given subcutaneously at 3- to 4-week intervals or, if rapid immunization is indicated, at 1-week intervals. However, the longer interval is probably better. A booster dose of 0.5 mL is recommended 1 year after basic immunization and at 3 to 6 years of age or in the presence of actual or potential exposure to the disease in children under 6 years.

b. *Contraindications.* Defer immunization in presence of cerebral damage, active infection, or acute respiratory disease. Discontinue if encephalopathic symptoms appear. Give smaller graduated doses if a systemic reaction occurs.

3. *Analysis*—a. *Efficacy*— (1) *Animal.* This product meets Federal requirements.

(2) *Human.* Antibody response data of 1961 to 1963 (Ref. 4) appear satisfactory, but it is not clear that this can be extrapolated to the current product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this particular product are presented. No market experience is reported.

c. *Benefit/risk ratio.* This cannot be judged in view of the absence of data on reactions to this particular product.

4. *Critique.* This is a fluid pertussis vaccine made by the pioneer firm in developing pertussis vaccine in the United States, but differing from their classical "Sauer vaccine" in that it is made in liquid medium instead of on a solid Bordet-Gengou medium. No data are provided on human safety or human antibody responses; the last package insert is dated 1966. This is an inactive product. Only illegible photostats of labels are presented. The emphasis in the package insert on using the fluid vaccine for "rapid immunization" cites no reference supporting this recommendation.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed, and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This is an aluminum phosphate adsorbed pertussis vaccine, currently not on the market. It contains 15 opacity units per 0.5 mL dose and 4 antigenic units per dose. It is centrifuged, resuspended in 0.9 percent saline, mixed with aluminum phosphate, and 0.01 percent thimerosal is added.

2. *Labeling*—a. *Recommended use/indications.* This vaccine is recommended as an efficient method of immunizing infants and children against whooping cough when a monovalent immunizing agent is indicated; these circumstances are not defined further. Recommendations for routine immunization are standard.

b. *Contraindications.* The usual contraindications are noted, particularly with regard to children having any history or signs of encephalopathy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Evidence of direct human efficacy is not presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data are reported in the submission (Ref. 4) concerning 27 children who received the adsorbed pertussis vaccine in 1967, of whom 5 had systemic reactions as measured by fever. No other information regarding human safety is included.

c. *Benefit/risk ratio.* The data provided are inadequate to make a determination.

4. *Critique.* This is an aluminum phosphate adsorbed pertussis vaccine, currently not on the market, but one that would meet current standards for animal safety. Whether it is efficacious and safe in humans is not possible to determine from the data submitted.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed, and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine Manufactured by Texas Department of Health Resources

1. *Description.* This product is prepared from Phase I stains of *Bordetella pertussis* and is an unwashed suspension of the organisms in physiological sodium chloride solution, killed, and preserved by thimerosal in final concentration of 1:10,000.

The vaccine is tested for antigenic potency by the mouse-protection test, and the degree of protection must equal or exceed that of the U.S. standard pertussis vaccine. The total immunizing dose contains 12 units.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for active immunization of children. Three doses of 1.0 mL of the vaccine are given deep subcutaneously at 3- to 4-week intervals. The labeling also recommends that booster doses of 0.3 or 1.0 mL be given at about 2 years of age, again at the age of 5 or 6 years, during epidemics, and after known exposure to the disease. Pertussis vaccine plain is not recommended for immunization of children under 6 months of age. "In this group, the pertussis vaccine with the mineral adjuvant is the material of choice."

b. *Contraindications.* These include any respiratory or other acute infections. The presence of cerebral damage in an infant is an indication for delay in immunizations. It is advised that in such childred and in those experiencing severe febrile reactions with or without convulsions, immunization procedures should be delayed and/or given in fractional doses. This is partly incorrect, and the label should state that in children who experience shock, convulsions, encephalopathy, excessive screaming, or thrombocytopenia, after vaccinations with a pertussis vaccine, no further injections of any pertussis vaccine should be given.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are provided relative to this particular product, but reference is made to the general data accumulated in the United States, including a chart of decreasing incidence of pertussis in Texas over time (Ref. 5).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* This product has been produced since 1945. The number of released doses is not given, but it is stated that there is a lack of reaction reports to the single fluid antigen in Texas.

c. *Benefit/risk ratio.* The benefit-to-risk assessment appears to be satisfactory but is not well documented.

d. *Labeling.* There are two flaws in the label as described above:

(1) The lack of a clear statement that DPT is usually the vaccine of choice for routine immunization of children.

(2) No mention of convulsions, shock, encephalopathy, excessive screaming, or thrombocytopenia following a dose of pertussis vaccine (plain or combined) as an absolute contraindication for further immunization of pertussis (but immunization can usually be contained with DT).

4. *Critique.* It is not known how many doses of this product have been distributed. The immunization dose is 1 mL instead of ½ mL, which is unusual. The labeling is partly misleading as described above.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Pertussis Vaccine Manufactured by Wyeth Laboratories, Inc.

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must recommend revocation of licensure for administrative reasons.

5. *Recommendations.* the Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

References

(1) Bedson, S. P., W. C. Cockburn, et at., "Prevention of Whooping Cough by Vaccination by a Medical-Research Council Investigation," *The British Medical Journal*, 1:1463–1471, 1951.

(2) BER Volume 2048.

(3) BER Volume 2078.

(4) BER Volume 2005.

(5) BER Volume 2101.

Generic Statement

Diphtheria and Tetanus Toxoids and Pertussis Vaccine (DTP) (See Generic Statement for Monovalent Components)

Description

This product is a combination of diphtheria and tetanus toxoids with pertussis vaccine, intended for the primary immunization and maintenance of immunity against diphtheria, tetnaus, and pertussis in children 6 years of age or less.

Production

DTP comprises diphtheria and tetanus toxoids and pertussis vaccine prepared in a manner usually similar to that of the monovalent preparations, and combined into a single preparation. Both fluid and adsorbed products are currently licensed and used in the United States. One manufacturer produces a partially purified fraction of pertussis organisms.

Use and Contraindications

DTP is recommended for the primary immunization of infants and children 6

years of age or younger. Recommended schedules are provided by the Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics, and the American Public Health Association.[1] Primary immunization comprises a series of 4 doses administered subcutaneously or intramuscularly and the absorbed preparations should be given intramuscularly.

The Advisory Committee on Immunization Practices recommends that the first 3 doses be given at 4- to 6-week intervals with a fourth dose approximately 1 year after the third injection. Ideally, immunization should begin at 2 to 3 months of age or at the time of a 6-week checkup if that is more practical. It is advisable not to administer DTP to individuals 7 years of age or older because untoward reactions to the pertussis component may be severe.

Contraindications are of two general types. The first of these is a severe hypersensitivity response to a prior injection. The other is a definite or suspected untoward reaction to the pertussis component of DTP. (See Generic Statement for Pertussis Vaccine.)

As with the individual components, the administration of DTP should be deferred in the presence of a febrile illness, because of possible confusion as to the etiology of persistent fever. Individuals receiving corticosteriods or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time.

Safety

There is no evidence that the combination of tetanus and diphtheria toxoids with pertussis vaccine synergistically increases the likelihood of adverse reactions over that observed with the individual components.

The toxoid components are tested for detoxification and the final product must be tested for safety according to Federal requirements.

Efficacy

Laboratory and animal procedures for determining the potency of DTP, as specified by Federal requirements, are carried out. In the case of the pertussis component of DTP the mouse protection test affords a reasonably satisfactory means of correlating an animal model with protection in humans (See Generic Statements for Monovalent Products). An immunologic advantage of DTP over the monovalent toxoids is that the pertussis component exerts some adjuvant effect on diphtheria and tetanus toxoids.

Special Problems.

1. The available information indicates that the components of DTP, singly or in combination, are more immunogenic in the adsorbed preparations than in the fluid products. It is therefore questioned by some whether continued production and use of fluid toxoids and vaccines have any advantage.

2. DTP has been one of the most widely used vaccines. Most experiences, therefore, with adverse reactions to the components have been derived from experience with the combined product rather than from the monovalent preparations. Problems with individual components are similar to those of the monovalent products and may be summarized as follows. (See Generic Statements for Monovalent Diphtheria and Tetanus Toxids and Pertussis Vaccine for detailed discussion.)

a. *Diphtheria.* Diphtheria toxoid, fluid or adsorbed, single or in combination, even with the adjuvant effect of pertussis vaccine, is not as effective an immunizing agent as might be desired. Evidence for this includes the occasional occurrence of diphtheria in immunized individuals and infections with nontoxigenic strains. Furthermore, there is concern about the permanence of immunity and the effectiveness of the present booster program in the light of the decreased frequency of exposure to the organism in the community, a phenomenon that may have provided repeated natural enhancement of immunity in the past. Whether increased purification of the toxoid may reduce immunogenicity is also unknown. Other problems with the diphtheria component include nonspecific reactivity and the lack of an animal model that would obviate field testing of improved toxoids in humans.

b. *Tetanus.* There is evidence that recent changes in manufacturing procedures, designed to reduce reactivity, may have lowered the immunizing potency of current tetanus toxoids compared to those in use 30 years ago.

c. *Pertussis.* Because the pathogenesis of pertussis and the biology of *Bordetella pertussis* are poorly understood, knowledge of the immue response and the pathophysiology of both the disease and immunization is limited. Without better definition of the components of the organism and their relationto disease and immunity, attempts to improve immunogenicity and reduce reactivity of pertussis vaccines are seriously hampered. Additional unknown facts about pertussis and pertussis immunization that requires study include the true incidence of the disease, whether present vaccines need to reflect currently prevalent strains of *Bordetella pertussis*, the permanence of vaccine-induced immunity, and the true frequency and significance of the various untoward reactions. Furthermore, laboratory testing procedures used in the production and evaluation of pertussis vaccines require improvement and standardization.

Recommendations

Recommendations regarding DTP are the same as those in the generic statements for the monovalent components of this product. They may be summarized as follows:

1. *Diphtheria*—a. Upgrading of surveillance of the diphtheria-immune status of the population is recommended in order to anticipate the possible development of a susceptible population in the future.

b. Efforts should be made to develop an animal model or other laboratory technique for evaluating antigenicity that correlates well with immunogenicity in humans.

c. Public support for the development of a better immunizing agent against diphtheria should be provided. Worthy objectives include not only more immunogenicity but also less reactivity.

2. *Tetanus*—a. Continued efforts should be made to establish, for routine lot-to-lot control, the usefulness of the quantitative technique of the evaluation of tetanus toxoids against the International Standards. This technique is required by the European Pharmacopoeia.

b. Because some current tetanus toxoids appear to have somewhat less antigenic potency than those employed in the past, monitoring of the immune status of a human population sample should be conducted over years in order to ascertain the necessity for continuing booster doses.

3. *Pertussis*—a. Adequate public support should be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization. The purpose of such studies would be to develop a more effective and safer vaccine.

[1] These three organizations are referred to as National Advisory Committees in other Generic Statements of this Report.

b. Enhanced surveillance of pertussis and the complications of pertussis immunization is strongly recommended.

c. Certain procedures concerning the production and evaluation of pertussis vaccine need to be reevaluated for improvement in precision. These include the mouse weight-gain test, the agglutination test in man, the maximum allowable potency of the human dose, and the inclusion of a clearcut warning on the package label about untoward reactions.

d. Until better laboratory methods for correlating animal models with immunogenicity in man are developed, fractionated vaccines must be tested in field trials as they are developed.

e. Legislation should be enacted that provides public authorization for recompense to individuals who incur rare, but unpredictable and unpreventable, serious reactions to vaccines, including pertussis vaccines.

Basis for Classification

The basis for classification of this combined vaccine is the same as that used for the individual components. Since DTP is universally recommended for primary immunization of infants and children, assurance of efficacy is especially germane, and is reasonably obtainable. Serologic evidence of efficacy for the DT components is therefore considered necessary, despite the acknowledged adjuvant effect of pertussis.

References

(1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4–5, June 24, 1972.

(2) "Diphtheria—Tetanus—Pertussis," *in* "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication No. (Center for Disease Control), 76–8221:25–30, 1977.

(3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," *Morbidity and Mortality Weekly Report*, Suppl., Health, Education, and Welfare Publication No. (Center for Disease Control), 77–8241:August 1977.

(4) Vaccinum Tetanicum Adsorbatum, supplement to Volume III, pp. 174–178, European Pharmacopoeia 1977, Maisonnuve, S.A., 57 Saint Ruffine, France.

SPECIFIC PRODUCT REVIEWS

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* Contains "purified" diphtheria (10 to 20 Lf per 0.5 mL) and tetanus toxoids (5 to 10 Lf per 0.5 mL), aluminum phosphate adsorbed, combined with a suspension of *Bordetella pertussis* organisms (8 to 16 opacity units per 0.5 mL). After combination, the potency of each component meets or exceeds Federal requirements. The amount of aluminum phosphate will not exceed 2.5 mg per single human dose (0.5 mL). The product is preserved with 0.1 percent thimerosal. The concentration of formaldehyde may not be greater than 0.01 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for use in children 5 years of age and younger for basic immunization, periodic reinforcing or booster doses, 0.5 mL intramuscularly at 2 to 3 months of age, 3 injections given 4 to 6 weeks apart followed by reinforcing dose 6 to 12 months later and booster prior to entering school.

b. *Contraindications.* Contraindications include acute respiratory infections and corticosteroid or immunosuppressive therapy. If an encephalitic reaction occurs, further immunization should be carried out with DT adsorbed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data are provided (Ref. 1) to demonstrate immunogenicity when a product which included equivalent amounts of diphtheria and tetanus toxoids and pertussis vaccine but also poliomyelitis vaccine and which had phemerol (benzethonium chloride) rather than thimerosal as a preservative was used in primary immunization. Thirty-eight children age 4 to 6 months and 39 children, age 7 to 12 months, were immunized and bled prior to immunization and 2 weeks after the third injection. Diphtheria and tetanus antitoxin titers and pertussis agglutination titers were satisfactory in all children, as measured in the postimmunization serum. Booster responses were studied in 290 who received 0.2 mL of DTP 13 years after primary immunization; antibody levels were determined at 1 week, 2 weeks and 2, 6, 12, and 24 months. The responses to tetanus and diphtheria were satisfactory in all. Those who failed to show a fourfold or greater increase in actitoxin titers had prebooster levels of >0.01 u per mL. The vaccine used contained less pertussis antigen than recommended, and 25 of 138 (of whom 24 had initial titers of <80) failed to show a fourfold increase in pertussis agglutinin titer.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* When 0.2 mL of DTP was administered to older persons, including adults (305 subjects), local reactions were severe (46 percent), moderate (30 percent), mild (22 percent), and none in only 2 percent. Severe reactions were associated with mild systemic reactions. Reactogenicity in children is not defined in the submission.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The data of immunogenicity appear satisfactory although the actual immunogen utilized included poliomyelitis vaccine and a different preservative.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria Toxoid and Pertussis Vaccine Adsorbed Manufactured by Dow Chemical Company

1. *Description.* No data have been provided by the manufacturer for this product for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding this specific product, and in the absence of any labeling for this product, the Panel must necessarily recommend revocation of this license.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Dow Chemical Company

1. *Description.* There are two diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, products

which differ only in the technique of adsorption. Both represent combinations of toxoids prepared from organisms grown in Mueller-type media, *Bordetella pertussis* grown on solid charcoal agar medium without blood substances. The toxins are detoxified with formaldehyde and concentrated by alcohol fractionation (Pillemer method). Each dose (0.5 mL) contains 10 Lf diphtheria toxoid, 5.33 Lf tetanus toxoid, and 15 opacity units of pertussis vaccine. The preservative is 1:10,000 thimerosal.

The pertussis component includes 4 strains of *Bordetella pertussis* which are bulk standardized at 90 opacity units.

The refined toxoids are adsorbed on either aluminum phosphate (0.23 mg aluminum) or potassium alum (0.14 mg aluminum).

2. *Labeling*—a. *Recommended use/indications.* The package circular recommends these preparations for routine immunization of infants and children, 8 weeks to 6 years of age, against diphtheria, pertussis, and tetanus. Three 0.5 cc intramuscular injections at intervals of 4 to 6 weeks are recommended for primary immunization with a reinforcing injection about 12 months after the third dose. A booster dose of 0.5 cc is recommended at 4 to 6 years of age.

b. *Contraindications.* Convulsions following an earlier injection contraindicates further administration of vaccines containing pertussis. The product is not recommended for use in children over 6 years of age. The label recommends deferral of elective injections in the following situations: acute respiratory disease, or other active infection, during treatment with immunosuppressive agents, outbreaks of poliomyelitis in the community. Fractional doses are recommended in infants with cerebral injury, asthma, a strong family history of allergy, somnolence, or fever of greater than 102°F with an earlier dose.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A review of the literature did not reveal any studies which included a Dow (Pitman-Moore) DTP in a trial of prophylactic efficacy.

Immunogenicity to each component is reported. With regards to the pertussis component, Bordt reports (Ref. 2):

Age group	No. subjects	No. with titer <1:4 prevaccine	Percent conversion† <1:4 to >1:32 (0.1 mL)
<6 months	20	19	74
6 mos. to 2 yrs.	38	35	94
2 yrs. to 6 yrs.	37	32	94

The question as to whether 74 percent conversion in infants less than 6 months of age is adequate cannot be answered from the available data.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the report by Conner and Speers (Ref. 3), 220 injections were given to children aged 2 months to 5 years and reactions followed. Two whole cell DTP vaccines were used; one was this product. The proportion of children who received this product is not stated. Reactions were observed in 43.6 percent of recipients; none were encepholopathic, and no febrile convulsions were seen. Local reactions (inflamation or nodule formation at injection site in 29.6 percent) and systemic reactions (30.9 percent) occurred frequently.

4. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory for the aluminum phosphate product, would be satisfactory for the potassium alum product if it is shown to be effective for primary immunization, and is satisfactory for the potassium alum product when used for booster immunization.

5. *Critique.* Inasmuch as there are two products in terms of the "adsorbant" component, the Panel considered each independently, although both carry the same brand name.

The submission and supporting data provide satisfactory evidence or safety and immunogenicity for the aluminum phosphate product when used for primary immunization of infants and children.

In contrast, data were not submitted or available to provide satisfactory evidence for the immunogenicity of the potassium alum preparation.

6. *Recommendations.* The Panel recommends that this product, when prepared with aluminum phosphate, be placed in Category I and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product, when prepared with potassium alum, be placed in Category I as regards its use for booster immunization, and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product, when prepared with potassium alum, be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of the product when sued for primary immunization. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Eli Lilly and Company

1. *Description.* This product is an alum-precipitated preparation of purified diphtheria and tetanus toxoids (Pillemer method) and extracted pertussis antigen. Each total human dose (1.5 mL) contains 15 Lf tetanus toxoid, 50 Lf diphtheria toxoid, and 12 protective units of pertussis antigen. The preservative is 1:10,000 merthiolate.

The methods of preparing the toxoids are classical, but the method for preparting the extracted pertussis antigen is not given. It is stated that the procedure permits cellular debris to be discarded.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for simultaneous active immunization of children not over 6 years of age against diphtheria, tetanus, and pertussis.

b. *Contraindications.* Use in the presence of acute infections should be postponed. Personal or family history of central nervous system damage or convulsions is an indication to use fractional dosage of individual antigens or 1/10 the recommended dosage of DTP.

Postvaccinal neurologic disorders, such as convulsions or encephalopathy, are a contraindication to further use of pertussis antigen (note apparent contradiction to above recommendation on fractional doses). It is noted that corticosteroid may interfere with the immune response.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* This particular product has never been subjected to a controlled clinical trial of its prophylactic efficacy. This is of particular concern because of the unique nature of the pertussis component. It does meet the requirements of the mouse potency test which has been correlated with human efficacy for whole-cell vaccines and Pilemer's purified pertussis antigen in the British Medical Research Council

Field Trials. The product has been shown to stimulate mouse protective antibodies (measured by incumbating serum with organisms, then injecting intracerebrally in mice) and agglutinating antibodies measured by a slide test (apparently not quantitated). The significance of the latter tests is unknown. (See Weihl (Ref. 4).) The toxoid components appeared to produce an adequate response.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Two studies (Refs. 3 and 4) purport to show that this vaccine produced a lower incidence of local and systemic reactions than whole-cell vaccine. It is not clear if a single lot of "Extracted" DTP was employed and how many (and which manufacturer's) whole-cell DTP vaccines were involved in the comparison. This study may be a melange of the experience of the investigators who carried out separate evaluation (C. Weihl, H. D. Riley, and J. Lapin.)

This is an extensively used product. Data from the manufacturer's complaint files do not indicate an excessive number of complaints or the existence of a serious problem.

c. *Benefit/risk ratio.* Assuming that the vaccine is efficacious, the benefit-to-risk assessment would be satisfactory, but there is insufficient information to determine this for primary immunization. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

d. *Labeling.* Although postvaccinal neurological disorders, including convulsions, are listed as contraindications to further use of the vaccine, the labeling goes on to recommend fractional dosage. This contradictory.

The reference to avoiding the use of the vaccine when polio is present in the community is outdated and should be deleted.

4. *Critique.* This is the only vaccine considered by the Panel which is not a whole-cell vaccine or differs substantially from the pertussis vaccines used in the British Medical Research Council Field Trials, which established the correlation of vaccine efficacy with potency assayed by the intracerebral mouse protection test. This particular type of fractionated pertusis antigen has never been subjected to a controlled field trial of prophylactic efficacy. In view of its widespread usage, this is a matter of some concern, especially since the feasibility of performing such a trial is extremely remote. While the mouse protection test provides a reasonable interim basis for assuming that the vaccine is likely to be efficacious, additional studies to provide a quantitative assessment of the agglutinin response are indicated to provide further assurance. This is especially indicated by the uniqueness of this product and the reasonably good relationship of agglutinin titers and vaccine efficacy established in the British Medical Research Council Field Trials. Unfortunately, data on agglutinin response furnished by the manufacturer are of a qualitative nature based on a rapid slide agglutination test.

In the matter of safety, the data gives the general impression that the vaccine containing extracted pertussis antigen in somewhat less reactive than whole-cell pertussis vaccine in terms of local and minor systemic reactions. There is not sufficient basis to assume that this vaccine is any more or less safe than whole-cell vaccines in terms of the very low risk of serious encephalopathic reactions which accompanies the use of pertussis vaccines.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Although meeting mouse protection test requirements, this particular type of fractionated vaccine has never been subjected to a controlled field trial of prophylactic effectiveness. Such field trials do not appear to be feasible in the near future because of the relative rarity of the disease and for other practical reasons previously discussed in this report. Serological data from agglutination tests, although indicative of an immune response, are not considered definitive evidence of protection. These factors led to a divided vote by the Panel. Therefore the Panel, by a split vote of three to two, recommends that this product be placed in Category I for primary immunization.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product contains diphtheria and tetanus toxoids, adsorbed, combined with pertussis vaccine, and suspended in isotonic saline with 1: 10,000 thimerosal added as a preservative. The diphtheria toxin and the tetanus toxin are detoxified with formaldehyde, and refined by the Pillemer Alcohol Fractionation Method, adsorbed with aluminum phosphate. Phase I pertussis vaccine is prepared by growing the organism in modified Cohen-Wheeler Broth. A single 0.5 mL dose contains 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxid, and no more than 16 opacity units of *Bordetella pertussis.* Aluminum phosphate is contained in the final product at a concentration not greater than 0.8 mg per mL.

2. *Labeling*—a. *Recommended use/indications.* The package circular recommends this preparation for the simultaneous primary immunization of infants and children under 6 years of age against diphtheria, tetanus, and whooping cough, and for booster innoculations for this age group. Four 0.5 cc doses given intramuscularly are recommended, 3 doses at 4- to 6-week intervals with the fourth dose approximately 1 year later. A booster dose of 0.5 cc is recommended at 4 to 6 years of age (preferably at time of school entrance).

b. *Contraindications.* This product is not recommended for use in children over 6 years of age, nor for use in adults at any time. An acute febrile illness is considered an indication to defer immunization. The labeling states that neurologic disorders in infants and children do not now appear to be a sufficient reason for withholding immunization. If an unusual neurological response to any given dose is observed, the physician is advised to proceed with caution using fractional doses of antigens or deferring immunization until the child is at least 1 year of age. Corticosteroids are mentioned as having an immunosuppressive effect, and it is suggested that a booster dose be given 1 month or more after such therapy is discontinued.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data regarding human immunogenicity or efficacy are provided in the submission. A number of reprints of reviews are included, all of which attest to the general safety and efficacy of DTP preparation in humans.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data regarding human safety are presented. References are made to the general body of knowledge supporting the safety of DTP products, but none provide specific data regarding the Lederle DTP, adsorbed product (Ref. 4a).

The manufacturer's marketing experience is listed in general terms only. In the past 5 years a few million doses of this DTP have been distributed. During that time, 62 complaints were received by the producer, but these are not detailed. It is noted that the main

complaints have been pain on injection, local erythema, and febrile reactions in some instances including convulsions. No deaths are reported.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization cannot be determined with certainty, owing to the lack of human data on immunogenicity. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* The major problem apparent in a review of this product is the lack of satisfactory evidence for the immunogenicity of the diphtheria and tetanus components of this vaccine, when used in primary immunization.

The labeling is in general satisfactory, but should be revised and updated along the lines suggested by this Panel in the Generic Statement on Labeling.

5. *Recommendation.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This product consists of 10 Lf of diphtheria toxoid, 7.5 Lf of tetanus toxoid, 10 opacity units of thimerosal-killed pertussis bacilli suspended in culture supernatant, 1.0± 0.35 mg of aluminum phosphate, and 1:10,000 thimerosal in each immunizing dose of 0.5 mL. The pertussis component consists of 4 protective units per dose.

The pertussis vaccine is prepared from the growth of multiple Phase I cultures on the casein hydrolysate medium of Cohen and Wheeler.

2. *Labeling*—a. *Recommended use/indications.* The preparation is recommended for primary immunization of infants and children up to the age of 6 years. It is recommended that immunization start at the age of 2 to 3 months of age. Three intramuscular injections of 0.5 mL are given at intervals of at least 4 to 6 weeks. The third injection should be followed approximately 1 year later by a fourth injection to complete the basic series.

Reimmunization is recommended (0.5 mL) at the age of 4 to 6 years.

Emergency booster doses are recommended on serious exposure to pertussis if a booster dose of DPT has not been given within the preceding year.

b. *Contraindications.* Any respiratory or other acute infection is reason for deferring injection. If marked or systemic reactions follow the first dose, subsequent doses should be decreased to 0.1 mL and repeated every 4 weeks. If the child to be immunized has central nervous system abnormalities, the initial and subsequent doses should not exceed 0.1 mL per injection.

The risk of encephalopathic symptoms is described, but the package insert does not specifically advise that no further pertussis vaccine shoud be given if such symptoms occur after the first injection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* McComb (Ref. 5) studied immune response in infants given 3 doses of Massachusetts Public Health Biologic Laboratories' DTP vaccine. Unfortunately no serological specimens were taken before immunization. More than 60 children were tested for diphtheria and tetanus antitoxin after immunization and all had titers in excess of 0.1 unit. Eighty-four percent of 38 children under 2 years of age and 61 percent of children over 2 years of age had pertussis agglutinin titers of 1:320 and over after immunization. Provenzano (Ref. 6) studied 66 infants age 3 to 28 months who were given 3 doses of Massachusetts Public Health Biologic Laboratories' DTP vaccine. The geometric mean titer 3 months after injection was 109 agglutination units. Infants given more than 3 doses, including some plain pertussis vaccine, had titers almost twice as high. Serological data from this study are presented in more detail by Levine (Ref. 7), including information on individual serological responses. (Eight of 48 children had no pertussis agglutinin after the recommended schedule; the log titers varied between 1.6 and 2.8.)

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the study of McComb (Ref. 5), the rate of febrile reactions was less than 10 percent and that of irritability 7 to 13 percent. In the study of Provenzano (Ref. 6), the rates of reactions also appeared acceptable.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

d. *Labeling.* Labeling generally conforms to the Public Health Service Advisory Committee on Immunization Practices recommendations. The label should clearly state that should a child experience convulsions, shock, encephalopathy, or thrombocythemia following an injection of DTP, the child should receive no further pertussis vaccine, but subsequent immunizations should be given with DT only.

4. *Critique.* A multitude of published studies demonstrate the efficacy of this product. The package insert does not define the risk of giving additional pertussis vaccine to a child who has previously had a severe reaction to pertussis vaccine.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with the recommendations of this Report.

Diphtheria and Tetanus Toxoids and Perstussis Vaccine Adsorbed Manufacturd by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This manufacturer maintains a single license for two preparations of diphtheria and tetanus toxoids and pertussis vaccine. The first, apparently the older of the two products, is prepared by precipitating all three antigens with alum prior to combination, and contains 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, and 12 opacity units of pertussis vaccine per 0.5 mL dose. The second product is prepared by combining diphtheria and tetanus toxoids, absorbed, onto aluminum phosphate, with pertussis vaccine. This preparation contains 15 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid with 12 opacity units of pertussis vaccine per 0.5 mL dose. Each preparation contains 4 protective units of pertussis vaccine per dose.

2. *Labeling*—a. *Recommeded use/indications.* The recommendations for the use of these two preparations differ slightly from each other, but both are acceptable by the standards of current immunization advisory groups. For each, 0.5 mL intramuscular doses are recommended, beginning before 2 months of age and separated by at least 1 month. Reinforcing doses are recommended 1 year later and between 3 and 5 years of age.

b. *Contraindications.* It is recommended that further injections of the preparation not be given if a neurologic reaction to the vaccine

occurs. It is also recommended that elective immunization be deferred during an epidemic of poliomyelitis. The recommendations for the alum precipitated preparation are dated nearly 17 years ago and those for the aluminum phosphate adsorbed preparation nearly 14 years ago.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* These products met Federal requirements when manufactured.

(2) *Human.* Data are not available.

b. *Safety*—(1) *Animal.* These products met Federal requirements when manufactured.

(2) *Human.* These products were marketed for nearly 12 years through 1964, during which time many million doses were distributed. There were 132 reports of reactions, none of which was said to be significant.

C. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined in the absence of efficacy data in humans.

4. *Critique.* This combined diphtheria and tetanus toxoid and pertussis vaccine is apparently licensed in two forms, one of which is alum precipitated, and the other of which is aluminum phosphate adsorbed. Neither has been marketed since 1964. Efficacy data related to this product are not available.

5. *Recommendations.* The Panel recommends that these products be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because these products are not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This trivalent fluid vaccine contains, per each 0.5 ML dose, 10 Lf of diphtheria toxoid, 2 Lf of tetanus toxoid, not more than 20 opacity units of pertussis vaccine, and 1:10,000 thimerosal as a preservative, suspended in isotonic saline. Each dose contains 4 protective units of pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the active immunization of infants and young children against diphtheria, tetanus, and pertussis simultaneously. Three intramuscular doses of 0.5 mL each are recommeded at 4- to 6-week intervals beginning age 2 or 3 months with a reinforcing dose 1 year later. The manufacturer does not specify preference for the fluid or adsorbed product.

b. *Contraindications.* An acute illness is considered reasons to defer immunization with this product. It is also recommended that routine immunization with this product not be given if the child exhibits a personal or family history of central nervous system disease or convulsions. There is also a warning about immunization during an epidemic of poliomyelitis. The occurrence of any type of neurologic symptom or sign following the administration of this product is considered an absolute contraindication to further use.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No human efficacy data are available for this trivalent fluid vaccine.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Six reports of adverse reactions, all of minor consequence, were received by the manufacturer during a 5-year period when many hundred thousands of dose of this vaccine were distributed.

c. *Benefit/risk ratio.* The risk from this product appears to be minor; in the absence of human efficacy data for primary immunization, the benefit-to-risk assessment cannot be determined with precision. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* This combined fluid preparation for immunization against diphtheria, tetanus, and pertussis appears to meet Federal regulations for efficacy and safety in animals and appears to be safe for humans. However, data regarding its immunogenicity in man are not available.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This trivalent product for immunization against diphtheria, tetanus, and pertussis contains, per each 0.5 mL dose, 6.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and not more than 15 opacity units of pertussis vaccine, adsorbed, with aluminum potassium sulphate. Each dose contains 4 protective units of pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the active immunization of infants and young children against diphtheria, tetanus, and pertussis simultaneously. Three doses of 0.5 mL each intramuscularly are recommend at 4- to 6-week intervals beginning at age 2 or 3 months with a reinforcing dose administered 1 year later.

b. *Contraindications.* An acute illness is considered reason to defer immunization with this product. It is also recommended that routine immunization with this product not be given if the children exhibits a personal or family history of central nervous system disease or convulsions. There is also a warning about immunization during an epidemic of poliomyelitis. The occurrence of any type of neurologic symptom or sign following the administration of this product is considered an absolute contraindication to further use.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

2. *Human.* The efficacy of this product was satisfactorily established by a 1950 study (Ref. 8) in which 100 infants were immunized and subsequently evaluated for the presence of immunity to diptheria, tetantus, and pertussis. Serologic responses were measured in 20 to 25 children for each of the vaccine components; all children studied had satisfactory respones to primary immunization.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the 1950 study (Ref. 8) of 100 infants given more than 300 injections of this product, no serious systemic or local reaction was observed. During the 5 years, 1968 through 1972, many million doses of this preparation were marketed, during which time 47 adverse reactions were reported. Four of these were serious, including three deaths, one of which was ascribed to an

anaphylactic reaction. There was one case of encephalitis.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This is a widely used trivalent preparation for immunization of young infants and children against diphtheria, tetanus, and pertussis which appears to be associated with significant reactions very rarely and which has been shown to be efficacious in humans.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Manufactured by Parke, Davis & Co.

1. *Description.* This product consists of a saline suspension of 12 protective units of pertussis vaccine (in three 0.5 mL doses) together with 50 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid per 0.5 mL dose in 0.9 percent saline solution with 0.01 percent thimerosal as a preservative. It is presumably derived from the same mixture of selected strains of *Bordetella pertussis* as are used in the monovalent fluid vaccine.

2. *Labeling*—a. *Recommended use/indications.* For immunization of infants against diphtheria, tetanus, and pertussis starting at age 6 weeks to 3 monhs, give three 0.5 mL doses intramuscularly 4 weeks apart with a reinforcing dose 1 year later and a booster at age 3 to 6 years, or as a precaution in the presence of actual or potential exposure. For wound boosters, the use of tetanus toxoid or tetanus diphtheria toxoid is preferred. (Mention of the possible use of this product for rapid immunization should be deleted.)

b. *Contraindications.* This product is contraindicated in the presence of thrombocytopenia. When a patient is on immunodepressant therapy immunization should be deferred.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Only market experience is cited which suggests no problem.

c. *Benefit/risk ratio.* The benefit-to-risk assessment appears to be satisfactory when used for booster immunization since this product is typical of a vaccine that has been widely and successfully used with no unusual incidence of reactions (but it should be noted that recent English studies suggest that reactions are fewer with the adsorbed vaccine). For primary immunization the risk appears to be low; data relating to the efficacy of this agent for primary immunization are not available and accordingly benefit-to-risk assessment cannot be established with precision.

4. *Critique.* This is a classical fluid DTP with no adverse data reported and a history of extensive marketing, but no quantitative data on reactions and limited data on marketing experience are provided. On the basis of official tests and general experience the product appears acceptable, provided human data on efficacy are furnished. The extremely high dose of diphtheria toxoid should be justified or modified.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This product contains 4 protective units of pertussis vaccine, 15 Lf of diphtheria toxoid, and 5 Lf of tetanus toxoid per 0.5 mL dose. The antigens are adsorbed on aluminum phosphate in 0.9 percent saline solution. Thimerosal 0.01 percent is added as a preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is presented as providing efficient, convenient, and rapid immunization against the three diseases in question. Immunization is started at 6 weeks to 3 months with 3 doses of 0.5 mL each given 4 to 6 weeks apart and a reinforcing dose 1 year later. All injections are intramuscular. A booster is recommended at age 3 to 6 years or in the presence of actual or potential exposure, if 1 year or more has elapsed after the last dose.

b. *Contraindications.* Not recommended for children over 6 years, and should be deferred in children receiving immunodepressants or having acute illness. There is no mention of thrombocytopenia or encephalopathy as problems or contraindications.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The data provided by the manufacturer for its quadrivalent DTP poliomyelitis vaccine show satisfactory immunogenicity when used for primary immunization. (See the review of the quadrivalent product.)

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* This product appears to be somewhat more reactive than might be expected (see Table 4 and section VC2 of manufacturer's data submission (Ref. 9)) but yardstick for evaluation is not apparent. Reported reactions for market experience appear within reasonable limits.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This is a classical adsorbed DTP which has been widely used with little adverse experience reported. It is prepared by well-established methods, tested for laboratory potency by a well-validated method, and appears only slighty more reactive than the ideal preparation. It seems acceptable for release as safe and effective, although comparative reactive data would be desirable as would information on the significance of the strains used in the pertussis vaccine component.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccines Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This is a quadrivalent product containing per 0.5 mL dose 15 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 12.5 opacity units of *Bordetella pertussis* suspension, and poliomyelitis vaccine, trivalent, antigenically equivalent to 1 mL of fluid poliomyelitis vaccine. The poliomyelitis component is prepared from Type 1, 2, and 3 poliovirus grown in monkey kidney tissue culture, and inactivated with formaldehyde and supplemental ultraviolet irradiation. Each dose further contains 32.5 mcg of protamine sulfate,

2.5 mg of aluminum phosphate, 0.0125 mg of benzethonium chloride as a preservative, and is adjusted to pH 7.0. A 0.5 mL dose further contains up to 0.00000025 unit of penicillin, and 1 unit of streptomycin. The antibiotics are used in propagating polio virus for the manufacturing process and are thus present in only trace amounts.

The protamine sulphate is apparently present in the vaccine as an aid to the aluminum phosphate adsorption. All four components of the vaccine are adsorbed on the aluminum phosphate.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the primary immunization of infants beginning at an unstated age and children up to the age of 6 years against diphtheria, tetanus, pertussis, and poliomyelitis. An initial series of three 0.5 mL doses is recommended intramuscularly at 4- to 6-week intervals, followed by an additional dose of the quadrivalent product or poliomyelitis vaccine alone after 6 to 12 months. If immunization was begun in infants under 3 months of age, four 0.5 mL doses are recommended in the initial series.

b. *Contraindications.* No absolute contraindications are listed. Local and febrile reactions are noted, and the labeling advises that in instances of marked reactions, immunization may be completed with monovalent antigens, and warns that if there are encephalopathic symptoms, further injections of products containing pertussis vaccine are contraindicated.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* There is extensive documentation of the immunogenicity of the quadrivalent product in humans. The data obtained in the first major clinical trial was summarized by Barrett (Ref. 10). The lots used in this initial trial, however, were significantly substandard in potency of the pertussis component. Accordingly, a second major clinical trial was conducted in the years 1959 to 1960, using at various times both research and production lots of the quadrivalent product. These trials involved several hundred children, and a great deal of detailed data are provided to substantiate the immunogenicity in humans of all four components of this product.

In summary, there is substantial evidence of the human immunogenicity of all four components of this product when used as recommended.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* One study of the quadrivalent product is cited in the manufacturer's submission (Ref. 11) in which 851 children were studied, presumably in the course of primary immunization. There were 30 reactions possibly due to the immunization procedure, including 16 instances of tenderness at the injection site, 10 of fever, and 4 of rash. In the booster phase of the study, six instances of local or febrile reactions were reported. In another study of reactivity of the quadrivalent product, 50 children from Jamaica between the ages of 3 and 5 months were given an initial dose of 1 of 3 lots of this product. Although the criteria are not absolutely clear, 12 of the 50 children were described as having a significant local reaction, and 17 of the 50 children were described as having a significant systemic reaction. Eight children had erythema, 22 had induration, 11 complained of mild to moderate pain, none had severe pain, 19 had mild to moderate degrees of swelling, and 32 had some fever during the first 48 hours. No severe reactions were reported.

The submission (Ref. 11) further notes four instances of severe reaction, three of which included convulsions, reported during the years 1959 to 1963. A letter from a private physician, dated September 25, 1967, notes that physicians in the Boston area generally considered that the quadrivalent product had a higher frequency of minor reactions than was true of the trivalent product. In summary, however, adequate substantiation of the human safety of this product is provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This product is unique in that analysis of the producer's submission presents a strikingly different set of problems from those encountered with other diphtheria-pertussis-tetanus products. The submission clearly provides satisfactory evidence of safety and immunogenicity when used for primary immunization in humans.

Nevertheless, the last lot of this product was released in the year 1968, and the labeling is by now strikingly out-of-date with current practice and recommendations.

There is little doubt that there is still a role for killed poliomyelitis vaccine in selected patients, but there is clearly not a major role as long as live oral poliomyelitis vaccine remains an accepted part of public health practice in the United States. This product therefore exemplifies an ironic circumstance in which there is adequate documentation of safety and efficacy, yet little if any use in preventive medical practice.

5. *Recommendations.* The panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Poliomyelitis Vaccine Manufactured by Parke, Davis & Co.

1. *Description.* This unique quadrivalent product was designed to solve the stability problem that developed when DTP and killed poliomyelitis vaccine were mixed together in a single vial. This product consists of a dual chambered disposable syringe, preloaded with 1 dose each of killed poliomyelitis vaccine and DTP, adsorbed. For maximum stability the two components are physically separated in the preloaded syringe.

The composition of the DTP component is the same as Parke-Davis Quadrigen. The poliomyelitis component is concentrated in a 0.3 mL dose, and contains 8.3 mcg of formalin, less than 0.0000005 unit of penicillin, and less than 8.3 mcg of streptomycin. Benzethonium chloride 0.008 mg is added as a preservative.

2. *Labeling*—a. *Recommended use/indications.* Most of the labeling detailed the action of the preloaded double chambered bypass syringe. The recommended use and indications are otherwise the same as in the Quadrigen label.

3. *Critique.* All additional comments under labeling, analysis, critique, and recommendations are identical to those in the Parke-Davis Quadrigen submission and review (Ref. 12). This product has similarly not been released since the year 1968, and all discussion and recommendations about Quadrigen apply with equal validity to this product.

4. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Texas Department of Health Resources

1. *Description.* The product contains approximately 17.5 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid, and not more than the equivalent of 16 opacity units of pertussis per each

immunizing dose of 0.5 mL dose. The adjuvant is aluminum hydroxide, not to exceed 1.2 mg per mL, and the preservative is thimerosal 1:10,000. The total human immunizing dose contains 12 units of pertussis antigen.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for all infants for primary immunization, starting at 2 to 3 months of age. The initial course consists of three intramuscular injections given at not less than 1 month and preferably not more than 3-month intervals, followed by a reinforcing dose given about 12 months following the third dose. Injections are to be given intramuscularly preferably into the midlateral muscles of the thigh or the deltoid. In children over 6 years of age, the single antigens or tetanus and diphtheria toxoids adsorbed (for adult use combined antigen) is preferred. A routine booster of DTP is recommended at 3 through 6 years of age. For exposure recall, the tetanus toxoid fluid is recommended.

b. *Contraindications.* Any respiratory or acute infection is reason for delaying immunization.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The decline of the morbidity curves for diphtheria, tetanus, and pertussis in relation to introduction of vaccines in Texas is given as evidence of efficacy (Ref. 13). The Panel considers this evidence insufficient as proof of efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Since the introduction of this DTP vaccine in 1959 and the distribution of a few million doses, 17 reports of reactions have been received. The complaints have concerned fever but also contain the following report evidently from a single clinic: "High incidence of severe reactions; 20 to 30 percent of those immunized had severe reactions with cyst formation."

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization would be satisfactory if human efficacy is demonstrated and is satisfactory for booster immunization.

d. *Labeling.* The recommendations generally follow those of the Public Health Service Advisory Committee on Immunization Practices and are in general adequate except that there appears to be a misprint "tetanus and diphtheria toxoids absorbed" instead of adsorbed. The choice of fluid tetanus toxoid instead of adsorbed toxoid for exposure recall is questionable.

4. *Critique.* The major shortcoming is the lack of documentation of efficacy of this particular product; more specifically data on serologic response are lacking. The report of "20 to 30 percent of those immunized had severe reactions with cyst formation" (Ref. 13) requires some clarification.

Data on efficacy as reflected in serologic response are needed. Better observations could be made of vaccine reactions. Information on serological types of pertussis used in manufacturing may be of interest in view of recent data from Britain.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This product is a combination of purified tetanus and diphtheria toxoids and killed *Bordetella pertussis* cells adsorbed on aluminum phosphate adjuvant. The pertussis vaccine is prepared from strains providing serotype antigens 1 through 6 grown on a charcoal-agar modification of Cohen-Wheeler medium. The bacteria are killed and detoxified by heating at 56° C for 30 minutes. Each 0.5 mL dose of vaccine contains 7.5 Lf diphtheria toxiod, 5.0 Lf tetanus toxoid, and not more than 16 opacity units of pertussis vaccine. The preservative is thimorosal. The total human dose (1.5 mL) contains 12 antigenic units of pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization of infants and children through 6 years of age against diphtheria, tetanus, and pertussis. Recommendations for dosage and administration follow Public Health Services Advisory Committee on Immunization Practices' recommendations.

b. *Contraindications.* Defer use in acute respiratory infections or other active infections or during outbreaks of poliomyelitis. Immunization of infants with cerebral damage should be delayed until after 1 year and then single antigens in fractional doses should be employed. The occurrence of any type of neurological symptoms or signs after injection is said to be an absolute contraindication to further use.

3. *Analysis*—a. *Efficacy*—(1). *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data for this manufacturer's product were submitted. Claims for efficacy are baed on citations of relevant literature for this type of product (Ref. 14).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data dealing with this product were submitted. No reference to marketing experience or complaint file information was included.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization would be satisfactory if human efficacy is demonstrated, and is satisfactory for booster immunization.

d. *Labeling.* The labeling is adequate and straightforward. It has not been revised since 1970, and could perhaps be updated slightly although no serious problems exist.

4. *Critique.* The submission [Ref. 14] is lacking in specific information relative to human safety and primary immunogenicity of this manufacturer's product. There is no basis for immediate concern at this lack of information but it should be obtained in due course.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions in accord with this Report are recommended.

The Panel also recommends that data on the reactogenicity of this specific product be collected and made available to the Bureau of Biologics.

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Generic Statement

Anthrax Vaccine, Adsorbed

Anthrax is an acute bacterial disease caused by *Bacillus anthracis*. The reservoir is any of several animal species (cattle, sheep, goats, horses, pigs) and the organism produces extremely resistant spores which may persist in soil and contaminate animals or their products. The disease is primarily an occupational hazard for industrial workers who process hides, hair (especially goat), bone meal, and wool, as well as for veterinarians and agricultural workers who may contact infected animals.

Most infections are cutaneous; if untreated they may spread to regional lymph nodes and may cause a fatal septicemia. Primary inhalation and gastrointestinal infections do occur, but with low frequency, and are highly fatal.

Description of Product

Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonproteolytic, nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*. It contains no more than 0.83 mg aluminum per 0.5 mL dose, 0.0025 percent benzethonium chloride as a preservative, and 0.0037 percent formaldehyde, which is believed to act as a stabilizer.

The product is tested according to the Public Health Service regulations for biological products and specific additional standards for anthrax vaccine. In addition to tests for general safety and sterility, the product is subjected to a potency assay of its protective activity in guinea pigs, which are challenged with virulent *Bacillus anthracis*.

Indications and Contraindications

Immunization with this vaccine is indicated only for certain occupational groups with risk of uncontrollable or unavoidable exposure to the organism. It is recommended for individuals in industrial settings who come in contact with imported animal hides, furs, wool, hair (especially goat hair), bristles, and bone meal, as well as laboratory workers involved in ongoing studies on the organism.

Contraindications to its use include:

1. A history of clinical anthrax infection which may enhance the risk of severe reactions.

2. Severe systemic reactions with marked chills and fever following a prior injection—in this case further attempts at immunization should be abandoned.

3. The presence of acute respiratory disease or other febrile illnesses in order not to confuse the cause of further fever.

4. Therapy with corticosteroids or other immunosuppressive agents—in this case immunization should be deferred until such therapy is completed. If on long-term therapy, a more intensive immunization schedule should be considered.

Safety

In general, safety of this product is not a major concern, especially considering its very limited distribution and the benefit-to-risk aspects of occupational exposure in those individuals for whom it is indicated. Local reactions are typically mild, with erythema and slight local tenderness for 24 to 48 hours. Some individuals may have more severe local reactions with edema, erythema greater than 5 x 5 cm, induration, local warmth, tenderness, and pruritus. Only a few systemic reactions with marked chills and fever have been recorded. All reactions reported have been self-limited.

Efficacy

The best evidence for the efficacy of anthrax vaccine comes from a placebo-controlled field trial conducted by Brachman (Ref. 1) covering four mills processing raw imported goathair into garment interlinings. The study involved approximately 1,200 mill employees of whom about 40 percent received the vaccine and the remainder received a placebo or nothing. The average yearly incidence of clinical anthrax in this population was 1 percent. During the evaluation period, 26 cases of anthrax occurred. Twenty-one had received no vaccine, four had incomplete immunization and one had complete immunization. Based on analysis of attack rates per 1,000 person-months, the vaccine was calculated to give 93 percent (lower 95 percent confidence limit = 65 percent) protection against cutaneous anthrax based on comparison with the control group. Inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease.

The Center for Disease Control has continued to collect data on the occurrence of anthrax in at-risk industrial settings. These data were summarized for the period 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of this product.

Special Problems

Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented. This question is not amenable to study due to the low incidence and sporadic occurrence of the disease. In fact, the industrial setting in which the studies above were conducted is vanishing, precluding any further clinical studies.

In any event, further studies on this vaccine would receive low priority for available funding.

Recommendations

The Panel believes that there is sufficient evidence to conclude that

anthrax vaccine is safe and effective under the limited circumstances for which this vaccine is employed.

Reference

(1) Brachman, P. S., H. Gold, S. A. Plotkin, R. Fekety, M. Werrin, and N. R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," *American Journal of Public Health*, 52:632–645, 1962.

SPECIFIC PRODUCT REVIEW

Anthrax Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* Anthrax vaccine adsorbed is an aluminum hydroxide adsorbed preparation of protective antigen of *Bacillus anthracis*. The product is prepared from a sterile filtrate of a microaerophilic culture of an avirulent, nonproteolytic, nonencapsulated strain. The product contains 0.83 mg of aluminum per single human dose (0.5 mL) and is preserved with 0.0025 percent benzethonium chloride. Not more than 0.0037 percent formaldehyde is added as a stabilizer.

2. *Labeling*—a. *Recommended use/indications.* This product is intended solely for immunization of high-risk of exposure industrial populations such as individuals who contact imported animal hides, furs, bone meal, wool, hair (especially goat hair), and bristles. It is also recommended for laboratory investigators handling the organism. Primary immunization consists of 6 subcutaneous 0.5 mL injections at 0, 2, and 4 weeks and 6, 12, and 18 months. Subsequent boosters at yearly intervals are recommended.

b. *Contraindications.* Prior anthrax infection is an absolute contraindication. Immunization should be avoided in acute respiratory disease or other active infections. Corticosteroid therapy may suppress response. Further immunization should be discontinued in those rare individuals who suffer severe systemic reactions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman (Ref. 1) in a placebo-controlled field trial in mills processing imported goat hair. This vaccine appeared 93 percent protective (lower 95 percent confidence limit = 65 percent protective) against cutaneous anthrax. No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence. The Michigan Department of Public Health vaccine is patterned after that of Merck Sharp & Dohme with various minor production changes. It has been distributed by the Center for Disease Control since 1966, first as an investigational new drug and since 1972 as a licensed product. A review of the Center for Disease Control data pertinent to this product for the period 1962 to 1974 in at-risk industrial settings indicates that no cases have occurred in fully immunized workers (see Generic Statement).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Accumulated data for the Center for Disease Control suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare.

c. *Benefit/risk ratio.* This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory under the prevailing circumstances of use.

d. *Labeling.* The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24(a) (21 CFR 620.24(a)) defines a total primary immunizing dose as 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months).

4. *Critique.* This product appears to offer significant protection against cutaneous anthrax in fully immunized subjects. This is adequately established by the controlled field trial of the very similar Merck Sharp & Dohme experimental vaccine and by the Center for Disease Control surveillance data conducted on industrial high-risk settings.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Reference

(1) Brachman, P. S., H. Gold, S. A. Plotkin, R. Fekety, M. Werrin, and N. R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," *American Journal of Public Health*, 52:632–645, 1962.

Generic Statement

BCG Vaccines

Tuberculosis is a communicable disease of world-wide importance caused by *Mycobacterium tuberculosis*. The disease typically involves the lungs, but is capable of causing disease in any organ system of the body. The World Health Organization estimates the number of infectious cases of tuberculosis in the world today to be in the range of 15 to 20 million.

Tuberculosis has declined sharply in the United States during the past several decades. United States Public Health Service data indicate that in 1953 there were 84,000 new cases of tuberculosis and 19,700 deaths due to tuberculosis; in 1977 there were only 31,145 new cases and the number of tuberculosis deaths had declined to 3,000. Factors contributing to the observed decline in tuberculosis morbidity and mortality include the gradual increase in socioeconomic level that has characterized the U.S. economy, improved nutrition, the introduction of effective chemotherapy of active tuberculosis, and the increasing use of isoniazid in preventive therapy. There remain, however, localized foci or "pockets" of tuberculosis transmission in the United States, particularly in areas in which preventive medical services are suboptimal or cannot be adequately delivered.

In many other countries, the use of BCG vaccine is credited with a major role in reducing tuberculosis morbidity. BCG vaccination has been the major thrust of the World Health Organization's efforts to control tuberculosis in countries with high rates of transmission of the disease. Although available in the United States, this product has been used but little for the prevention of tuberculosis.

BCG vaccines posed a particular problem for the Panel, owing to the widely disparate results of controlled field trials, and the lack of a reproducible animal model which accurately reflects protective efficacy in humans.

1. *Rationale for vaccination against tuberculosis.* Earlier in this century, a large majority of people became infected with tubercle bacilli as demonstrated by skin test positivity. However, only a small proportion of those who were infected developed overt tuberculous disease. Most people who were infected appeared to have acquired a degree of resistance against developing overt tuberculosis upon subsequent exposure, which, earlier in this century, was frequent and virtually unavoidable.

Immunity in tuberculosis is now much more easily understood in terms of modern immunologic concepts, and the "unitary concept" of the pathogenesis of tuberculosis in man is generally accepted. Thus, primary infection with tubercle bacilli results in specific sensitization of host cell-mediated immune mechanisms, and is reflected clinically in the ability to elicit a positive tuberculin skin test. If the primarily infected person has received a large dose of tubercle bacilli, or if his cell-mediated immune mechanisms do not, for one reason or another, respond optimally, the individual may go on to develop overt clinical tuberculosis. Most frequently, however, the tuberculous infection is localized by the host cell-mediated immune mechanisms, resulting in a dormant or latent infection which may (a) remain dormant for life, or (b) disappear and reactivate at some time in the future. Reactivation is frequently but not invariably associated with conditions known to impair host cell-mediated immune mechanisms, such as immuno-suppressive therapy, certain malignancies, or malnutrition.

There is abundant clinical and experimental evidence that tuberculin positivity, reflecting activated cell-mediated immune mechanisms, is associated with protection against exogenous exposure to tuberculosis. Such individuals are, however, at risk of reactivation or "breakdown" tuberculosis. Tuberculin negative individuals are susceptible to primary infection, but by definition are not at risk of "reactivation" tuberculosis. The disease may be spread by individuals with primary infection, reinfected susceptible individuals, or those with reactivation tuberculosis.

The use of BCG vaccine, an attenuated strain immunologically closely related to virulent *Mycobacterium tuberculosis*, attempts to gain the advantage of protection conferred by activated host cell-mediated immune mechanisms without risking progressive disease in man.

2. *History of BCG vaccine.* The bacillus of Calmette and Guerin, known as BCG, was originally derived from a virulent strain of *Mycobacterium bovis*, attenuated by 231 serial passages over a period of 13 years on beef-bile-containing medium. The early studies of Calmette and Guerin indicated that animals immunized with this culture developed increased resistance to a challenge dose of virulent tubercle bacilli. BCG vaccine was first administered by mouth to newborn infants in 1921. Since then the vaccine has been administered to more than 500 million persons of all ages.

The organism was maintained by serial passage at the Pasteur Institute, and in the decades following its description, was subcultured and distributed to hundreds of laboratories in many countries. In those laboratories, many of which produced their own BCG vaccines, the strain was similarly maintained by serial subculture. It became apparent in the mid-1950's that serial subculturing in many different laboratories on differing media had resulted in the production, by inadvertent selection, of many different "daughter" BCG strains which differed, sometimes widely, in gross morphology, growth characteristics, biochemical activity, sensitizing potency, and even animal virulence. Nor was it possible, of course, to carry out direct comparisons of any of the BCG "daughter" strains to the original bacillus of Calmette and Guerin. In the last two decades most production laboratories producing BCG vaccine have adopted a seed lot system, maintaining production strains in a lyophilized state, in an attempt to minimize the genetic variation that is unavoidable in serial subculture. The production strains are generally named by the city in which the production laboratory is located, e.g., Paris, Copenhagen, London, Montreal, Rio de Janeiro, etc. Thus, there is no single BCG vaccine; there are, rather, dozens of different BCG "daughter" vaccines.

Description and Production of BCG Vaccine

The proper name of this product is BCG vaccine, and consists of a freeze-dried preparation containing live bacteria of the bacillus of Calmette and Guerin, an attenuated strain of *Mycobacterium bovis*. The Strain must have been maintained in the form of a primary seed lot, the basic material from which secondary seed lots are prepared. Vaccine production may be either from primary or secondary seed lots. The source of the strain used in vaccine manufacture is not specified in current Federal requirements, which state only that the source of the vaccine shall be identified by complete historical records.

In most production laboratories, the bacilli are grown as a pellicle on the surface of liquid Sauton medium, or dispersed throughout Sauton medium. An early harvest, 6 to 9 days, is considered important for good survival after freeze-drying. After filtering and pressing, the semi-dry mycobacterial mass is homogenized at a controlled temperature, diluted, and subsequently freeze-dried.

Routine quality control carried out by production laboratories includes an identity test, test of contamination, safety test in guinea pigs, estimate of total bacillary mass by opacity and dry weight, viability determined by oxygen uptake, germination rate, or colony count, and tests of heat stability. Such routine tests are particularly important for ensuring batch-to-batch uniformity.

The Panel is cognizant of the proposed new standards for BCG vaccine published in the **Federal Register** of March 18, 1974 (39 FR 10158-10160). These standards define the necessity of demonstrating that production lots of BCG vaccine are incapable of producing progressive tuberculosis in guinea pigs, and induce tuberculin skin test positivity using 5 to 10 units of tuberculin purified protein derivative (PPD) in 90 percent of persons, previously tuberculin negative, given BCG vaccine. In addition to the clinical requirement for tuberculin skin test conversion, potency testing is required by a determination of the number of colony forming units, and the intradermal guinea pig test (Jensen's test). (Note: In the **Federal Register** of March 13, 1979 (44 FR 14541), FDA issued final standards for BCG vaccine based on its proposed regulations issued March 18, 1974.)

Indications and Contraindications

This has long been a controversial issue in the United States. The recommended use of BCG vaccine is to prevent tuberculosis, but controversy has arisen when attempts were made to define the groups of individuals or populations that would benefit from BCG vaccination.

The recently published recommendations of the Public Health Service Advisory Committee on Immunization Practices with regard to BCG vaccines read as follows (Ref. 1):

Thorough application of modern methods of case detection, chemotherapy, and preventive treatment can be highly successful in controlling tuberculosis. Nevertheless, an effective BCG vaccine may be useful under certain circumstances. In particular, BCG may benefit uninfected persons with repeated exposure to infective cases who cannot or will not obtain or accept treatment.

Specific recommendations—a. BCG vaccination should be seriously considered for persons who are tuberculin skin-test negative and who have repeated exposure to persistently untreated or ineffectively-treated, sputum-positive pulmonary tuberculosis.

b. BCG vaccination should be considered for well-defined communities or groups if an excessive rate of new infections can be demonstrated and the usual surveillance and treatment programs have failed or have been

shown not to be applicable. Such groups might exist among the socially disaffiliated and those without a regular source of health care, possibly including some alcoholics, drug addicts, and migrants. Groups such as health workers who may be at particular risk of exposure to unrecognized pulmonary tuberculosis should, where possible, be kept under surveillance for evidence of newly acquired tuberculous infection. It must be recognized that only the occurrence of new infections reflects whether transmission is actually occurring.

In other areas of the world, particularly in those countries in which there is greater transmission of tuberculous infection within the population, BCG vaccination is practiced on a much wide scale. In highly endemic countries, vaccination of all newborn infants is recommended.

Unquestionably, BCG vaccine plays a major role in the control of tuberculosis in many countries of the world. In a country such as the United States, in which transmission of tuberculosis is at a low level, BCG vaccine may properly be viewed as an adjunct to tuberculosis control, supplementing methods of case detection, chemotherapy, and preventive treatment in those limited segments of the population in which an excessive rate of new infections can be demonstrated and the usual surveillance and treatment programs have failed or cannot be readily applied. Tuberculin-negative persons unavoidably exposed in other parts of the world to populations in which there is significant tuberculosis transmission might also benefit from BCG vaccine.

Since BCG is a live mycobacterial vaccine, it should not be given to persons with impaired immune response, particularly impaired cell-mediated immune mechanisms, such as occurs with certain congenital immunodeficiency states, lymphoreticular malignancies, sarcoidosis, or when immunologic response has been suppressed with corticosteroids, alkylating agents, antimetabolites, or radiation.

Although no harmful effects of BCG on the fetus have been observed, it is probably prudent to avoid vaccination during pregnancy unless there is an excessive risk of unavoidable exposure to infective tuberculosis.

Safety of BCG Vaccine

The early history of BCG vaccination was tranished in 1930 by the Lübeck, Germany catastrophe, in which 72 of 251 infants died of tuberculosis following BCG vaccination. That disastrous episode was subsequently shown to be due to contamination of the vaccine by a strain of virulent tubercel bacilli. Excluding, Therefore, that episode, the safety of BCG vaccine has never been seriously contested. Progressive disease has occasionally been reported in immunosuppressed hosts, particularly in hosts with defects of cell-mediated immune mechanisms. In a summary of the world's literature through 1968, only 13 fatalities were cited as due to BCG vaccination (excluding the 72 fatalities noted above).

Efficacy of BCG Vaccination in Man

Table I presents, in summary form, the results of eight controlled trails of BCG vaccination against tuberculosis. A strikingly wide range of efficacy is seen, ranging from 0 to 80 percent. Three trials, those in Georgia (1947), in Georgia-Alabama (1950), and in Illinois (1947), showed no or very litte effect. The Puerto Rico trial (1958) and the South India trial (1968) showed mild to moderate degrees of protection. Finally, the trial in North American Indians (1953), Chicago infants (1961), and the Medical Research Council trial in Great Britain (1972) showed excellent protection.

These trials vary in composition of study groups, age at vaccination, methods of vaccine administration and dosage, and origin of vaccine strains.

TABLE 1—RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS [1]

Population group and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of followup (years)	Vaccination group	Number of subjects	Cases of tuberculosis		Protective efficacy (percent)
							No.	Rate [2]	
	1935–1938								
North American Indians (8 tribes) (Stein & Aronson (Ref. 2)).	0–20 years	Negative to 0.005mg PPD—Seibert (250 TU).	Henry Phipps Institute, Philadelphia.	9–11	Unvaccinated	1,457	238	1,563	80 [3]
					BCG	1,551	64	320	
	1937–1948				Unvaccinated	1,665	65	[4] 223	
Chicago infants, high-risk areas (Rosenthal (Ref. 3)).	Under 3 months	No initial tuberculin testing.	Tice Lab., Chicago [4].	12–23					75
					BCG	1,716	17	[4] 57	
	1947				Unvaccinated	2,341	3	11	
Georgia, school children (Comstock & Webster, (Ref. 5)).	0–6–17 years	Under 5 mm to 0.002 mg RT 18 (100 TU).	Tice Lab., Chicago [4].	20					None
					BCG	2,498	5	17	
	1947–1948				Unvaccinated	494	8		
Illinois, school for mentally retsrded (Bettag (Ref. 6)).	Adolescents and young adults.	Negative in 1/1000 and 1/100 OT.	Tice Lab., Chicago [4].	12					None
					BCG	531	12		
	1949–1951				Unvaccinated	27,338	73	43	
Puerto Rico, general population (Palmer (Ref. 7)).	1–18 years	Under 6 mm to 0.0002 mg RT 19–20–21 (10 TU).	State Dept. of Health, NY.	5½–7½					31
				(means: 6.3)	BCG	50,634	93	30	
	1950				Unvaccinated	17,854	32	13	
Georgia, Alabama, general population (Comstock & Palmer, (Ref. 8)).	5 years and over	Under 5 mm to 0.0001 mg RT 19–20–21.	Tice Lab., Chicago [4].	14					14
					BCG	16,913	26	11	
	1950–1952				Unvaccinated	12,699	240	126	
Great Britain, urban population (British Medical Research Council (Ref. 9)).	14–15½ years	Under 5 mm to 0.1 ml 1-100 Old Tuberculin (100 TU).	Staten's Serum-Institute Copenhagen.	15					78
					BCG	13,598	56	28	

TABLE 1—RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS [1]—Continued

Population group and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of followup (years)	Vaccination group	Number of subjects	Cases of tuberculosis		Protective efficacy (percent)
							No.	Rate [2]	
South India, rural population Frimondt-Moller (Ref. 10)).	1950–1955 All ages	Under 5 mm to 5 TU RT 19–20–21. [3]	BCG Lab., Madras	9–14	Unvaccinated	5,808	46	89	52
					(mean: 12.3) BCG	5,069	28	61	

[1] Adapted from: British Medical Research Council (1972) Bulletin of the World Health Organizations, 46:381.
[2] Annual rate per 100,000 population, usually allowing for losses from observations.
[3] The protective efficacy against death from tuberculosis was 82 percent for a period of 18–20 years (Aronson (Ref. 4)).
[4] This laboratory has issued a number of strains at different times and it is not known whether the strains used in these three trials were the same or not.
[5] Assuming a mean observation period of 17.5 years.

Methods of case detection have been particularly variable, and become critically important in those trials in which the detected incidence of tuberculosis in the control group was already quite low. For example, the British Medical Research Council trials used intensive followup with chest films, whereas most American trials relied primarily on reports from health departments.

How can such widely disparate results be explained, if at all? Among suggestions that have been put forward are that the differences stem from nutritional or from genetic differences between the populations involved. The nutritional differences do not tally particularly well with the variations found in efficacy, and there is insufficient information available to assess whether genetic differences might be responsible. Three other possibilities merit serious attention.

First is the explanation for the poor results found in the Georgia-Alabama trials by Palmer (Ref. 7) and his colleagues. Palmer suggested that in areas where nonspecific tuberculin sensitivity was common, as is true throughout much of the Southeastern United States, a large proportion of the population had already acquired some natural immunity against virulent tuberculous infection from a typical mycobacterial infections. In this situation, vaccination with BCG would only supplement the immunity that already existed and would not make as large an apparent contribution as in an area that was relatively free from atypical mycobacterial infections. This hypothesis has been experimentally supported in guinea pigs, showing that infection with other mycobacteria did indeed confer protection against subsequent virulent challenge. This protection, however, was always less than was conferred by BCG. Palmer suggested that this explanation could, at least in part, reconcile the widely differing findings of the Medical Research Council trial in Great Britain and that in the Southeastern United States.

Hart (Ref. 11), however, subsequently showed that while differences in the frequency of other mycobacterial infections could well have contributed to this difference, it would scarcely be the whole story. Hart calculated that if none of the subjects in the Georgia-Alabama trial had any natural protection from other mycobacterial infections, the apparent efficacy of the vaccine in that population would have risen from the actual 14 percent to only 25 percent. Hart postulated that some other influence must be operating, and suggested as an inescapable conclusion that the vaccine used in the Georgia-Alabama trial must have been less potent than the Danish strain used in the Medical Research Council trial.

This is, then, the second possibility that merits attention; namely, that different products all labeled as BCG may differ widely in their immunizing effect, and that this could be the main reason, or even the only one, for the mutually contradictory results of different BCG trials. The manufacturer of the vaccine used in the Georgia-Alabama trial has also claimed that vaccine was administered by inappropriate technique.

At this date, it is difficult if not impossible to ascertain whether the vaccines or the technique of administration or both were responsible for the divergent results noted in controlled field trials. There is independent evidence, however, that BCG strains used in vaccine production by the laboratory supplying vaccine for two of the field trials that showed no protection were very weak in terms of multiplication, allergenic potency, and protection in animals.

The third possibility is one recently suggested by Sutherland (Ref. 12). Sutherland has observed that areas with a high incidence of tuberculosis in the unvaccinated group showed a high efficacy of BCG vaccine, whereas those with a low incidence of tuberculosis in the unvaccinated group showed a low efficacy, suggesting that the efficacy of BCG may be greater in an area where there is much tuberculosis than in an area where there is only little. If this relationship is genuine, it suggests that superinfection of vaccinated subjects with virulent tubercle bacilli or other mycobacteria may be necessary to maintain the protection conferred by BCG vaccine. This concept is not without its parallels in other infectious diseases, but has not heretofore been suggested for tuberculosis and BCG vaccine. A review of the eight trials noted above demonstrates an association between the degree of protection and the degree of challenge.

All of the controlled field trials cited previously were carried out using liquid BCG vaccines. There have thus far been no field trials of freeze-dried BCG vaccines reported, though one is currently in progress in India. To date the only evidence supporting the efficacy in man of freeze-dried BCG vaccine is extrapolated from uncontrolled experience. The results suggest, but do not prove, that the freeze-dried vaccine prepared by Glaxo Laboratories is as effective in man as the liquid Copenhagen vaccine used in the Medical Research Council trial in Great Britain.

On the basis of presently available information, judgments concerning the safety and efficacy of BCG vaccines licensed for use in the United States must be made by inference from historical data plus whatever inference can be drawn from tuberculin conversion in man.

Special Problems

Marked differences in the immunogenic and sensitizing potency of BCG strains were demonstrated over 20 years ago. During continuous serial subculturing (the traditional way of maintaining strains prior to the introduction of seed lot systems), the emergence of mutant strains was unavoidable. Mutants that have a faster growth rate in vitro than do the parent cells can, in a relatively short period of time, emerge as the dominant strain.

There have been striking spontaneous changes in such attributes as morphology, pigmentation, rate of growth, and even in the ability to protect animals against experimental infection. In the case of such marked phenotypic change, the "daughter" strain can no longer be regarded as the same as the parent strain. Seed lot systems have been used to preserve BCG strains for little more than a decade. Thus, there is no single scientifically defined entity known as BCG vaccine; there are rather many different BCG vaccines, with varied biological characteristics and almost surely varied immunizing potency in man. Such a state of affairs is, to say the least, highly undesirable.

Evidence concerning the relative merits of various established BCG strains is indirect and derived largely from animal studies that are sometimes mutually contradictory. There is no doubt that strains differ widely in terms of virulence and also in terms of protective efficacy in certain animal models.

The need for further strengthening of animal model systems was highlighted by the recent report of Wiegeshaus (Ref. 13) and associates. In order to determine if the method by which a vaccine was tested was a major factor contributing to the results, an experiment was conducted in which a series of five different vaccines was distributed to each of nine participating laboratories. Each investigator evaluated the potency of the vaccines in one or more animal models of his own choosing. This, in effect, held the method of vaccine preparation constant, while permitting all other variables to change. The ranking of the five vaccines was essentially random, thus demonstrating that the method by which the vaccine is tested in animals markedly influences its apparent potency.

Nevertheless, many authorities consider that there is some correlation between the potency of vaccine for animals and its protective potency for man. BCG vaccine with a high potency in animals may be expected to induce strong and long-lasting protection against turberculosis in man, whereas a vaccine with low potency for animals may be virtually worthless for vaccination of humans. Thus, it would seem reasonable to choose for the production of vaccine only strains that are metabolically fully active, have good immunogenic potency in animals, and induce strong and lasting tuberculin sensitivity in humans.

One further controlled field trial of BCG vaccine is currently in progress in India, supported by the World Health Organization and the United States Public Health Service. This is the only controlled field trial of freeze-dried vaccines and has utilized vaccines from two production laboratories at two dosage levels. This may well be the last opportunity to carry out well-controlled field trials of tuberculosis immunoprophylaxis, and the results will be awaited with considerable interest.

Recommendations

Public support should be made available for further development and evaluation of BCG vaccines in animal model systems in order to provide models that are known to reflect protective efficacy in man accurately.

The results of the field trail currently in progress in India should be reviewed, when available, with particular attention to the adequacy of the scientific basis on which to recommend that all BCG vaccines distributed in the United States be prepared from the same seed lot strain of demonstrated efficacy in man.

Basis for Classification

The Panel considers that there is reasonable evidence of safety and efficacy of the three licensed BCG vaccines and therefore recommends that they be classified in Category I. This recommendation is not based on unassailable evidence of the safety and efficacy of these individual products, but rather on the general totality of experience reported in previous field trials of BCG vaccines. The Panel arrived at its decision more by a consideration of the alternatives than by clear conviction that a Category I classification was fully deserved.

There is no evidence on which to classify these products as Category II unsafe and/or ineffective; although a classification in Category III was seriously considered. Given the lack of an animal model system directly correlated with efficacy in humans, such a classification would place an impossible demand on manufacturers to carry out controlled field trials of their BCG vaccines.

Therefore, the Panel recommends that these products be placed in Category I, with the added stipulation that these products be reviewed again when the current World Health Organization-United States Public Health Service field trail in India is completed. If there emerges compelling evidence of efficacy of one or another BCG strain in that trial, subsequent review might well mandate U.S. licensed manufacturers to use that strain for vaccine production.

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Specific Product Reviews

BCG Vaccine Manufactured by Connaught Laboratories Limited

1. *Description.* This is a freeze-dried vaccine prepared from a strain of living attenuated bovine tubercle bacilli. The reconstituted vaccine for intracutaneous use is adjusted to contain between 10×10^6 and 30×10^6 viable cells per mL. Extensive details are provided of the manufacturing process itself. The origin of the Connaught Laboratories' BCG seed lot is presented in detail, and summarized as follows: Dr. Armand Frappier of the Institute of Microbiology and Hygiene of the University of Montreal received the strain on July 11, 1937, from Dr. Guerin of the Institute of Pasteur in Paris. It was apparently maintained in cycles of alternating 14-day passage on bile-potato medium followed by glycerimated-potato medium, followed again by bile-potato medium. A subculture was sent to Connaught Laboratories in April 1948 and the culture was thereafter maintained in cycles consisting of five consecutive biweekly passages on glycerinated-water-potato medium, followed by one passage on glycerinated-bile-potato medium for 2 weeks. The strain was lyophilized in 1967, when a seed lot system was introduced.

2. *Labeling*—a. *Recommended use/indications.* Under "selection of persons" in the package insert, the vaccine is stated to be given only to tuberculin negative individuals. It is recommended for use in the following groups of individuals.

All tuberculin negative individuals:

(1) Who by occupation are exposed to tuberculosis such as nurses, medical students, and hospital attendants.

(2) Who are in the population groups or areas with high tuberculosis morbidity and mortality rates.

(3) With a known exposure to tuberculosis, or where an exposure may occur, as in the household contacts of patients with tuberculosis admitted to or discharged from hospitals or sanitoria.

b. *Contraindications.* It is said to be inadvisable to vaccinate individuals suffering from "general malaise" although that entity is not further defined, or intercurrent acute infections such as measles, whooping cough, eczema, or furunculosis. Caution is expressed that BCG vaccines should not be given with other antigens, and that there be sufficient time for reactions to either BCG vaccine or to other antigens to subside before vaccination is carried out with the other.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* In experiments carried out in 1963 to 1965 (Ref. 1), when Connaught Laboratories was initially working with lots of freeze-dried vaccine, series of protection tests were carried out in both mice and guinea pigs using three vaccines, Glaxo Laboratories' freeze-dried BCG vaccine, Connaught Laboratories' freeze-dried BCG vaccine, and a Japanese freeze-dried BCG vaccine. In both mice and guinea pig experiments, the Glaxo Laboratories' and Connaught Laboratories' products showed clear-cut evidence of protective efficacy in both mice and guinea pigs, whereas the Japanese freeze-dried product produced no protection at all in mice, and was substantially less effective than the Glaxo Laboratories' or Connaught Laboratories' products in guinea pigs.

The product meets Federal requirements. Current animal efficacy tests on lots of vaccine are apparently limited to a guinea pig potency assay, measuring only tuberculin skin test conversion.

(2) *Human.* No controlled studies of the efficacy of Connaught Laboratories' freeze-dried BCG vaccine have been conducted. There are several older studies in the Canadian literature showing the efficacy of a liquid vaccine prepared by Dr. Frappier, both in nurses and in new-borns, but these data were not cited in the Connaught Laboratories' submission. Several studies of conversion rates have been carried out with the Connaught Laboratories' freeze-dried product, indicating that the Connaught Laboratories' product is comparable to other freeze-dried products in respect to producing very high skin test conversion rates.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of world literature relating to the safety of BCG vaccine is cited in the submission to the Panel (Ref. 2) as evidence of safety of the Connaught Laboratories' freeze-dried product. The submission notes a few cases of postvaccination abscesses and ulceration following Connaught Laboratories' BCG, but in each case these cleared up quickly and there was no evidence of tuberculosis.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This is generally a thorough and complete submission from Connaught Laboratories. The information supplied by the manufacturer, the tests that this product is required to pass, and the general body of data concerning the safety and efficacy of BCG vaccines in humans are sufficient to place this product in Category I, in accordance with the discussion of this issue in the generic statement. The labeling is clear, but should be revised to reflect the current recommendations of the Public Health Service Advisory Committee on Immunization Practices.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

BCG Vaccine Manufactured By Glaxo Laboratories, Ltd.

1. *Description.* This is a freeze-dried BCG vaccine, being a suspension of a living culture of a strain of the bacillus of Calmette and Guerin. It is prepared from a Glaxo Laboratories' substrain of the Copenhagen strain of BCG, dispersed in Sauton's medium with Triton, and cultured for 14 days at 37 °C. The concentration is adjusted so that viability counts falls between 4 x 10G56 to 9×10^8 viable particles per mL for a low potency vaccine and 8×10^8 to 25×10^8 for a high potency vaccine for intradermal injection. Five x 10^7 to 25×10^7 viable particles per mL of vaccine are used when the vaccine is intended for percutaneous administration.

2. *Labeling*—a. *Recommended use/indications.* The labeling is essentially a verbatim statement of the 1966 Public Health Service's Center for Disease Control statement of the special panel of public health and tuberculosis specialists. This states, in effect, that BCG vaccine should be used only for the uninfected individual or small groups of uninfected individuals living in unavoidable contact with one or more controlled infectious persons who cannot or will not obtain or accept supervised treatment.

b. *Contraindications.* BCG vaccine is contraindicated in tuberculin-positive individuals. In addition, it should not be given to patients who are immunosuppressed, whether as a result of underlying disease or treatment.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* There is general agreement that there is

no animal test of potency of BCG vaccine known to correlate directly with protective efficacy in man. This is so stated in the Glaxo Laboratories' submission.

2. *Human.* Several published works are cited in the submission to the Panel (Ref. 3) indicating the high skin test conversion rate when Glaxo Laboratories' freeze-dried BCG vaccine was used as directed. Additionally, the study of Springett and Sutherland (Ref. 4) is cited in which the efficacy of Glaxo Laboratories' freeze-dried BCG vaccine is retrospectively compared to the earlier experience in Birmingham when Copenhagen BCG vaccine in liquid form was used. In their analysis, the Glaxo Laboratories' freeze-dried vaccine performed just about as well as did the liquid Copenhagen vaccine. The authors point out that this was not really a controlled randomized trial, but rather a retrospective analysis using estimates of tuberculous experience in unvaccinated subjects. This is the only evidence, and indirect evidence at that, of effectiveness of any freeze-dried BCG vaccine.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The work of the British BCG Control Center is reported in its entirety (Ref. 3), and provides substantial evidence of the safety of Glaxo Laboratories' freeze-dried BCG vaccine.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears satisfactory.

4. *Critique.* This submission appears quite adequate. This information supplied by the manufacturer, the tests that the product is required to pass, and the general body of data regarding the safety and efficacy of BCG vaccine in humans are sufficient to place this product in Category I. The strain history is clarified, the Glaxo Laboratories' substrain being obtained from the Staten Seruminstitut in Copenhagen during the course of the Medical Research Council trial and immediately lyophilized. This culture has served as the master seed lot for vaccine production at Glaxo Laboratories since freeze-drying vaccine was marketed in 1957. The only remaining issue is whether the vaccine has retained full immunizing potency after freeze-dried and storage. The Panel believes that the retention of potency under these conditions is quite likely. (See discussion of this issue in the Generic Statement.)

There is no direct evidence that percutaneous vaccine is equal in protective efficacy to intradermal vaccine. One study (Ref. 5) is cited showing good comparability of tuberculin conversion rates when both routes were evaluated concurrently. In some recent studies, however, vaccine given by percutaneous multiple puncture methods has been less effective, as measured by skin test conversion, than vaccine given intradermally.

The labeling should be updated to reflect the current recommendations adopted by the Public Health Service Advisory Committee on Immunization Practices. Additionally, it would be of help to mention the size of needle to be used in intradermal injection.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

BCG Vaccine Manufactured by University of Illinois

1. *Description.* The BCG vaccine is a freeze-dried preparation of a culture of the Calmette and Guerin strain of *Mycobacterium bovis*, prepared from a substrain of the Pasteur Institute strain and freeze dried in lactose buffered salt solution. When reconstituted it contains 1×10^8 to 8×10^8 colony forming units per mL. A memorandum on the origin of the BCG strain used in the vaccine is included in the revised data submission from the manufacturer.

2. *Labeling*—a. *Recommended use/indications.* A package insert as such was not provided, but there is a 12 to 15 page document in the revised submission that appears to be a package insert. The vaccine is recommended as indicated for tuberculin-negative persons who are exposed to risks of tuberculosis infection. No mention is made of medical or paramedical personnel, but some emphasis is placed on the desirability of BCG vaccine for children who live in, or plan to travel in, areas where tuberculosis is prevalent, or are in situations where there is likelihood of exposure to adults with active or recently arrested pulmonary or renal tuberclulosis.

b. *Contraindications.* The vaccine is contraindicated in persons with a strong tuberculin reaction, fresh smallpox vaccination, or in burns. Severe immunodeficiency states, whether congenital, disease produced, or drug induced, are also listed as a contraindication.

3. *Analysis*—a. *Efficiacy*—(1) *Animal.* There is an extensive review of animal data in the submission to the Panel (Ref. 6), particularly in mice and guinea pigs, showing the protective efficacy of BCG vaccine in the animal systems, including data as recently as 1966 to 1970, relating to the current Tice product. It should be noted, however, that the efficacy of BCG vaccine in animal systems is not well-correlated with efficacy in humans.

(2) *Human.* The submission to the panel (Ref. 7) provides an extensive review of both the controlled and uncontrolled studies carried out in the Chicago area from 1937 through the early 1950's. Some of this material has already been published. In the report by Rosenthal in 1961 (Ref. 8), there was good evidence that the vaccine was effective in reducing the rate of tuberculosis in children who had been vaccinated by a multiple puncture method at birth. Both liquid an freeze-dried vaccines were used.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Over the past 35 years, many thousands of vaccinations were performed using Tice vaccine. No fatalities have been directly attributable to BCG vaccine in the controlled field trials in Chicago. This is acceptable evidence of safety of this vaccine. In addition, the world literature attesting to the safety of BCG vaccine, as summarized by Mande, is noted (Ref. 9). From 1931 to 1968, 13 fatalities have been reported as due to BCG vaccine, with probably over 500 million doses of BCG vaccine having been given.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears to be satisfactory.

4. *Critique.* The 1961 Rosenthal study (Ref. 8) is sometimes criticized as not being completely double-blinded, but overall it may be accepted as substantial evidence of efficacy of the vaccine. Studies carried out since that time have not been as well or at all controlled. There is, however, no mention in the submission of the several field trails using Tice vaccine that showed minimal or no protection. These include the Muscogee County Georgia study, the Georgia-Alabama study, and the Bettag study in an Illinois State school.

Nevertheless, information supplied by the manufacturer, the tests that this product is required to pass, and the general body of data relative to the safety and efficacy of BCG vaccines in man are considered sufficient to place this product in Category I, in accordance with the discussion of this issue in the Generic Statement. The labeling should be revised to include the current recommendation of the Public Health Service Advisory Committee on Immunization Practices.

5. *Recommendations.* With the exception of one Panel member who recommended that this product be

placed in Category IIIA, the Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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Generic Statement

Cholera Vaccine

Asiatic cholera is an acute diarrheal disease caused by *Vibrio cholerae*, which in its severe form is characterized by a massive loss of fluid and electrolytes. If untreated, this disease may result in circulatory collapse and death within 1 day. In reality, such severe cases are the exception rather than the rule, and epidemiological data indicate thart for each severe case there are 25 to 100 mild to asymptomatic cholera infections. For the most part, significant epidemics are limited to areas with poor sanitation. The possible appearance of imported cases of cholera in countries with good sanitation is enhanced by transportation and increased international travel. Since 1960, the seventh recorded pandemic of cholera has extended westward from Southeast Asia across the Indian Subcontinent, the Middle East, into the African Continent, and into portions of Southern Europe. A small outbreak of cholera occurred in Louisiana in late 1978.

It is now well-established that the disease is produced by a heat labile enterotoxin produced by *Vibrio cholerae* multiplying within the small bowel.

Infection follows the ingestion of water or food contaminated with human excretions containing *Vibrio cholerae*.

Highly satisfactory treatment of severe cholera is available consisting of prompt and adequate replacement and subsequent maintenance of fluid and electolyte losses and correction of metabolic acidosis. Adjunctive antibiotic therapy (usually with tetracycline) results in faster elimination of the organism and shortens the period of diarrhea. With prompt and adequate treatment, using intravenous and/or oral regimens, mortality is less than 1 percent. Unfortunately, adequate supplies of proper intravenous fluids and knowledge of treatment are often unavailable.

Immunization with cholera vaccine has been practiced for over 75 years, but no adequately controlled studies defining its relatively limited effectiveness were conducted until 1963. In the United States, the principal use of cholera vaccine is for military personnel and for individuals traveling to countries where cholera is endemic and/or where evidence of immunization is required. Although cholera is a quarantinable disease, under international health regulations, international certificates of vaccination for travelers from infected areas are no longer required in the United States and many other countries. In spite of the international health regulations and the total lack of any evidence that cholera vaccine prevents individuals from becoming carriers, some countries still require evidence of vaccination of travelers. The United States does not require vaccination of travelers from any country, and it is generally recommended that areas faced with an epidemic should not rely solely on vaccination but devote resources to provision of adequate treatment facilities, disease surveillance efforts, and improvment of sanitation.

Nature of Product

Cholera vaccine, as licensed in the United States, is a bivalent whole cell bacterial suspension containing equal quantities of Ogawa and Inaba serotypes of *Vibrio cholerae* at a concentration of 8 x 10^9 bacteria per mL. Only Ogawa and Inaba organisms of the "classical" biotype are employed since animal and field experience has shown that there is no advantage to the inclusion of organisms of the currently pandemic "El Tor" biotype that are antigenically identical and belong to either the Ogawa or Inaba serotypes.

Production

Organisms of the two serotypes are grown separately on agar, or in the case of one manufacturer, in a casein-hydrolysate broth. The bacterial count is standardized usually by opacity determination prior to addition of 0.5 percent phenol. The two serotype antigens are combined in equal amounts and diluted in 0.5 percent phenolized saline to a suspension of 8 x 10^9 organisms per mL for the final vaccine.

Although 0.5 percent phenol is the only killing-preserving agent currently employed in licensed vaccines, formalin, mild heat, and organic mercurials also have been employed in other countries. No clear-cut advantage or disadvantage of any particular killing-preserving agent is descernible form available data in man.

The final vaccine is tested according to the U.S. standards. In addition to tests for sterility and general safety, the vaccine must be tested for nitrogen content, freedom from toxicity (weight gain in mice), and antigenicity (protective activity in mice challenged intraperitionally with each serotype suspended in mucin).

Use and Contraindications

This product is intended for active immunization against cholera. Primary immunization of adults has traditionally consisted of two subcutaneous or intramuscular injections of 0.5 and 1.0 mL respectively, given 1 week to 1 month apart. Reduced doses have been recommended for children 10 years of age or under. Booster doses are recommended every 6 months as long as the likelihood of infection exists.

In the light of published data now available (Ref. 1), no advantage is gained by the 1.0 mL volume for the second dose, and the recommended schedule can be restated as follows:

Dose number	Dose volume (mL)			
	Intradermal[1] age (years)	Subcutaneous or intramuscular age (years)		
	>5	<5	5–10	>10
1	0.2	0.2	0.3	0.5
2	0.2	0.2	0.3	0.5
Boosters	0.2	0.2	0.3	0.5

[1]Higher levels of protection (antibody) may be achieved in children<5 years by the subcutaneous or intramuscular routes. In adults, somewhat lower levels of protection may be obtained by the intradermal route, but this route may be used as a means of minimizing reactions where a high level of protection is not necessary (e.g., most foreign travelers).

Absolute contraindications to the use of cholera vaccine are virtually nonexistent. Severe reactions have been reported but are extremely rare. As with other antigens, individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum response. Immunization should be withheld during febrile illnesses to avoid confusion as to the cause of further fever.

Safety

Immunization with cholera vaccine is generally accompanied by mild to moderate tenderness at the injection site, although more severe local reactions may occur occasionally. Such reactions may persist 2 to 3 days.

Local reactions may be accompanied in some instances by mild fever, malaise, and headache. With adherence to the U.S. standards, excessive antigen content [i.e., significantly more than 8×10^9 organisms per mL] should be largely eliminated as a cause of potential reactions.

Each batch of cholera vaccine must pass the standard Bureau of Biologics requirements for safety before it is released.

In summary, untoward reactions are not a major problem with cholera vaccine when properly produced and administered.

Effectiveness

Properly controlled field trials of cholera vaccines were first conducted in the early 1960's. Over subsequent years a series of field trials have been carried out in Bangladesh, the Philippines, and India (Ref. 2). A variety of vaccines, some experimental, have been tested and their apparent efficacy has varied widely, as have results from one trial to another. In general, protection in the range of 30 to 90 percent has been observed and has persisted for 3 to 6 months. However, in a recent study a monovalent vaccine of higher potency has shown good protection for as long as 3 years.

The seasonal nature of cholera complicates evaluation of the duration of protection, but protection is minimal or nonexistent with most vaccines in the subsequent cholera season (i.e., usually 1 year later). More prolonged protection has been observed in trials of an experimental oil adjuvant vaccine in the Philippines and with a fluid vaccine of high antigen content in Bangladesh. The oil adjuvant vaccine produced severe local reactions in the majority of recipients.

Field trials of monovalent vaccines in Bangladesh and the Philippines have shown that primary immunization with the Ogawa vaccine gave no protection against Inaba infection, whereas Inaba vaccine offered some cross-protection against Ogawa infection. These studies validate the need for bivalent vaccine because the infecting serotype often cannot be predicted.

Although no precise correlation can be established between potency as determined in the mouse and human effectiveness in field trials, a general relationship seems to exist (Ref. 3). The mouse protection test shows the same trend in cross-protection between serotypes as observed in field trials. The ability to stimulate vibriocidal antibody in children is reasonably well correlated with vaccine potency determined in the mouse (compare Figures 3 and 4 (Ref. 3)). With bivalent vaccines, protection in man is correlated with acquisition of circulating vibriocidal antibody. Monovalent Ogawa vaccine stimulates vibriocidal antibody against the Inaba serotype, but fails to protect against Inaba infection, except perhaps in adults in endemic areas.

Therefore, the mouse protection test seems to be the most reasonable potency assay now available, although the disease in the mouse, a fulminating septicemia, bears no resemblance to cholera in man.

Although the vaccine prevents clinical cholera in approximately 50 percent of recipients for 3 months or longer, cost-effectiveness data indicate that cholera vaccination is of little value as a public health measure in combating a threatened cholera epidemic. Cholera vaccines do not interrupt transmission or prevent acquisition of the carrier state. It seems wiser to expend resources to improve diagnosis, to make available simple rehydration facilities (which are needed regardless of vaccination), to improve surveillance, to conduct health education programs, and, where possible, to improve sanitation. Unfortunately, few health authorities can resist the intense political and public clamor for mass vaccination programs which at best will offer limited protection to only a small segment of the population at risk, even in the rare instances when they can be efficiently carried out.

Special Problems

The major limitation of immunization against cholera with presently available vaccines is their inability to induce an efficient and durable immunity in the gut. Parenteral immunization does not seem to be an efficient means of stimulating the secretory immune system against cholera. Oral immunization with killed vaccines or live avirulent vaccine is a current research objective.

Recognition of the fact that *Vibrio cholerae* induces disease by production of a potent heat-labile enterotoxin (which is a classical exotoxin) has raised extensive interest. This antigen is not present in significant quantities in any available vaccine. A highly purified toxoid, detoxified with glutaraldehyde (because formalin-toxoid showed reversion), has failed to confer significant protection when administered parenterally in field trials in Bangladesh and the Philippines. It is possible that this antigen combined with the whole cell vaccine may have additive or synergistic effects, but this awaits future product development and field trial. Oral administration of toxoid is also being considered, in the hope of inducing secretory antibody. This assumes great importance, because available data from animal models clearly indicate the need for neutralization of the toxin before it can act on epithelial cell surfaces lining the gut.

Recommendations

1. The Panel recommends that public support for development of an improved cholera vaccine should be continued. Such support is necessary because unsatisfactory sanitary conditions in many countries, including some in the Western Hemisphere, make it clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

2. Due to limited effectiveness of presently available vaccines, the Panel does not recommend that they be employed as a primary public health measure for mass immunization of populations threatened with cholera. The Panel recommends that the major efforts to control cholera comprise those of a sanitary nature and, in addition, include development of surveillance systems and provision of adequate facilities for diagnosis and treatment. Vaccine at present can be recommended for individuals who may visit countries that still require evidence of immunization beyond the current requirements of International Health Regulations. Cholera vaccine may also be prescribed as a secondary measure in the prevention of cholera in special circumstances for individuals or groups who need or may desire an additional measure of protection beyond that provided by sensible precautions in consumption of food and drink.

Basis for Classification

Because of the limited efficacy of cholera vaccine and the need for field trials in foreign lands for proof of efficacy, the Panel considered that the mouse protection test, which has been well-correlated with efficacy, and fidelity to methods of well-established vaccine production are all that can be relied upon as a basis for classification.

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SPECIFIC PRODUCT REVIEWS

Cholera Vaccine Manufactured by Eli Lilly and Company

1. *Description.* The vaccine is a suspension of killed vibrio organisms prepared from the Inaba and Ogawa (equal parts) serotypes of *Vibrio cholerae*. The organisms are grown on nutrient agar, suspended in isotonic sodium chloride solution, and killed with 0.5 percent phenol, which serves as the preservative. The vaccine is standardized to contain 8,000 million organisms per mL. Total nitrogen content of the final vaccine does not exceed 0.05 mg nondialyzable nitrogen per dose.

2. *Labeling*—a. *Recommended use/indications.* The vaccine is recommended for active immunization against cholera. The dose is a single 0.5 mL injection subcutaneously or intramuscularly, but a second injection of 1 mL, presumably 1 month or more later, is recommended when insanitary conditions may be encountered. Booster doses of 0.5 mL are indicated every 6 months if protection is needed. A reduced dosage schedule is recommended for children 5 to 9 years and a further reduction for children of 6 months to 4 years of age.

b. *Contraindications.* Vaccine should not be given during acute illness, convalescence from surgery or trauma, or in other conditions that would depress the immune response. The manufacturer cautions against simultaneous use of steroids, etc., during immunization and comments on their danger in the presence of exposure to infectious disease.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission (Ref. 1) cites various articles on the effectiveness of cholera vaccine in field trials. It fails to note that at least one of these trials was actually conducted with Eli Lilly and Company's cholera vaccine. The trial in question gave some of the best protection results observed to date.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A large number of doses have been distributed in the last 5 years with only 11 complaints, 3 of which are presumably irrelevant.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore, within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* Despite the generally modest evidence regarding any specific cholera vaccine, as well as cholera vaccines in general, this product is of relatively high acceptability when circumstances indicate its use. The label points out the shortcomings of cholera vaccine and is generally adequate. However, the importance of hygienic measures to control this disease should be pointed out in the package insert, which should also note the recent evidence suggesting that the second dose may be reduced to 0.5 mL. The lengthy discussion on corticosteroids in the face of infectious diseases is execssive and should be shortened.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Cholera Vaccine Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Cholera vaccine is a bivalent mixture of *Vibrio cholerae* containing Ogawa and Inaba serotypes, each at a concentration of 4×10^9 cells per mL (total count 8×10^9 per mL). Lederle Laboratories Division's vaccine contains organisms grown in casein hydrolysate broth and killed and preserved with 0.45 percent phenol.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against cholera. The recommended dosage consists of 0.5 mL and 1.0 mL injections 4 weeks apart with reimmunization every 6 months. No provision is made for reduced dosage for children.

b. *Contraindications.* Not recommended for use in the presence of acute infections.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on immunogenicity of this product in man was provided. This particular product has not been employed in a controlled field trial, but is similar in potency to products which have been so evaluated and found to give modest protection (±50 to 70 percent) for 3 to 6 months.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data from the manufacturer's complaint files revealed a very low rate of reaction complaints, all of a relatively minor nature.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore, within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

d. *Labeling.* The labeling needs to be revised to correct one minor inaccuracy in that the United States Public Health Service no longer requires vaccination of travelers entering the United States

from infected areas. In fact, cholera vaccine is no longer required by International Health Regulations, but a number of nations still unilaterally require it.

4. *Critique.* A field trial would be impractical for obvious reasons as previously discussed in this Report. Vibriocidal antibody levels in recipients could be determined, but would be hard to interpret and would inevitably be seen with vaccines meeting U.S. standards of potency. The labeling fairly states the limited expectation for efficacy of such a product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Cholera Vaccine Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The manufacturer has provided very little material except to say that it contains 4 billion cells each of killed whole bacteria of the Inaba and Ogawa strains per mL. The diluent is physiological saline with 0.5 percent phenol.

2. *Labeling*—a. *Recommended use/indications.* No package insert is provided. However, the label states that 2 doses at 7- to 10-day intervals given subcutaneously are recommended, the first being 0.5 mL and the second 1.0 mL.

b. *Contraindications.* None is mentioned.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* None is described.

(2) *Human.* None is described except reference to other studies. However, in the submission (Ref. 2) there is one reference to McBean (Ref. 3), in which a few patients were given this preparation both subcutaneously and intradermally to compare the two routes. Apparently titers were satisfactory.

b. *Safety*—(1) *Animal.* This submission states that the bulk vaccine and the final product meet Federal requirements.

(2) *Human.* No evidence is provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product cannot be determined because of insufficient information.

4. *Critique.* This submission is incomplete. Little or no information regarding efficacy is supplied, and the submission regarding animal safety is minimal. There are no data submitted regarding human safety. Apparently this manufacturer is simply retaining its license but the product does not appear to be marketed.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Cholera Vaccine Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* Each mL of vaccine contains 8×10^9 killed *Vibrio cholerae*, 4×10^9 Ogawa and 4×10^9 Inaba strain, suspended in isotonic sodium chloride solution. The organisms are grown on agar and killed and preserved with 0.5 percent phenol.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against cholera. It is pointed out that immunization is mandatory for travel in many parts of the world. However, none of the shortcomings of cholera vaccine is mentioned.

(1) *Adults.* Initial injection of 0.5 mL; a second injection of 1.0 mL given 1 week to 1 month or more later. Booster injections: 0.5 mL every 6 months while danger of infection exists.

(2) *Children.* Two injections given 1 week to 1 month apart, in the following dosage according to age: 6 months to 4 years: 0.1 mL, 0.3 mL; 5 to 9 years: 0.3 mL, 0.5 mL; and 10 years and over: adult schedule.

(3) *Booster injections.* Give the same amount as the first dose indicated above every 6 months while danger of infection exists.

b. *Contraindications.* It is stated "None known." Adverse reactions are mentioned.

3. *Analysis*—a. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Referral (Ref. 4) to the general literature only, with no information specifically for this product.

b. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* One study by Verway (Ref. 5) compares vibriocidal antibody responses among volunteers given either Cholera Research Laboratory vaccine (apparently manufactured by Eli Lilly and Company) or a vaccine from the National Drug Company. Since the National Drug Company's product is now the Merrell-National Laboratories' product, there are data in support of human immunogenicity for this product.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of the product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* The labeling could be improved by mentioning that only one injection is required for international travel, although two injections may give somewhat better protection. The short duration of protection from cholera vaccine is not mentioned, although the need for booster injections is pointed out. Under contraindications it is merely stated that none are known, whereas the vaccine probably should not be given during acute illnesses and in persons who have previously experienced severe reactions to the vaccine.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Cholera Vaccine Manufactured by Wyeth Laboratories, Inc.

1. *Description.* Each 1 mL of the vaccine contains not more than 4×10^9 *Vibrio cholera*, serotype Inaba, not more than 4×10^9 *Vibrio cholera*, serotype Ogawa which has been on trypticase soy agar containing pancreatic digest of casein, soy poptone, and sodium chloride. The organisms are removed from the agar surface, suspended in 0.02 molar phosphate buffered saline, and phenol added to a concentration of 0.5 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against cholera. The recommended dose and intervals between doses are clearly delineated in the labeling.

b. *Contraindications.* Intercurrent active infection is listed as a contraindication to vaccination.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Nine controlled studies have been carried out in the Phillipines, Bangladesh, and in India (Ref. 6). Vaccines of this type have shown from 39 to 93 percent protection. Mosley (Ref. 7) has demonstrated that a doubling of the mean vibriocidal antibody titer by active immunization was associated with a 50 to 60 percent reduction of the cholera case rate. It is not clear whether or not a Wyeth Laboratory preparation, per se, was used in any of these trials.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Local reactions are reported to be common; in addition, some patients experience malaise and

fever. No specific data, however, are provided in the submission (Ref. 8) with regard to the safety of Wyeth Laboratories' cholera vaccine.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* Within the general limitations of presently available killed/whole bacterial cell cholera vaccines as discussed in the generic statement, this product is acceptably safe and effective. The labeling, while presently satisfactory and in conformity with national recommendations, should be revised to reflect the recommendations of the Panel as found in the Generic Statement on Labeling.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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Generic Statement

Plague Vaccine

Plague is an acute infectious disease caused by a gram-negative bacillus, *Yersinia pestis*, which has its natural reservoir in wild rodents. In its classical form usual features include lymphadenitis and septicemia. Often toxemia, high fever, petechial hemorrhages, and shock are concomitant features. There are three clinical forms: bubonic, primary septicemic, and primary pneumonic. Untreated bubonic plague has a case fatality rate of about 50 percent, while untreated primary septicemic or pneumonic plague is almost uniformly fatal. Sylvatic plague exists in the Western one-third of the United States, but cases in man are sporadic (20 cases were reported in the United States in 1975) and routine immunization of general population has not been recommended.

Description and Production

Plague vaccine U.S.P. is produced from *Yersinia pestis* strain 195/P, which is grown on E medium and the harvested organisms are killed by addition of 37 percent formaldehyde (final concentration, 0.5 percent formalin). Phenol is added to a final concentration of 0.5 percent as a preservative. The vaccine contains trace amounts of media constituents but no detectable blood group substances.

Indications and Contraindications

Immunization is recommended for those persons who must be in known plague-endemic areas, such as Laos, Cambodia, and Vietnam and certain areas in the Western Hemisphere. In addition, antiplague immunization seems appropriate for selected groups such as laboratory workers, field personnel and epidemiologists who are involved in plague research and/or study. Despite its reactogenicity, when indicated, there apparently are no absolute contraindications.

Safety

Plague vaccine produces both local and systemic reactions. Local reactions consist of edema and/or induration at the site of inoculation. Such reactions may demonstrate a wheal and flare response and may temporarily limit the use of the involved extremity. Systemic reactions vary from malaise, mild headache, and generalized muscular aches to anaphylactoid responses.

In carefully observed subjects (2,688 injections of E medium vaccine into 523 individuals) (Ref. 1), local reactions occurred in 11 to 24 percent of individuals while systemic reactions occurred in 4 to 10 percent. Urticarial responses occurred in 0.07 percent. With reduction in booster dosage from 0.5 mL to 0.25 mL, a 65 to 70 percent reduction in systemic and local reactions ensued without apparent loss of immunogenicity.

Efficacy

The efficacy of killed plague vaccine in humans has not been defined in well-designed controlled field trials. However, the efficacy of plague vaccine (E medium) has been demonstrated to the satisfaction of the Panel by reviewing the experience of U.S. military personnel in Southeast Asia from 1963 to 1972 (Refs. 2 and 3). This latter experience briefly summarized is as follows: (1) A rate of one case of diagnosed plague infection per million man-years of exposure occurred among vaccinated Americans operating in Vietnam; (2) thousands of Vietnamese (approximately 5,000 cases per year per 15 million population, i.e., 333 cases per million man-years) contracted plague during this period with confirmation in many and with frequent fatilities; and (3) Americans frequently contracted murine typhus caused by *Rickettsia mooseri*, an agent which is carried and transmitted in Vietnam by the same flea/rodent hosts as *Yersinia pestis* (the Oriental rat flea *Xenopsylla cheopis* and domestic rats, *Rattus species*). In one study, 12 percent of American patients with proven murine typhus had serological evidence suggesting that they were concomitantly infected with *Yersinia pestis*, but none developed clinical evidence of bubonic plague.

One factor that could not be documented from the available data derived from the Vietnam experience is what proportion of the U.S. personnel had received no more than three doses of plague vaccine prior to their field service and potential exposure. A reasonable estimate would be that approximately 75 percent of personnel fell into this category. A second variable that could not be documented was the extent of and criteria for use of antibiotics such as tetracyclines since many febrile illnesses were treated empirically with broad-spectrum antibiotics.

Despite evidence that strongly suggests that plague vaccine is effective, an optimal vaccination schedule remains to be determined. The administration of booster doses at 3-month intervals as recommended by the manufacturer or even at 6-month intervals as carried out by the U.S. military has many drawbacks, particularly in the context of the reaction rates. In addition, recent studies suggest that such frequent injections are unnecessary.

Investigators at the U.S. Army Medical Research Institute of Infectious Diseases and at the Walter Reed Army Institute of Research have shown that

after an individual has received a primary series of three injections and approximately five booster innoculations of plague vaccine, a plateau in passive hemaggulutination titer is achieved, which is not exceeded by further immunizations and that long-term interruptions of booster injection schedules did not result in a marked decline in these antibody titers. They have also demonstrated that 86 percent of 29 vaccines developed a demonstrable passive hemmagglutination titer (geometric mean titer of 1:27) within 60 days after one injection of 1 mL of plague vaccine; and that 90 percent developed significant titers (geometric mean titer of 1:140) within 15 days after receiving a second dose of 0.2 mL 1½ months after the first dose. A booster dose of 0.2 mL given 6 months after the second dose resulted in a geometric mean titer of 1:576 15 days later in 93 percent of the vaccines. As is the case with all vaccines, it would be of great advantage to have serological tests or reproducible animal systems that correlate closely with protective value for man. For plague, a standardized mouse protection test (reported as mouse protection index) has been considered to be valuable. Mouse protection indices of 10 or less have been associated with immunity against plague. The average mouse protection index for sera collected from nonimmune subjects is 16; mouse protection index values of ≦5 are observed in sera collected from patients convalescing from plague. There is a reasonable correlation between a passive hemagglutination titer of ≧1:128 and mouse protection index of ≦10; however, in one series the correlation failed to hold in 6 to 36 subjects (17 percent).

Special Problems

1. The available data concerning immune responses in man have not been incorporated into recommendations for use of the product.

2. The following recommendations on plague immunization should be considered:

a. A primary series of three intramuscular injections (1 mL, 0.2 mL, and 0.2 mL) 1 and 6 months apart, respectively.

b. Booster intramuscular inoculations of 0.2 mL at 12, 18, and 24 months.

c. Where technically feasible, serological testing for passive hemagglutinating antibodies should be done 1 month after each of the booster inoculations (mouse protection index tests would also be useful but are less generally available).

d. In persons achieving a titer of 1:128 after the third and fifth inoculation, further booster does should be administered under the following circumstances:

(1) When the passive hemagglutination titer falls below 1:32.

(2) Empirically every 2 years when the patient cannot be tested serologically.

3. The percentage of individuals who are apparently nonresponders is of concern. However, such individuals may well have partial protection against *Yersinia pestis* in spite of a total failure to demonstrate immune responses by laboratory tests. Again drawing from the experience in Vietnam, there was no obvious problem posed by the projected 8 percent of persons who fell into this category of nonresponders. In fact, some special forces personnel, demonstrated to have been seronegative prior to their service in areas with considerable plague activity, were observed to seroconvert without specific plague-like illnesses during their field service. Again the possible role of antibiotic usage could not be evaluated as a modifier in this situation.

4. It is obvious that regular serological testing can be followed only among selected small groups such as laboratory workers, field personnel, epidemiologists, etc., and cannot be applied to the massive inoculation programs such as used by the military or in other population groups where the risk is deemed sufficient to necessitate immunization. Where serological monitoring is not feasible, booster doses should be administered empirically every 2 years after the fourth or fifth booster dose has been given (about 2 years after the primary series was begun).

Recommendations

1. *Animal models.* In view of the difficulties with field trials, there continues to be the need for the development of animal systems that can be closely correlated with serological responsiveness on the one hand and protective efficacy in man on the other. Such an animal model or test system is not currently available.

2. The available data regarding immune responses should be reflected in recommendations for use of the product.

3. Plague vaccine U.S.P. (E medium) is judged by the Panel to be safe and effective. Revised labeling for civilian use of plague vaccine, following an amendment of license in November 1974, has not been seen by the Panel and remains to be reviewed.

Basis for Recommendations

Judgment of efficiacy in the case of plague vaccine is based upon epidomiological evidence obtained in military populations rather than formal field trials or serological data directly correlated with protection in man. Nonetheless, the Panel believes that the plague vaccine as prepared for military use should be classified in Category I because the available data provide evidence of efficacy. The Panel believes that the data obtained from this epidemiologic investigation and adequate to substantiate effectiveness in this case.

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SPECIFIC PRODUCT REVIEW

Plague Vaccine Manufactured by Cutter Laboratories, Inc.

1. *Description.* This is a suspension of whole plague bacilli (*Yersinia pestis*, strain 195/P) formalin killed in a concentration of 2 thousand million organisms per mL. The suspending medium contains 0.9 percent sodium chloride U.S.P., 0.04 percent formalin, 0.5 percent phenol as a preservative, and only trace amounts of beef heart extract, yeast extract, agar, and hydrolysed derviatives of soya casein and agar. A difference between the composition of the military and civilian products has been resolved.

2. *Labeling*—a. *Recommended use/indications.* The vaccine is recommended for use in persons who have to be present in known plague endemic areas. The scheduled dose for adutls is 1.0 mL, intramuscularly followed 3 months later by a dose of 0.2

mL intramusculary. Proportionately smaller doses are specified for children aged 6 to 9 and for children aged 6 months to 5 years. Booster doses are recommended at 6 monthly intervals during residence in known plague endemic areas and consist of 0.2 mL intramuscularly. The standard precautions concerning the use of individual presterilized needles and syringes are included.

b. *Contraindications.* The labeling states that there are no real contraindications but advises not to give injections during upper respiratory infections.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This vaccine meets Federal requirements. Massive information is given concerning the immune response in rabbits and monkeys and the protection achieved in guinea pigs and mice.

Extensive data are available to show that the vaccine produces and antibody response in most recipients. Evidence that the vaccine was effective in protecting U.S. military personnel in Vietnam is provided in the work of Cavanaugh (Refs. 1 and 2).

b. *Safety*—(1) *Animal.* This vaccine meets Federal requirements.

(2) *Human.* Extensive clinical trials in man are cited in the submission to the Panel (Ref. 3) showing the occurrence of sore, swollen, and red arms in a small percentage of subjects receiving their first injections, and in a far greater percentage receiving a full dose as a second injection (this is the reason that the recommended second dose is now 0.2 mL). An isolated reference is cited (Ref. 4) calling attention to the observation in 1 military clinic of 22 patients manifesting urticaria or other Type I allergic reactions after an injection of plague vaccine. The author describes skin tests on these subjects that support the belief that the reactions were due to the vaccine and not to constituents of the medium. The author makes no attempt even to estimate the relative frequency of such reactions.

A great deal of additional data concerning reactions to this vaccine are available in the literature.

c. *Benefit/risk ratio.* In view of the data available that support the belief that the plague vaccine under consideration provides a significant degree of protection against plague, it is considered that the use of this vaccine in individuals who are liable to be exposed to plague is entirely justified. Therefore the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* The vial and package labels are clearly and explicitly marked. The package insert is on the whole much better then average. It is quite clearly written; however, Cutter Laboratories should provide a revised package insert based on civilian use.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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Generic Statement

Typhoid Vaccine

Typhoid fever is a worldwide disease caused by the bacillus *Salmonella typhi*, which probably affects well over 1 million people a year. It consists of an infection starting in the lower small intestine but spreading to produce septicemia which, if not adequately treated, can cause many weeks of illness; the death rate, prior to antibiotic therapy, was 10 to 15 percent. Recently, strains that are resistant to antibiotics have appeared in several parts of the world, so that the risk of contracting a severe, prolonged illness if infected with *Salmonella typhi* is still present. Infection results from the consumption of food or water that has been contaminated directly or indirectly by the excretions of a case or a carrier. The disease is uncommon in the United States but quite common in almost all countries with unsatisfactory sanitation.

Typhoid vaccine is therefore widely used to protect travelers and others who may run a significant risk of contacting the infection.

Nature of Product

Typhoid vaccine consists of whole typhoid bacilli (*Salmonella typhi*), killed and preserved in any one of several ways. It is usually distributed as a suspension in saline or buffered saline at a concentration of 1 billion organisms per mL. One manufacturer supplies it—on military contract—as an acetone-killed and dried powder, together with a vial containing a suitable reconstituting fluid. The strain of *Salmonella typhi* used by all manufacturers is strain Ty 2.

The use of combined typhoid, paratyphoid A and B vaccine ("TAB" or "Triple typhoid vaccine"), was discontinued in the United States because there is no evidence for the efficacy of the paratyphoid A component, and the paratyphoid B component was found to be effective only in much larger concentrations than were included in "TAB" vaccines.

Production

The typhoid bacillus is usually grown for 24 hours at 35 to 37 °C on veal infusion agar, and washed off with saline as a concentrated suspension. It is killed by heat, phenol, thimerosal, or acetone, and resuspended at the indicated concentration, with either 0.5 percent phenol or 0.01 percent thimerosal added as a preservative. (The product for military use is prepared as noted earlier.) One manufacturer grows it in a semisynthetic medium in a fermenter. Some manufacturers centrifuge and crude harvest, discard the supernatant, and resuspend the sedimented bacteria in order to reduce the concentrations of reaction-producing soluble antigens and ingredients carried over from the medium.

The final vaccine is tested according to the U.S. standards. In addition to tests for sterility and safety, the vaccine must be tested for nitrogen content and potency. The later is determined by a protection test in mice immunized with graded doses of vaccine and challenged with an intraperitoneal injection of a mucin suspension of a mouse virulent strain (Ty 2), compared against a U.S. standarad vaccine preparation. The vaccine under test must have a potency of at least 0.6 times the standard.

Use and Contraindications

The standard regimen for adults consists of 2 doses of 0.5 mL each subsutaneously at an interval of 3 to 4 weeks. Booster doses, when indicated, given at 3-year intervals, consist of 0.5 mL subcutaneously or 0.1 mL intradermally (acetone-killed vaccines are not recommended for intradermal injection because of the likelihood of excessive reactions). Proportionately reduced doses are recommended for children. Administration of the vaccine should be deferred in the presence of acute infections. It is generally believed that immunosuppressive agents may interfere with the effectiveness of the

vaccine, although this is not well defined. Persons who have exhibited marked reactions to previous injections should be given reduced doses for booster injections.

Safety

Inoculation with typhoid vaccine is frequently followed by local tenderness and swelling at the injection site, often accompanied by mild to moderate fever generally lasting overnight but rarely more than 24 hours. Such reactions appear to be due, in primary immunization, to endotoxins, but there is clearcut evidence that untoward reactions—probably of the Arthus or delayed-sensitivity types—are especially common among individuals who have had repeated inoculations of typhoid vaccine. For this reason, booster injections should be given in smaller doses (0.1 mL) intradermally. In general, this procedure does appear to reduce the incidence and severity of untoward reactions; however, it has been found that acetone-killed and dried vaccines, for as yet unexplained reasons, cause a high incidence of severe local reactions with intradermal injections and hence this route is contraindicated with such vaccines.

Major reactions with permanent sequlae or death following typhoid vaccination are virtually unknown, and it is clear that there is no evidence that bacterial endotoxins in the quantities present in bacterial vaccines can cause permanent sequlae. Moreover, the risk of excessive reactions is reduced by the mandatory ceiling on the nitrogen content of the vaccine. The vaccine must conform to the Bureau of Biologics' requirements for safety testing in animals.

Efficacy

Until fairly recently, typhoid vaccines were prepared and used on a purely empirical basis. However, in recent years at least 10 well-controlled field trials have been carried out with various types of typhoid vaccine, in 5 different countries. It has been found that the efficacy of a particular vaccine varies considerably with the method of killing and the preservative added. Thus acetone-dried or formalin-killed whole cell vaccines have given up to 90 percent protection against "ordinary" exposure; heat-killed, phenol-preserved vaccines gave somewhat less, or, if freeze-dried, considerably less protection. Alcohol-killed and preserved vaccines have given mediocre (30 to 50 percent) protection and chemical extracts and a vaccine prepared without H antigen have given little or no protection. (None of these last three classes of vaccine is in use within the United States.) It should be noted that studies in human volunteers indicate that against very large infectious doses of typhoid bacilli, even the best vaccines are ineffective.

As regards laboratory tests, the mouse protection test required by the Bureau of Biologics correlates with the field results in the case of acetone-killed and dried vaccines and also with freeze-dried heat-killed phenol-preserved vaccines. However, the mouse protection test correlates poorly with the results in man with alcohol-type vaccines. No such comparisons have been made with thimerosal-preserved vaccines.

The excellent field results with acetone-killed and dried vaccines were obtained with vaccines reconstituted just before use. However, the efficacy of such vaccines when distributed in the liquid state cannot be assumed to be identical.

Introduction of thimerosal as a preservative has not been tested by field trials. Nevertheless, laboratory tests show that thimerosal preservation is generally less deleterious than phenol and heat. The essentials concerning the various existing vaccines are shown in Table I.

It should be noted that no field trials have been carried out with typhoid vaccine prepared by any U.S. manufacturer. Nevertheless, the available typhoid vaccines are produced by methods similar to those employed for the production of vaccines that proved effective in field trials, or have introduced changes that could not, *a priori*, be considered necessarily deleterious to the efficacy of the product. In spite of the uncertainties introduced by differing techniques of inactivation and preservation, the Panel considers that there is reasonable evidence of efficacy of available typhoid vaccines.

Special Problems

The major problem associated with typhoid vaccine is the lack of a laboratory test of potency that correlates consistently with field results with various vaccines in man. Furthermore, changes in preparation of the vaccine, even those that may be expected to be beneficial, create uncertainty in its evaluation. Meanwhile, however, it would be useful to study further the correlation of laboratory tests with human trials of formalin-preserved vaccine (see Table I).

This problem however, can only be treated empirically until the mechanisms of immunity to typhoid fever are defined. Present knowledge indicates that immunity is not dependent on either H or Vi antigens alone, but that H antigen may be an essential component; however, it is possible that another, perhaps unidentified, antigen is also essential. It is not clear whether immunity is primarily humoral or cellular, systemic or local. If and when these questions are answered it should then be possible—in collaboration with studies in the field or in human volunteers—to identify a laboratory test that correlates satisfactorily with human protection. Related to the above is the problem of preparing a less reactive vaccine.

TABLE I.—INFORMATION ON CHARACTERISTICS OF CURRENT TYPHOID VACCINES

Type	Effectiveness in field trials	Mouse protective potency	Antibody response in man			Stability	Reactions
			H	O	Vi		
Heat-killed, formalin preserved.	+++	++	+	+	+	?	?
Acetone-killed, kept in dry state.	++ to +++	++	+	+	++	+++	+++ (intradermal) + (s.c. or i.m.)
Heat-killed, phenol preserved.	+ to ++	+	++	+	±	++	+ (any route)
Alcohol-killed and preserved.	±	++	+	+	++	++	++
Thimerosal killed and preserved.	?	++	+	+	+	++	+
Acetone-killed, thimerosal preserved.	?	++	+	+	+	Variable	+

± = borderline.
? = unknown.
+, ++, +++ = relative scale of response.*
*Because of variation in field and laboratory procedures only a relative scale is used in the table.

Recommendations

1. Appropriate support should be given to studies aimed at clarifying the immune mechanism(s) in typhoid fever.

2. Field or volunteer studies designed to test promising vaccines or their fractions for protection against typhoid fever should be supported.

3. The search for laboratory tests that correlate well with results of vaccination in man should be continued.

Basis of Classification

Proof of efficacy of typhoid vaccine is tied almost exclusively to field trials that are not feasible except in high endemic areas of the world. Classification of efficacy is therefore based upon production and preservation of vaccines known to be successful in such trials and supported by a mouse protection test correlated with field results. Methods of inactivation and preservation of those vaccines that have not been previously subjected to field trials have been accepted by the Panel because on theoretical grounds there is no basis to believe that they would interfere with efficacy.

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SPECIFIC PRODUCT REVIEWS

Typhoid Vaccine Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* The vaccine is made from heat-killed *Salmonella typhi* (Ty 2 strain), suspended in phosphate buffered saline to a concentration of not more than $1,000 \times 10^6$ cells per mL. The material prepared since 1969 is preserved with 0.01 percent thimerosal. The vaccine contains 8 protective units per mL.

2. *Labeling*—a. *Recommended use/indications.* The labeling follows the Public Health Service Advisory Committee on Immunization Practices recommendations and is indicated for intimate contacts with known cases of typhoid fever or carriers; for medical or hospital personnel; and for individuals contemplating travel to endemic areas.

b. *Contraindications.* (1) Acute respiratory disease; (2) in children with histories of febrile convulsions or cerebral damage; and (3) patients on corticosteroid and/or immunosuppressive drugs—since the immune response may be suppressed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No field trials have been performed with this product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The manufacturer reports that no complaints have been received in the 10-year period from 1961 to 1972 during which many hundred thousand doses were distributed. Local reactions occurred with intradermal injections in all (27/27 adults) with a past history of typhoid vaccine (2.43 cm to 6.5×7 cm erythema).

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined with certainty because there is no supporting field trial evidence of efficacy for this specific product. However, it is likely that the benefit-to-risk assessment of this product is satisfactory. (See Generic Statement.)

4. *Critique.* Although this vaccine should meet required standards of preparation (it is heat-killed and was phenol preserved), since 1969 it has been preserved with thimerosal. The latter is presumed to be at least as desirable a method of preservation as is phenol. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine Manufactured by Eli Lilly and Company

1. *Description.* This typhoid vaccine is a suspension of the Ty 2 strain of *Salmonella typhi* grown in a semisynthetic liquid medium. The organisms are killed by acetone which is then removed. The organisms are resuspended in buffered physiological saline, containing 0.01 percent thimerosal as preservative. The final vaccine contains no more than 1 thousand million typhoid organisms per mL, no more than 0.023 mg of nitrogen per mL. The final product is standardized to 8 protective units per mL.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against typhoid fever under the following circumstances: (1) Intimate exposure to a known carrier; (2) community or institutional outbreaks; and (3) foreign travel to endemic areas. The label cautions against intradermal administration.

These recommendations agree fully with those of the Public Health Service Advisory Committee on Immunization Practices, as does the recommended schedule for dosage and administration.

b. *Contraindications.* It is recommended that vaccination be avoided during an acute illness. The labeling further contains a caution about the administration of typhoid vaccine during chronic steroid therapy, implying that steroid therapy may so modify host defense mechanisms that an otherwise effective vaccine may be rendered ineffective.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In a study carried out by Eli Lilly and Company (Ref. 1) when a change to acetone inactivation of the vaccine was made, 60 adult males were randomly divided into 3 groups, 2 receiving separate lots of acetone-killed vaccine, 1 receiving Eli Lilly and Company's heat-phenol inactivated vaccine. Each received two 0.5 mL doses 4 weeks apart, and some received a third dose 4 weeks later. There were observed for 48 hours each dose. No significant differences were noted among vaccine in height of H, O, or Vi antibody titer according to vaccine used. The actual data, however, are not provided.

The general body of data supporting the efficacy of acetone-killed vaccine is cited in the manufacturer's submission

(Ref. 1), but Eli Lilly and Company's vaccine per se was not used.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the study cited above, there was no difference in local reactivity among recipients of the three vaccines, although the absolute numbers were not cited. Six of the subjects complained of constitutional reaction including chills or malaise during the 48-hour observation period, but all remained afebrile, and the complaints came equally from all three vaccine groups. There were no allergic reactions.

The manufacturer's marketing experience indicates that a few million doses of the vaccine were distributed in the 5-year period 1968 to 1972, and that 18 complaints were received of local or systemic reactions.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined with certainty owing to the lack of supporting field trial evidence of efficacy of acetone-killed vaccines perserved in the liquid state with thimerosal. However, it is likely that the benefit-to-risk assessment of this product is satisfactory. (See Generic Statement.)

4. *Critique.* This vaccine is killed by acetone but its preservation by thimerosal introduces a variable which has not yet been tested by field trial. However, animal studies and theoretical considerations strongly suggest that this vaccine should be effective in field trials. The latter may not be feasible with this product in the foreseeable future.

The labeling should be revised to reflect more current knowledge of the effect of corticosteroid therapy on immunoglobulin synthesis, particularly with regard to the dose and duration of steroid therapy. In addition, references to the need for "separate heat-sterilized syringe and needle" are quite dated, and should be revised to reflect contemporary practice as well as contemporary knowledge of hepatitis B.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* The final vaccine contains no more than 1 thousand million bacterial cells per mL (strain Ty 2) suspended in phosphate buffered saline containing 0.01 percent thimerosal. The bacilli are killed by thimerosal at room temperature, but no further details of the manufacturing process are given.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for persons for whom immunization against typhoid fever is indicated. The indications are not specified, but reference is made to the Public Health Service Advisory Committee on Immunization Practices recommendations. For primary immunization two doses of 0.5 mL subcutaneously on two occasions, separated by 4 or more weeks, are given to adults and children over 10 years of age. For children 6 months to 10 years the procedure is the same except that the dose is 0.25 mL.

Under conditions of continued or repeated exposure a single booster dose should be given at least every 3 years.

Boosters can also be given with an intradermal dose of 0.1 mL, which generally would give less reaction.

b. *Contraindications.* None are mentioned, although a warning is given to review the history of the patient regarding possible sensitivity to the product.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements and exceeds the potency of an analagous heat-killed, phenol-preserved vaccine in the mouse protection test.

(2) *Human.* No information was provided on this particular product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled, partially controlled, or uncontrolled studies have been carried out by the Massachusetts Public Health Biologic Laboratories. No fatal reaction following administration of typhoid vaccine has been documented by the Massachusetts Public Health Biologic Laboratories. However, it is well known that there many be may local reactions and some general reactions in adults following administration of the vaccine. No data from the complaint file are given.

c. *Benefit/risk ratio.* Assuming the product is effective, and the person to be vaccinated is at some risk of acquiring typhoid fever, the benefit-to-risk assessment should be satisfactory. (See Generic Statement.)

4. *Critique.* No clinical tests have been carried out on this particular product, but data from unpublished mouse protection tests suggest that the manufacturing process yields a vaccine equal or superior to vaccines of proven efficacy (see Generic Statement). The label is vague on indications for use.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The brief submission by Merck Sharp & Dohme represents a phenol-inactivated typhoid vaccine. The appropriate strain of typhoid bacilli is used and the final concentration is 1 billion organisms per mL. It is diluted in a buffered solution of physiologic sodium chloride. The preservative is phenol, 0.5 percent. The bacteria are inactivated by phenol, apparently without heat. No other information is given regarding its production.

2. *Labeling*—a. *Recommended use/indications.* The package insert, now 11 years old, recommends a dosage schedule at variance with current recommendations. The description of the method of preparation is outdated.

b. *Contraindications.* The labeling statement is acceptable.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product met Federal requirements when it was produced. No other information is supplied.

(2) *Human.* The only information provided is related to studies of generic typhoid vaccines.

b. *Safety*—(1) *Animal.* The manufacturer's submission states that the product meets Federal requirements.

(2) *Human.* No data are provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* This is a typhoid vaccine, apparently phenol inactivated, which appears to meet U.S. standards for animal safety. No other information regarding its efficacy or safety is provided. The labeling is outdated.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Typhoid Vaccine Manufactured by Texas Department of Health Resources

1. *Description.* This product contains approximately 1 thousand million organisms of *Salmonella typhi* per mL, strain Ty 2, killed by heat and phenol. Diluent is 0.02 M phosphate bufered saline, pH 7.2 to 7.3; 1:10,000 thimerosal is added. Each milliliter of vaccine

contains 8 potency units in accordance with the U.S. standard typhoid vaccine.

2. *Labeling*—a. *Recommended use/indications.* Routine immunization is not recommended in the United States. Selective immunization is, however, indicated in the following situations: (1) Intimate exposure to a known typhoid carrier as would occur with continued household contact; (2) community or institutional outbreaks of typhoid fever; and (3) foreign travel to areas where typhoid fever is endemic.

Primary immunization; dosage and schedule: (a) Adults and children over 10 years of age: 0.5 mL subcutaneously on two occasions, separated by 4 or more weeks; and (b) children 6 months to 10 years of age: 0.25 mL subcutaneously on two occasions, separated by 4 or more weeks.

Booster doses should be given at least every 3 years under conditions of continued or repeated exposure to typhoid as follows: Adults and children over 10 years of age, 0.5 mL subcutaneously or 0.1 mL intradermally; and children 6 months to 10 years of age, 0.25 mL subcutaneously or 0.1 mL intradermally.

b. *Contraindications.* Immunization of persons with acute febrile illness or other active infection should be deferred.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No information from studies conducted on this particular product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled studies are presented. Over the past 10 years, several million doses of the vaccine have been distributed in Texas without reports of serious reactions.

c. *Benefit/risk ratio.* Assuming the product is effective, the benefit-to-risk assessment should be satisfactory. (See Generic Statement.)

4. *Critique.* The vaccine is killed and preserved by heat and phenol. In addition, thimerosal is added as a preservative. The latter should not affect the vaccine adversely although field trials have not yet confirmed this assumption. However, such field trials with this vaccine are not feasible in the foreseeable future.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine (Acetone Inactivated) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This typhoid vaccine contains 1 billion acetone killed *Salmonella typhi* (Ty 2 organisms) per mL. The organisms are inactivated by precipitation with acetone and warming at 37 °C for 24 hours. The vaccine is distributed in dried form with a sterile diluent containing 0.5 percent phenol as a preservative for reconstitution.

2. *Labeling*—a. *Recommended use/indications.* For primary immunization for adults and children of 10 years of age and older, 2 doses of 0.5 mL each, injected subcutaneously or intramuscularly, are recommended with an interval of 4 or more weeks. For children 6 months through 9 years of age, the subcutaneous or intramuscular injection of 2 doses of 0.25 mL each is recommended at an interval of 4 or more weeks. For reinforcement of immunity for adults and children of 10 years of age and older, 0.5 mL injected subcutaneously or intramuscularly is recommended. For children 6 months through 9 years of age, the dose for reinforcement is 0.25 mL, injected subcutaneously or intramuscularly. The timing of reinforcement doses is not specified, but instead reference is made to military recommendations, inasmuch as this product is used primarily by the Armed Forces. Intradermal innoculation is contraindicated.

b. *Contraindications.* The manufacturer recommends deferral of immunization in the presence of an acute respiratory or other active infection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Field trials conducted by the World Health Organization employing vaccines very similar to this product have displayed a high degree of efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Typhoid vaccines in general produce high rates of local reactions and some systemic reactions, neither of which are serious. Severe reactions are very rare. This preparation appears to yield reactions at rates no greater than those expected.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this vaccine is satisfactory when compared with typhoid vaccines in general. (See Generic Statement.)

4. *Critique.* This is one of the few available typhoid vaccines which has been prepared by methods virtually identical to those vaccines which were most efficacious in field trials. Its efficacy is therefore well established.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine (Heat-Phenol Inactivated) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* The typhoid vaccine contains 1 billion *Salmonella typhi* (Ty 2 strain) heat-phenol killed organisms per mL. The organisms are killed by suspending them in sodium chloride, heating to 56 °C for 1 hour, and then adding 0.5 percent phenol and maintaining the batch at room temperature thereafter for 4 days. Phenol 0.5 percent is added as a preservative in the final diluent.

2. *Labeling*—a. *Recommended use/indications.* For primary active immunization of adults and children greater than 10 years of age, 2 doses of 0.5 mL each subcutaneously are recommended at an interval of 4 or more weeks. For children of 6 months to 10 years of age, 2 subcutaneous doses of 0.25 mL are recommended with an interval of 4 or more weeks. When necessary to comlete immunization in a shorter period of time, the manufacturer recommends the above doses administered subcutaneously on three occasions at weekly intervals.

If necessary to maintain immunity, the manufacturer recommends a reinforcing dose at least every 3 years. However, if an interval of more than 3 years has elapsed since the last dose, a single reinforcing dose is satisfactory. Reinforcing doses for adults and children over 10 years of age comprise either 0.5 mL subcutaneously or 0.1 mL intracutaneously. For children 6 months to 10 years of age, 0.25 mL subcutaneously or 0.1 mL intracutaneously is recommended.

b. *Contraindications.* The manufacturer recommends deferral of immunization in the presence of an acute respiratory or other active infection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Field trials conducted by the World Health Organization employing vaccines very similar to this product have displayed efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Typhoid vaccines in general produce high rates of local reactions and some systemic reactions.

neither of which are serious. Severe reactions are very rare. This preparation appears to yield reactions at rates no greater than those expected.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this vaccine is satisfactory when compared with typhoid vaccines in general. (See Generic Statement.)

4. *Critique.* This heat phenol inactivated typhoid vaccine is analogous to those found effective by field trials (see Table I) and would therefore appear to be efficacious.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Reference

(1) BER VOLUME 2050.

Passive Immunization Products

Generic Statement on Botulinus Antitoxin

Botulism is a paralytic disease caused by the action of a protein neurotoxin elaborated by *Clostridium botulinum*. *Clostridium botulinum*, a spore-forming organism closely related to *Clostridium tetani*, is widely distributed in nature and can regularly be found in soils and from marine sources. Six types of *Clostridium botulinum* (A–F) are recognized; each produces an immunologically distinct neurotoxin. These are among the most powerful toxins known; 1 microgram contains 200,000 minimal lethal doses for a mouse, and is very close to the lethal dose for man.

The disease usually results from the ingestion of uncooked food of animal origin, e.g., sausage, spiced meat, or smoked fish, or improperly canned fruits or vegetables, in which spores of the organism contaminated the product, germinated, and produced toxin. Food that is not obviously spoiled may still contain botulinus toxin. Thus, the disease is usually not an infection, but rather an intoxication. However, occasional cases of botulism result from infection of a surgical or traumatic wound with *Clostridium botulinum*, followed by toxin production in vivo. There is also strong suggestion that some cases of botulism result from toxin formation by *Clostridium botulinum* organisms in the human gastrointestinal tract.

Most human botulism is caused by types A, B, and E. Botulism caused by improperly canned vegetables or improperly preserved meat products is generally due to types A or B; most of the type E botulism reported in the United States has been traced to fish or fish products. Only two outbreaks of type F botulism have been reported. Types C and D produce disease almost exclusively in animals.

Although the spores are relatively heat resistant, requiring pressure sterilization to ensure killing, botulinus toxin is relatively heat-labile, being completely inactivated by a temperature of 100 °C for 10 minutes.

The disease is rare, but often fatal. From 1910 to 1919, 246 cases were reported in the United States. A series of studies by K.F. Meyer and his associates in the early 1920's defined the epidemiology of botulism, the foods most often incriminated, and the conditions necessary for the destruction of *Clostridium botulinum* spores. These studies led to strict controls on the commercial canning industry, and most cases of botulism in the last 25 years have followed consumption of improperly canned, home-preserved foods. From 1970 to 1973, 30 outbreaks of foodborne botulism, involving 91 cases and 21 deaths, were reported to the Center for Disease Control. Six cases of wound botulism were reported during the same period. Very recently, investigators in California have described a syndrome of infant botulism; the epidemiology and pathogenesis of botulism in children less than 1 year of age is currently under active investigation.

Treatment of botulism is directed toward three major goals. First, unadsorbed toxin should be removed from the gastrointestinal tract. This can be accomplished by an emetic if the suspected food was recently ingested, or more commonly by purging and enemas. Second, circulating neurotoxin can be neutralized by the administration of antitoxin. It is unlikely that antitoxin has any neutralizing effect on toxin already fixed to nerve tissue. Finally, assisted respiration is used to compensate for the neuromuscular blockade and to tide the patient over the period of respiratory paralysis.

Nature of Product

Botulism antitoxin trivalent, types A, B, and E, and botulism antitoxin, type E, consist of the partially purified globulin fraction from the serum of horses hyperimmunized with multiple sequential doses of botulism toxoid.

Production

Botulism antitoxin, types A, B, and E, are generally produced in the same animal by immunizing horses with subcutaneous injections of alum-precipitated formalinized toxoids prepared from *Clostridium botulinum*, types A, B, and E. To produce monovalent type E botulism antitoxin, only the type E toxoid is used for immunization. Hyperimmunization is begun with subcutaneous injections of gradually increasing amounts of the liquid toxoid at weekly intervals. Trial bleedings are taken periodically, and when antitoxin titers are sufficiently high, the serum is harvested by plasmapheresis. The plasma is pooled, defibrinated, subjected to pepsin digestion, followed by ammonium sulfate fractionation, dialyzed, and adjusted to yield approximately a 20-percent concentration of serum proteins. An average of 50 percent of the antitoxin activity originally present in the plasma is recovered in the final concentrate.

The digested, fractionated, dialyzed product is adjusted to a concentration suitable for filling, and tested for identity, safety, and potency in units per mL in toxin-antitoxin neutralization tests in graded dilutions in groups of mice. Phenol is added as a preservative to a concentration of 0.45 percent w/v, and the product is filled with a 20 percent excess or more, according to Federal standards related to the stated expiration date.

Recommended use/indications

Evidence concerning the exact amount of circulating antitoxin needed to neutralize experimental botulinus toxin poisoning is incomplete. Animal evidence suggests that the outcome of treatment depends largely on the time interval elapsing after the onset of symptoms, and before the peak of circulating administered antitoxin is reached. Therefore, it is strongly recommended that patients should be treated promptly with botulism antitoxin trivalent types A, B, and E, as soon as the clinical diagnosis of botulism is suspected. Prior to the injection of this material, if circumstances permit, the patient should be questioned regarding any history suggesting sensitivity to horses or horse serum, and should be tested for such sensitivity by conjunctival (1:10 dilution) or intradermal (1:100 dilution) tests with the serum for freedom from reactions. Suitable test kits for this purpose are sometimes available. Some experts advocate instead a tolerance test with 0.1 mL of a 1:100 dilution given subcutaneously. No test system is totally reliable, and the patient must be watched for at least 1 hour after the antitoxin has been injected.

Best results in the treatment of botulism are likely to be obtained if large doses of antitoxin are given early

in the disease, the object being to provide an excess of circulating antitoxin as early as possible. In order to ensure the most rapid neutralization of all toxin in the tissue and fluids, most authorities recommend prompt intravenous administration of one vial (7,500 International Units of type A, 5,500 International Units of type B, and 8,500 International Units of type E) injected very slowly at a dilution of 1:10, the solution to be at ambient temperature before being injected.

In order to provide a reservoir of antitoxin for subsequent adsorption, an additional equal dose may be given by intramuscular injection. Further doses are indicated in 2 to 4 hours if the signs and symptoms worsen. Because antitoxin remains in the circulation for over 30 days, the recommended dose should be given immediately, rather than in multiple small doses administered over a long period.

The recommended prophylactic dose for an individual who has eaten food suspected of being infected with *Clostridium botulinum* is 1,500 to 7,500 International Units of type A, 1,100 to 5,500 International Units of type B, and 1,600 to 8,500 International Units of type E given intramuscularly, depending on the amount of food eaten. If signs or symptoms of botulism appear, further treatment should be initiated with intravenous antitoxin.

Unless there is unequivocal evidence that the disease under treatment or preventive therapy is type E botulism, the trivalent antitoxin (types A, B, and E) is always recommended. If the disease is known to be type E botulism, therapy with monovalent type E antitoxin is justified. Individuals who exhibit apparent sensitivity to horse serum should nevertheless receive antitoxin, employing recommended schedules for gradual desensitization with increasing doses of antitoxin administered over several hours until the total dose has been given.

Safety

Federal regulations specify that botulism antitoxin be tested to ensure sterility and contain an appropriate preservative in specified amounts. The product must meet prescribed test results for freedom from pyrogenicity in animals.

The most significant problems regarding the safety of botulism antitoxin relate to sensitivity to horse serum. Two types of hypersensitivity reactions occur: anaphylaxis and serum sickness. These reactions cannot always be predicted in advance by sensitivity testing, and may not be prevented by desensitization.

Anaphylactic reactions to horse serum, fortunately the less common of the two, can occur without any known prior sensitization. They occur immediately or within a few minutes following injection, and are manifest by severe respiratory distress, collapse, and shock. Even with prompt administration of epinephrine, death may occur in 10 percent or more of cases.

Serum sickness following horse serum occurs 6 to 21 days after an individual's first injection. Prior sensitization is not required, although previous injections increase the likelihood of serum sickness and decrease the latent period between injection and onset of symptoms to as little as a few hours. The larger the dose of serum, the more likely is serum sickness to occur. Rates of serum sickness following horse serum vary, but range from 2 to 30 percent, and are directly dose dependent. In the most recent U.S. experience, however, only 7 percent of recipients of botulism antitoxin developed serum sickness. The overall rate of adverse reactions reported to the Center for Disease Control was 21 percent.

Efficacy

There is limited evidence that type E antitoxin is effective in preventing death in man when given after the onset of symptons, but there is little data on the efficacy of types A and B in man. In animals, type E and type A antitoxins appear to be effective, but the efficacy of type B antitoxin has never been conclusively demonstrated.

Almost all of the human botulism outbreaks in Japan have been due to type E. In 20 outbreaks before antitoxin was used, mortality rate was 28 percent; in 15 outbreaks after the use of type E antitoxin began, the mortality rate was reduced to 4 percent. The two groups may not have been comparable in other respects such as quality of supportive therapy or the duration of symptoms prior to treatment. In the more recent reports of type E botulism in the United States, as reported by Koenig and Whittaker, five of seven patient not given type E antitoxin died, but none of eight patients given type E antitoxin died. Again, the treated and untreated patients may not have been comparable in other respects. There is thus evidence, albeit uncontrolled, of the effectiveness of botulism antitoxin in man but only for type E.

Despite the lack of convincing evidence as to the efficacy of types A and B botulism antitoxin, the advisability of its use is firmly established in medical practice, and will presumably continue so unless chemical means are devised to circumvent the neuroparalytic effects of botulinus toxin.

Special Problems

Botulism is fortunately a rare disease in the United States. The number of cases reported in the past 10 years has varied annually from a low of 5 to a high of 34.

Since one consequence of rising food prices may well be an increase in home canning, education of the home canner and consumer is the most pressing need in the prevention and control of botulism. Public health agencies should provide information to the home canner about proper techniques and common errors involved in the preservation of foods.

The recent increase in contaminated commercial products suggest that new Federal regulations for canning low-acid foods are crucial to the prevention of processing errors by the canning industry. This should be a joint responsibility of the Center for Disease Control, the Food and Drug Administration, and the Department of Agriculture. Control measures developed and initiated by the smoked fish industry after three outbreaks involving smoked fish in the mid-1960's serve as a model for responsible action by the food industry.

Botulinus toxoid is available to permit development of botulism immune globulin of human origin. With so few cases occurring every year, this has understandably been given a rather low priority in research and development of biological products.

Serveral reports have appeared since 1967 describing the use of guanidine hydrochloride in the treatment of botulism. The drug is thought to act by enhancing the release of acetylcholine from nerve terminals. Reported cases have generally shown improvement with oral doses of 35 to 50 mg per kg per day, and in some instances the beneficial effect of the drug has been documented with neurophysiologic studies. Nevertheless, these studies have not been controlled, and the efficacy of guanidine hydrochloride and other drugs that act at the myoneural junction remains in question. For these reasons the use of these drugs should not preempt the administration of botulism antitoxin.

Recommendations

(1) Encourage educational programs directed at the home canner; (2) encourage the enforcement of Federal regulations established for the canning of low-acid foods and other high risk foods in the commercial industry; (3)

give consideration to the development of botulism immune globulin of human origin; and (4) support studies designed to elucidate the mechanism of action of botulinus toxin and the developemnt of pharmacologic agents that circumvent or minimize the neuroparalytic effects of the toxin.

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(8) Arnon, S.S., T.F. Midura, S.A. Clay, R.M. Wood, and J. Chin, "Infant Botulism: Epidemiological, Clinical and Laboratory Aspects," *Journal of the American Medical Association*, 237: 1946, 1977.

SPECIFIC PRODUCT REVIEWS

Botulism Antitoxin, types, A, B, and E and Botulism Antitoxin, Type E Manufactured by Connaught Laboratories Limited

1. *Description.* Botulism antitoxin, types A, B, and E, and monovalent type E, as supplied by Connaught Laboratories, is a refined and concentrated preparation of globulins modified by enzymatic digestion. The product is obtained from horses immunized with botulism toxoids, types A, B, and E, or type E alone. The product is purified and concentrated by ammonium salfate precipitation, pepsin digestion, and ultrafiltration. Phenol is added as a preservative at a concentration of 0.45 percent w/v.

Extensive details of the manufacturing process are provided. The trivalent product contains 7,500 International Units of type A antitoxin, 5,500 International Units of type B antitoxin, and 8,500 International Units of type E antitoxin per vial (10 mL). The monovalent product contains 5,000 International Units of type E antitoxin per 2 mL vial.

2. *Labeling*—a. *Recommended use/indications.* The product is recommended for the prevention and/or treatment of botulism.

b. *Contraindications.* There are extensive precautionary statements about testing for sensitivity to horse serum, but no absolute contraindications are specified.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements. A toxin-antitoxin neutralization test is carried out in mice for each individual component of the trivalent antiserum to determine the unitage.

(2) *Human.* No specific data are cited, but frequent references are made to the work of Dolman, in Vancouver, A statement is made in the submission (Ref. 1), as follows:

> To date our botulism antitoxin is used in Canada and is stocked by the National Communicable Disease Center, Atlanta, Georgia. From their reports in Morbidity and Mortality we can assume that when the antitoxin is administered the effect is lifesaving in most cases.

Such an assumption is unjustified. However, the report of the Tennessee epidemic (see Generic Review), not cited in the manufacturer's submission, demonstrated the efficacy of type E antitoxin.

b. *Safety—(1) Animal.* This product meets Federal requirements.

(2) *Human.* According to the Center for Disease Control's surveillance of reactions to botulism antitoxin, a 17-percent frequency of reactions to this product is mentioned in the Morbidity and Mortality Weekly Report.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The labeling is clear and adequate.

5. *Recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued.

Botulism Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for botulism antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendation. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Reference

(1) BER VOLUME 2061.

GENERIC STATEMENT

Diphtheria Antitoxin

Diphtheria is an infectious and communicable disease of man which usually involves the upper respiratory tract and sometimes produces skin infections. The causative agent is *Corynebacterium diphtheria*, a gram-positive bacillus with metachromatic granules. Upper respiratory diphtheria is characteristically associated with the production of a pseudomembrane in the nasal passage, pharynx, and/or larynx, and with the appearance of systemic symptoms due to absorption of an exotoxin. Fifty years ago there were approximately 200 cases per 100,000 population in the United States each year (roughly 200,000 cases annually). This has decreased to a rate of about 0.1 per 100,000 population in recent years (200 to 400 cases annually). Approximately 10 percent of patients with diphtheria succumb. Death may be due to respiratory obstruction by the membrane or to remote effects of the toxin upon the myocardium or peripheral nervous system.

Because the morbidity and mortality of diphtheria are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used by nearly 80 years in the treatment of the disease and for its prevention in exposed, susceptible individuals. This approach to control of the disease is only partially successful, because the disease is already well established by the time it is recognized, and toxin that has been absorbed and fixed to cells is unaffected by antitoxin.

Further, antitoxin does nothing to prevent spread of the toxigenic causative organism. Penicillin or other effective antibiotic agents will usually eradicate the organism but, because they have no effect against toxin, antibiotics are only an adjunct to therapy of clinical diphtheria.

Since neither passive immunization with antitoxin nor therapy with antimicrobial agents provides an entirely satisfactory approach to the control of diphtheria, active immunization of humans against the toxin is the safest, most effective control measure. The reduction in morbidity and mortality from diphtheria in the United States during the past half century is largely attributable to widespread immunization against the toxin. But

because significant segments of the U.S. population have not received adequate active immunization against diphtheria employing the toxoid, between 200 and 400 cases of diphtheria continue to occur yearly. For these individuals therapy with antitoxin is required.

Description

Diphtheria antitoxin is a preparation of hyperimmune serum prepared in horses immunized against diphtheria toxin.

Production

Diphtheria antitoxin is prepared by hyperimmunizing horses with diphtheria toxoid and diphtheria toxin until high levels of serum antitoxin activity are achieved. The horses must be demonstrated to be free of communicable disease.

Plasma containing satisfactory titers of antitoxin is concentrated by precipitation and dialysis and usually partially refined by pepsin digestion. Final concentration of antitoxin is at least 500 units per mL. Sterilization is achieved by microfiltration and an appropriate preservative is added. Each lot must meet requirements for sterility and freedom from pyrogenicity according to Federal regulations. Potency is tested by comparison with U.S. standard antitoxin.

Use and Contraindications

The major use of diphtheria antitoxin is for the treatment of clinical diphtheria. Treatment should be initiated immediately, prior to definitive bacteriologic diagnosis, in individuals in whom there is reasonable clinical suspicion of diphtheria. Delay in administration is to be avoided, because the antitoxin only neutralizes circulating toxin; toxin already fixed to tissue is unaffected. Delay allows increasing amounts of toxin to bind to tissue and is associated with a progressive increase in case fatality.

The dose of antitoxin recommended by most authorities is between 20,000 and 80,000 units, depending on the size of the patient, the severity, and duration of infection. The entire dose should be given at one time; some authorities recommended that up to one-half be given intravenously and the rest intramuscularly. Because sensitivity to horse serum is frequent in humans, sensitivity testing and a carefully taken history of any findings suggesting sensitivity to horses, horse dander, or horse serum are mandatory. Tests should be performed by both intradermal and conjunctival routes, with extreme precautions in case of any adverse reactions. Individuals with diphtheria exhibiting apparent sensitivity to horse serum nevertheless should receive antitoxin, employing recommended schedules for gradual "desensitization" with increasing doses of antitoxin administered over several hours until the total dose has been given.

Important adjuncts to therapy include general supportive measures, maintenance of the airway in patients with laryngeal diphtheria (diphtheritic croup), and administration of antimicrobial drugs active against *Corynebacterium diphtheriae* (erythromycin, lincomycin, penicillin, rifampin). Antimicrobial drugs, however, are only adjuncts to therapy and must not be used instead of antitoxin.

For the prevention of diphtheria in exposed, susceptible individuals (persons who are Schick test positive and/or who have not been immunized), diphtheria antitoxin, 1,000 to 5,000 units administered intramuscularly, may be used subsequent to testing for sensitivity to horse serum (see Special Problems).

There are no absolute contraindications to the use of diphtheria antitoxin in the presence of diphtheria.

Safety

Federal regulations specify that diphtheria antitoxin must be tested to ensure sterility and contain an appropriate preservative in specified amount. The product must meet prescribed tests for freedom from pyrogenicity.

The most significant problems regarding the safety of diphtheria antitoxin relate to sensitivity to horse serum. Two types of hypersensitivity reactions occur: anaphylaxis and serum sickness. These reactions cannot always be predicted in advance by sensitivity testing, and may not be prevented by densensitization.

Anaphylactic reactions to horse serum, fortunately the less common of the two, can occur without any known prior sensitization of any identifiable sort. They occur immediately or within a few minutes following injections and most characteristically comprise collapse and shock. Even with prompt administration of epinephrine, death may occur in 10 percent or more cases.

Serum sickness following horse serum occurs 6 to 21 days after an individual's first injection. Prior sensitization is not required, although previous injections increase the likelihood of serum sickness and decrease the latent period between injection and onset of symptoms to as little as a few hours. The larger the dose of serum, the more likely is serum sickness to occur. The major manifestations of serum sickness are fever, arthritis, lymphadenopathy and urticaria. Fatalities are rare except in instances of laryngeal edema. Symptoms persist for days or weeks. Rates of serum sickness following horse serum vary and are directly dependent on the dose. Indeed, the administration of 100 mL produces serum sickness in 90 percent of recipients.

Efficacy

The degree of effectiveness of diphtheria antitoxin in the therapy of diphtheria is not precisely established. Although many studies are reported, most are beset with problems of study design sufficient to cause concern about the exactitude of the results. For example, a number of studies indicate that individuals who received antitoxin in the first day or two of the illness exhibited fewer complications and increased survival compared to those receiving treatment later, but there are questions about the comparability of cases treated early and late. However, in the early experience, when supplies of antitoxin were erratic, the contrast between patients treated with it and those unable to be so treated was reported as very striking. Further, there appear to be secular changes in the severity and incidence of diphtheria, negating comparisons from year-to-year and decade-to-decade.

Nonetheless, most authorities believe that diphtheria antitoxin does exhibit salutary effects on the course, complications, and mortality of the disease, and that such effects are more pronounced the earlier in the course the antitoxin is given. However, it is clear that at best antitoxin fails to reduce mortality below about 5 percent.

Even less clear is the degree of effectiveness of antitoxin in the prevention of diphtheria in exposed, susceptible individuals. The administration of an antimicrobial drug in therapeutic doses to exposed, susceptible individuals avoids the use of horse serum and although not proven in controlled clinical trials, should be an effective alternative regimen. Erythromycin appears to be the most effective; penicillin, lincomycin, or rifampin are nearly as effective.

Special Problems

Diphtheria antitoxin as used for the production of passive immunity in the treatment or prevention of diphtheria exhibits two special problems.

1. Diphtheria antitoxin is only partially effective in treatment, apparently because it neutralizes only circulating toxin. Toxin that has already

left the circulation and is fixed to tissue is not inactivated, and no therapeutic agent has been identified that will interrupt the action of fixed toxin on tissue. Therefore, delayed therapy may not be effective.

2. Diphtheria antitoxin, comprising serum from horses immunized against the toxin, produces frequent symptomatic and occasional fatal hypersensitivity reactions.

Recommendations

1. The limited therapeutic effectiveness of diphtheria antitoxin and doubts about its prophylactic efficacy plus the success of widespread active immunization of populations indicate the need to intensify the efforts toward active immunization of as many individuals as possible. Therefore, it is recommended that support for widespread public immunization programs be augmented. Such preventive programs are far more effective in reducing morbidity and mortality from diphtheria than is antitoxin, whether used therapeutically or prophylactically. A widely immunized population would tend to eliminate the use of antitoxin and its attendant risk. (See Generic Statement on Diphtheria Toxoid and Tetanus and Diphtheria Toxoids for Adult Use (Td).)

2. Because passive immunization is still required for treatment of diphtheria in unimmunized individuals and occasionally in those apparently adequately immunized, consideration should be given to the development of diphtheria immune globulin of human origin.

3. Further information should be obtained regarding the possibility of a significant reduction in the reactivity of animal serum.

Basis for Classification

In the absence of controlled studies, difficult to obtain with this now rare life-threatening disease, the Panel could not insist on such evidence of efficacy. There is a sufficient body of historical data suggesting that diphtheria antitoxin is of some effect, albeit marginal, in the treatment and prophylaxis of diphtheria to justify classification in Category I.

Bibliography

See Bibliography for Diphtheria Toxoid.

SPECIFIC PRODUCT REVIEWS

Diphtheria Antitoxin Manufactured by Bureau of Laboratories, Michigan Department of Public Health

No data have been provided by the manufacturer for diphtheria antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Antitoxin Manufactured by Istituto Sieroterapico Vaccinogeno Toscano Sclavo

1. *Description.* This diphtheria antitoxin is prepared from the plasma of horses hyperimmunized against diphtheria toxin. The plasma is semirefined by a process of enzymatic action, ammonium sulfate precipitation, heat, and dialysis. The final product is sterilized by Millipore filtration and metacresol is added as a preservative to a concentration of 0.3 percent. The final product is marketed in 10,000 and 20,000 unit vials; the concentration is not specified.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the treatment of diphtheria and for the prevention of diphtheria in contacts who have not been previously immunized. For prevention, 10,000 units injected intramuscularly is recommended. For treatment, between 20,000 and 120,000 units, administered as a single dose, is recommended, with the larger doses being given to patients with more severe disease or disease of longer duration. It is recommended that approximately half of the dose be given intravenously and the rest intramuscularly.

Appropriate warnings are given about horse serum sensitivity and recommendations for intracutaneous or conjunctival testing for sensitivity are made. A satisfactory schedule is provided for the administration of antitoxin to individuals who display a positive sensitivity test. It is also stated that such individuals should not recieve intravenous antitoxin.

b. *Contraindications.* The only contraindication listed is an intravenous injection to individuals with a postive sensitivity test.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are cited. Only general comments about confirmation of the efficacy of the product by results obtained in Italy and elsewhere since 1956 are stated in the manufacturer's submission to the Panel (Ref. 1).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* It is stated that many thousand vials have been distributed in the past 5 years without significant complaints regarding reactions.

c. *Benefit/risk ratio.* The methods of manufacture and the distribution of this antitoxin over the years indicate that it is comparable to other diphtheria antitoxins. The benefit-to-risk assessment of this product appears to be satisfactory for reasons cited in the Generic Statement.

4. *Critique.* This is an equine diphtheria antitoxin made according to accepted standards. It would appear to be as safe and as effective as any diphtheria antitoxin.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be contained with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Diphtheria Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for diphtheria antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Antitoxin Manufactured by Massachusetts Public Health Biologic Laboratories

No data have been provided by the manufacturer for diphtheria antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Diphtheria Antitoxin Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* Diphtheria antitoxin, U.S.P., as produced by Merrell-National Laboratories, is prepared from the

plasma of horses hyperimmunized with both diphtheria toxoid and toxin. The antitoxin content of the plasma is concentrated by ammonium sulfate precipitation and refined by partial pepsin digestion. The final diluent is physiologic saline and the preservative is 0.4 percent tricresol. The antitoxin is packaged in 20,000 unit vials with a concentration of at least 500 units per mL.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the treatment of diphtheria and for prevention of diphtheria in exposed, susceptible individuals. The recommendations for its therapeutic use are complete, includings precautions, appropriate regimens for sensitivity testing and desensitization, dosage schedules, and the necessity for antimicrobial therapy.

Recommendations for prophylactic use in all exposed, susceptible individuals include sensitivity precautions, dosage, and emphasize subsequent active immunization. Serum sickness is described as a side effect. The package label is quite satisfactory.

b. *Contraindications.* None is specified, and it is stated that in individuals with diphtheria, antitoxin is mandatory.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Potency tests in animals are conducted according to Federal regulations.

(2) *Human.* No specific data are cited. The manufacturer states that early files on this product are no longer available. Excerpts from standard literature relating to diphtheria antitoxin are provided in the submission to the Panel (Ref. 2).

b. *Safety*—(1) *Animal.* This product is tested for total cresol, and for solids, pyrogenic activity, and sterility according to Federal regulations.

(2) *Human.* No information is provided other than the absence of any reported medical complaints during the past 5 years, during which time thousands of doses were distributed.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears to be satisfactory for reasons cited in the Generic Statement.

4. *Critique.* This product is still needed because of incomplete immunization of the U.S. populations and the continuing presence of diphtheria, and because a preparation produced in humans is not available. The package insert should reflect the preferability of erythromycin, lincomycin, or penicillin over antitoxin for prevention of diphtheria in exposed, susceptible individuals.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

References

(1) BER volume 2112.
(2) BER volume 2075.

Generic Statement

Gas Gangrene Antitoxin

Gas gangrene is a serious and often fatal anaerobic infection of soft tissue, muscle, and sometimes blood. It is best known as a dreaded complication of injuries to soldiers in wartime, but occasionally occurs among civilians in peacetime following trauma, or occasionally following surgery.

The etiologic agents of gas gangrene are the so-called "histotoxic" clostridia, including *Clostridium perfringens, Clostridium novyi, Clostridium septicum, Clostridium histolyticum, Clostridium bifermentans,* and *Clostridium fallax. Clostridium perfringens* is the most commonly recovered and the best studied. All of these organisms require nearly complete anaerobiosis and a reduced oxidation-reduction potential for growth. In common with other clostridia such as *Clostridium tetani,* the histotoxic clostridia are widely distributed in nature, being readily found in the gastrointestinal tract of man and animals, as well as in soils.

It is generally believed that the various toxins produced by the histotoxic clostridia account for their rapid spread in tissue, and for the profound toxemia that is such a prominent part of the clinical picture of gas gangrene. Each species produces a number of extracellular toxins, including lecithinases, collagenases, proteinases, and deoxyribonucleases. The most widely studied of these toxins has been the alpha toxin of *Clostridium perfringens,* a lecithinase that injures cell membranes and alters capillary permeability. Although the activities of a few of these toxins have been carefully defined, the cause of the profound toxemia and extreme morbidity that accompanies clinical gas gangrene remains unclear. In addition to the toxins themselves, the toxemia has been attributed to release of the products of tissue necrosis, interference with enzyme systems, and the profound acidosis.

Active immunization using toxoids prepared from the histotoxic clostridia has not proven practicable on a large scale. When such toxoids are used to hyperimmunize horses, however, antitoxic activity does develop. Equine antitoxin has therefore been used in passive immunization in humans, both in the prophylaxis and treatment of gas gangrene.

Nature of the Product

Polyvalent gas gangrene antitoxin is a preparation of hyperimmune serum from horses immunized against gas gangrene toxins.

Production

Gas gangrene polyvalent antitoxins are produced from plasma of hyperimmunized horses. The crude plasma/saline mixture, at a pH of 3.9, is treated with pepsin and ammonium sulfate. "Digestion" is continued for 24 to 48 hours, at which time 75 to 80 percent of the protein will not coagulate on boiling. The material is filtered, the protein in the filtrate is precipitated by ammonium sulfate, and the precipitate is washed and suspended in phenolyzed distilled water with toluene and chloroform as additional preservatives. The resultant material contains mainly gamma and beta globulins.

The final product is diluted with sodium chloride solution and preserved with 1:20,000 phenylmercuric borate plus approximately 0.4 percent phenol. Each vial of the final product contains 10,000 units *Clostridium perfringens* antitoxin, 10,000 units *Clostridium septicum* antitoxin, 3,000 units *Clostridium histolyticum* antitoxin, 15,000 units *Clostridium novyi* antitoxin, and 15,000 units *Clostridium bifermentans antitoxin.*

Use and Contraindications

The main purpose of the administration of polyvalent gas gangrene antitoxin is to prevent death from toxemia in established cases of clostridial infection, and is therefore an adjunct to adequate surgery.

The recommended dosage schedule is approximately 50,000 units (2 vials) every 4 to 6 hours before or after surgery for a period of 24 to 48 hours. Administration is normally via the intravenous route, but it may be used intramuscularly as well.

It must be emphasized that prompt and adequate surgical debridement is the sine qua non in therapy of gas gangrene. Important adjunctive measures include careful management of fluid and electrolyte balance, and prompt antibiotic therapy, including large doses of penicillin G. Serotherapy with polyvalent gas gangrene antitoxin and hyperbaric oxygenation have been considered adjunctive measures whose relative merits are not clear.

Gas gangrene antitoxin is contraindicated in individuals with a

history of sensitivity to horses, horse dander, or horse serum, and should be given with extreme caution to anyone who has previously received any injections containing horse serum.

Safety

Federal regulations specify that polyvalent gas gangrene antitoxin must be tested to ensure sterility and contain an appropriate preservative in specified amount. The product must meet prescribed tests for freedom from pyrogenicity.

The most significant problem regarding the safety of polyvalent gas gangrene antitoxin relates to sensitivity to horse serum. Two types of hypersensitivity reactions occur—anaphylaxis and serum sickness. These reactions cannot always be predicted in advance by sensitivity testing, and may not be prevented by desensitization. Anaphylactic reactions to horse serum, fortunately the less common of the two, can occur without any known prior sensitization within a few minutes following injection, and most characteristically include cardiovascular collapse and shock. Even with prompt administration of epinephrine, death may occur in 10 percent or more of cases.

Serum sickness following horse serum occurs 6 to 21 days after an individual's first injection. The larger the dose of serum, the more likely is serum sickness to occur. The major manifestations of serum sickness are fever, arthritis, lymphadenopathy, and urticaria. Symptoms persist for days or weeks. Fatalities are rare, except in instances of laryngeal edema. Rates of serum sickness following horse serum vary and are directly dose dependent. The frequency is approximately 1 percent per 1 mL of serum.

Efficacy

The efficacy of polyvalent gas gangrene antitoxin has been extraordinarily difficult to assess with precision, owing to the fact that it is at best an adjunct in the management of gas gangrene.

For the prophylactic treatment of gas gangrene following traumatic injuries there is general agreement that polyvalent gas gangrene antitoxin is of no value. The work of MacLennan and MacFarlane, who studied the occurrence of gas gangrene among British troops during World War II, suggested that the incubation period of the disease might be lengthened by the administration of gas gangrene antitoxin, but clear evidence of efficacy in prophylaxis of gas gangrene cannot be found.

The mainstay of therapy of gas gangrene has been and continues to be prompt surgery that includes complete removal of all infected tissue. Therapeutic regimens that have stopped short of such radical surgery have invariably failed, regardless of other adjunctive measures utilized. The adjunctive measures most often utilized include careful management of fluid and electrolyte balance, prompt antibiotic therapy, including large doses of penicillin G, passive immunization with polyvalent gas gangrene antitoxin, and hyperbaric oxygenation.

The best available data in support of therapeutic efficacy of polyvalent gas gangrene antitoxin derived from the British experiences in World War II, as summarized by MacLennan and MacFarlane. These studies were obviously not designed as rigidly controlled field trials, but did not evidence that the combined use of surgery and antitoxin was approximately 40 percent more effective than surgery alone.

Data on the efficacy of antitoxin in the treatment of gas gangrene since World War II is scanty at best, wholly uncontrolled, and consists mostly of individual case reports or small series of cases.

Although it is difficult to dismiss entirely the experiences recorded by MacLennan, who felt that passive immunization with gas gangrene antitoxin was of distinct benefit in the management of gas gangrene, its role in management remains uncertain. Some or all of its apparent effectiveness during World War II may now have been minimized or eroded completely by emphasis on early diagnosis, prompt surgery, and other adjunctive and supportive therapy including antibiotics.

Current surgical opinion reflects these uncertainties. The manual "Control of Infection in Surgical Patients," edited by Altemeier, Burke, Pruitt, and Sandusky, states simply "gas gangrene antitoxin has been found to be of little or no value in the prevention of clinical gas gangrene."

Special Problems

The major special problem identified is the lack of acceptable evidence of efficacy of polyvalent antitoxin in the management of clinical gas gangrene. The Panel sees no likelihood that such evidence will be forthcoming in the foreseeable future.

A second major problem in the evaluation of this product is the apparent lack of standardization of antitoxin unitage. International Units of antitoxin are defined so that no two represent the same protective power, i.e., *Clostridium novyi* is approximately 100 times greater than *Clostridium perfringens*, and *Clostridium bifermentans* is approximately 50 times greater than *Clostridium perfringens*. The protective power of "one vial" of the Lederle Laboratories Division's polyvalent gas gangrene antitoxin (pentavalent) in terms of mouse minimum lethal dose of toxin would be as follows:

Clostridium perfringens	500,000 to 700,000
Clostridium septicum	400,000 to 640,000
Clostridium histolyticum	approx. to 135,000
Clostridium novyi	approx. to 7,500,000
Clostridium bifermentans	2,850,000 to 5,700,000

Another aspect of this problem relates to the quantity of each of the antitoxins packed in a vial. This problem is illustrated in Table 1.

Recommendations

The Panel recommends that further research be encouraged on the nature of the toxins produced by the histotoxic clostridia, and the mechanism of action of their effects on mammalian tissue.

Basis for Classification

In the judgment of the Panel, there is not adequate evidence of efficacy of polyvalent gas gangrene antitoxin when used as recommended in either the prophylaxis or therapy of gas gangrene. Therefore, for this reason the Panel recommends that this product be classified in Category IIIB.

TABLE 1—ANTITOXIN CONTENT (INTERNATIONAL UNITS)

Author/Manufacturer	C. perfringens	C. septicum	C. novyi	C. histolyticum	C. bifermentans	Recommended dose
MacLennan (Ref. 1), MacFarlane (Ref. 2)/Medical Research Council.	7,500	3,750	2,500	—	—	>116,500 units (1 vial).
Gledhill/Burroughs Welcome	9,000	4,500	3,000	—	—	3 vials.
Lindsey (Ref. 3), United States National Standard; Lederle.	9,000	4,500	9,000	—	—	12 mL/vial, dose not stated.
Present product/Lederle	10,000	10,000	1,500	3,000	1,500	2 vials.

References

(1) MacLennan, J.D., "Anaerobic Infections of War Wounds in the Middle East," *The Lancet*, 2:123–126, 1943.

(2) MacFarlane, M.G., "The Therapeutic Value of Gas-Gangrene Antitoxin," *British Medical Journal*, 2:636–640, 1943.

(3) Lindsey, D., H.M. Wise, A.T. Knecht, and H.E. Noyes, "Influenza of Route of Administration on Effectiveness of Clostridial Antitoxin," *American Medical Association Archives of Surgery*, 78:328–330, 1959.

SPECIFIC PRODUCT REVIEWS

Gas Gangrene Polyvalent Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Company

1. *Description.* Gas gangrene polyvalent antitoxins are produced from plasma of hyperimmunized horses. After the antitoxin plasma is "refined and concentrated," it is diluted with sodium chloride solution and preserved with 1:20,000 phenylmercuric borate plus approximately 0.4 percent phenol. Each vial contains: 10,000 units *Clostridium perfringens*, 10,000 units of *Clostridium septicum*, 3,000 units of *Clostridium histolyticum*, 1,500 units of *Clostridium novyi*, and 1,500 units of *Clostridium bifermentans* antitoxin.

The refining process involves pepsin/ammonium sulfate treatment of a crude plasma/saline mixture (pH 3.9). "Digestion" is contained for 24 to 48 hours, at which time 75 to 80 percent of the protein will not coagulate on boiling. The material is filtered, the protein in the filtrate is precipitated by ammonium sulfate, the precipitate is washed and suspended in phenolyzed distilled water with toluene and chloroform as additional preservatives. The resultant material contains mainly gamma and beta globulins.

2. *Labeling*—a. *Recommended use/indications.*

* * * to prevent death from toxemia in an established or suspected case of clostridial infection until adequate surgery and antibiotic therapy can bring the infection under control. The usefulness of this antitoxin to prevent clostridial infection is controversial but is generally considered to be of little or no value when given prophylactically.

The recommended dosage schedule is approximately 50,000 units (2 vials) every 4 to 6 hours before or after surgery for a period of 24 to 48 hours. Administration is normally intravenous, but it may be used intramuscularly.

b. *Contraindications.* Sensitivity to horse serum, history of asthema angioneurotic edema, or other allergy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

Lindsey (Ref. 1) has demonstrated efficacy in extensively wounded goats when massive doses of trivalent antitoxin were employed, approximately 1,800 to 2,600 units of *Clostridium perfringens* antitoxin per kg.

(2) *Human.* The best available data derived from the British experience in World War II.

(i) MacLennan (Ref. 2) demonstrated the following:

Drug therapy	No antitoxin		Antitoxin[1]		
	Cases	Death	Cases	Death	Differences
Sulfonamides	26	22 (79%)	58	19 (33%)	46%

[1] The average dose for survivors treated with antitoxin was 40,000 to 50,000 units. The composition of the antitoxin is not defined, but it is assumed to be that recommended by the Medical Research Council with 1 therapeutic dose containing 7,500 international units *Clostridium perfringens antitoxins, 3,750 international units of Clostridium septicum*, and 2,500 international units of *Clostridium novyi*.

(ii) MacFarlane (Ref. 3) analyzed reports to subcommittee on anaerobic wound infections. The reports came from multiple sources between 1940 and 1943. Of 165 cases (not including those of MacLennan), 139 were classified as "toxic cases"; some received antitoxin, others had not. Results were as follows:

No antitoxin		Antitoxin		Difference
Cases	Death	Cases	Death	
25	21 (84%)	114	58 (51%)	33%

From these studies they concluded that the combined use of surgery and antitoxin was more effective than surgery alone.

(iii) The MacLennan and MacFarlane studies which suggested effectiveness of gas gangrene antitoxin used preparations which differed in composition and which were administered in differing dosages. The Lederle gas gangrene antitoxin differs in composition from those used by both MacLennan and MacFarlane.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Most reports contain no data on reactions; however, serum sickness would be anticipated. Frequency would be approximately 1 percent per 1 mL of serum.

c. *Benefit/risk ratio.* Benefit-to-risk considerations with reference to this product are not acceptable.

4. *Critique.* Major problems in the evaluation of this product have been discussed in the Generic Statement. The product is poorly standardized, and there is not adequate evidence of efficacy when used as recommended in either the prophylaxis of treatment of gas gangrene.

5. *Recommendations.* The Panel recommends that this product be classified as Category IIIB, and that the appropriate license be revoked owing to the lack of acceptable evidence of efficacy.

Tetanus and Gas Gangrene Polyvalent Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for this product for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

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Generic Statement

Pertussis Immune Globulin (Human)

The pathogenesis, symptomatology, complications, and epidemiology of pertussis and its prevention with killed-bacterial vaccine have been described previously in this Report.

Serum therapy was initiated in the 1930's and early reports on the effect of convalescent human sera and hyperimmune animal sera in prophylaxis and therapy of pertussis were quite favorable. Subsequently a refined product, gamma globulin of human origin, was introduced and was similarly accepted enthusiastically. Later controlled studies failed to demonstrate significant benefit.

Several factors may influence the effect of antibody therapy: (1) The site

of the infection and access of antibody to the site; (2) whether antiserum alters the pathophysiologic effects of the organisms' reactive factors; and (3) the classes of immune globulin in convalescent serum which presumably contribute to recovery.

Description

Pertussis immune globulin is predominantly the immunoglobulin fraction from a pool of serum from human donors who have been hyper-immunized with pertussis vaccine. Earlier the product was sometimes obtained from persons who were hyperimmunized with vaccine following recovery from pertussis.

Production

The source of this product is plasma from adults who have been repeatedly immunized with pertussis vaccine. This pertussis immune globulin is diluted with normal human immunoglobulin to achieve a standard concentration of protein. The donors are required to be free of causative agents of diseases that are not destroyed or removed by the processing methods, as specified by Federal regulations.

The plasma is fractionated by a cold alcohol method, yielding a preparation with over 90 percent of IgG. Thimerosal in dilution 1:10,000 may be added as a preservative. Pertussis immune globulin is submitted to standard tests for purity, sterility, safety, and protein content according to Federal regulations. Up to this time there has been no standard of potency which has been correlated with human efficacy. The two products licensed in the United States at the present time are compared in an in vitro agglutination test to a reference serum.

Use and Contraindications

The product has been recommended for intimately exposed children under 2 years of age who have not been vaccinated. The dose recommended by manufacturers is 1.25 to 1.5 mL intramuscularly, repeated in 5 to 7 days if exposure continues.

For treatment of infants with pertussis 1.25 mL intramuscularly for 3 to 5 doses, or 3 to 6.75 mL as a single dose is recommended. The product should not be administered intravenously.

Expert opinions as to the usefulness of pertussis immune globulin both in treatment and prophylaxis diverge. Thus the 1975 report of the American Public Health Association states that passive immunization is of no value in treatment or in prevention. However, the American Academy of Pediatrics which previously accepted its use in prophylaxis, in 1977 states that "There is no convincing evidence that Pertussis Immune Serum Globulin (Human) has any efficacy in preventing or treating pertussis, and its use is not recommended."

The product is contraindicated in individuals who are known to have an allergic response to immunoglobulin. Epinephrine should be at hand for treatment of rare reactions.

Safety

This product must meet Federal regulations as to safety. Adverse reactions to immune globulins are rare, and consist of anaphylactic and allergic reactions. The greatest risk consists of inadvertent intravenous injection of aggregated immunoglobulin which leads to shock.

Manufacturers are required to record reported reactions.

Efficacy

The use of pertussis immune globulin is empirical, because the nature of the protective factor in human serum is not known. However, the agglutinating antibody and/or a bactericidal antibody may play a role in protection. Furthermore, it is not clear whether protective factors are present in the IgG fraction. Some speculate that protection is located in the IgM fraction, because infants do not appear to obtain passive immunity from their mothers. Since *Bordetella pertussis* infection is primarily an infection of the bronchial epithelium, it is also possible that the protective factor is located in the IgA fraction of the immunoglobulins. Pertussis immune globulin (human) can protect mice under experimental conditions, but its relation to human efficacy has not been determined.

Studies conducted in the 1930's and 1940's when pertussis was still a virulent disease with a relatively high mortality rate suggested a prophylactic and therapeutic effect from convalescent human sera and animal hyperimmune sera. Unfortunately, these studies were not adequately controlled and comparison groups outside the experimental setting were often utilized.

In the last decades, a few controlled studies have been conducted with pertussis immune globulin. They did not demonstrate statistically significant differences between treatment and control groups. However, concurrent antimicrobial therapy may have masked any beneficial effect; it is also possible that the specific lots and dosage used were ineffective, and the numbers of study subjects were too few. At least in one study the dose was lower than the recommended one. Also, the stage of disease when the product was given has varied and the methods of allocation to study groups have not always been clearly described.

During the last decades, erythromycin and ampicillin have become the preferred methods for prophylaxis and treatment of pertussis.

Special Problems

1. Several studies, not adequately controlled, conducted in the 1930's and 1940's when pertussis was a more prevalent and virulent disease, provided evidence of therapeutic and prophylactic benefit from convalescent serum, human hyperimmune serum and rabbit hyperimmune serum. The initial experience with pertussis immune globulin (human) suggested similar effects, but more recent, well-controlled studies did not confirm this suggestion. Whether this indicates that alcohol fractionation of plasma in the preparation of immunoglobulin eliminates other protective components in unknown. It appears, however, that there is little evidence of efficacy of the current product.

2. No animal model or other laboratory technique for evaluation of potency has been directly related to efficacy in humans. The only animal model employed utilized intracerebral injection of *Bordetella pertussis* bacteria into mice; a protective effect of pertussis immune globulin can be demonstrated. Other potentially useful models such as intranasal challenge of mice have been insufficiently studied.

3. Knowledge of the immune mechanisms to pertussis in humans, particularly as to class of immunoglobulin, and the role of humoral immunity, especially the role of bacteriocidal antibody, is rudimentary. The role of cell-mediated immunity is unknown.

4. Whereas the product appears relatively safe for the recipient, the practice of hyperimmunizing the donors with pertussis vaccine is not without risk.

Recommendations

1. The available information is insufficient to classify pertussis immune globulin as effective. Further studies are required before such a decision can be made.

2. The Panel recommends that research be directed to identify the mechanism by which immunity to pertussis is acquired. Identification and characterization of protective antibodies, if such are present, are imperative to determine the value of pertussis immune globulin as presently constituted. Studies are also necessary

to determine the value of other preparations derived from immune serum aimed at conferring passive immunity.

3. Animal models which closely resemble human infection should be sought, in order to study the pathogenesis and immune mechanisms of pertussis. A mouse model of respiratory infection already exists and deserves further exploration.

4. Clinical trials should be conducted with other immunoglobulin preparations that may have better experimental evidence for efficacy. Such studies could be carried out where the incidence of pertussis in childhood is high, or in special situations such as outbreaks among adults.

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SPECIFIC PRODUCT REVIEWS

Pertussis Immune Globulin (Human) Manufactured by Cutter Laboratories, Inc.

1. *Description.* This product is a solution of immunoglobulin prepared from venous blood of humans hyperimmunized with pertussis vaccine. It contains 16.5 percent ± 1.5 percent protein dissolved in 0.3 M glycine and preserved with 1:10,000 thimerosal. The pH is adjusted withu sodfum carbonate. Each 1¼ mL dose contains a quantity of immunoglobulin equivalent to approximately 25 mL of human hyperimmune plasma.

Fresh citrated plasma is collected by plasmapheresis and fractionated into components of plasma using the Cohn cold alcohol method. The pool of plasma is chosen on the basis of minimum pertussis titer and no regard is given to the number of donors. The final product solution is sterilized by filtration. Pertussis agglutination titers are determined but the standard used is not given. Donors, whose health status has been checked, receive a basic series of three injections of Eli Lilly and Company's pertussis vaccine during a 12-month period and a fourth injection during a second 12-month period. A donor consent form is supplied.

2. *Labeling*—a. *Recommended use/indications.* The product is said to be indicated in the prophylaxis and treatment of pertussis. The dose is 1¼ mL given as soon after exposure as possible, and in therapy it is recommended that the same dose is repeated after 24 or 48 hours, sometimes again after 1 to 2 weeks. The product is given intramuscularly only, and not intravenously.

b. *Contraindications.* The product is contraindicated in individuals who are known to have an allergic response to immunoglobulin. There is a warning against intravenous use. Slight soreness may occur at the injection site; sensitizations is extremely rare but may occur. There have been a few instances of angioneurotic edema, nephrotic syndrome, and anaphylactic shock after injection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* Several studies with pertussis immune globulin are cited in the submission to the Panel (Ref. 1), seven of these utilized the product of this manufacturer. Whereas uncontrolled studies generally reported favorable results, the controlled studies failed to show any significant differences between control and treatment groups. The efficacy of the product, not only in treatment but also in prophylaxis, appears in doubt.

The only somewhat controlled study which reported favorable results is the one by Hatz (Ref. 2) who studied streptomycin with and without hyperimmune serum in treatment of pertussis. However, the conclusions appear not be to statistically validated.

It is disconcerting that controlled studies, generally carried out after 1950 when pertussis had become a relatively mild disease and effective antibiotics were available, all report a lack of statistically significant benefit from pertussis immune globulin. On the other hand, uncontrolled or poorly controlled studies carried out with whole immune serum in the 1930's and 1940's suggested great benefit, especially in prophylaxis. If the protective antibody is found in the IgM fraction of the immune globulin as suggested in "Infectious Diseases" by Krugman and Ward (Ref. 3), how can the IgG (which is the principal content of hyperimmune globulin) be of any help? Maternally acquired immunoglobulin is known not to be protective.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several clinical trials report no adverse effects. Rate instances of angioneurotic edema, nephrotic syndrome, and anaphylactic shock are listed as possible adverse reactions. No data from the complaint file are submitted

c. *Benefit/risk ratio.* The benefits of this product both in prophylaxis and treatment are in doubt, although there is little risk (isoimmunization, allergic reactions).

4. *Critique.* This is a well-documented submission except that data from the manufacturer's complaint file were not submitted. It is unclear how many donors make up the pool for pertussis immune globulin (the Bureau of Biologics requires a minimum of 10 individuals). The label states that the donors are given Cutter Laboratories' pertusais vaccine, other sections of the manufacturer's submission indicate that Eli Lilly's vaccine is used. Information on adverse reactions to repeated administration of pertussis vaccine in adults and the procedure utilized in the production of pertussis immune globulin (human) should be developed. This

information should include data on the type of vaccine used. The agglutination test, including standards, is not described. The submission contains a thorough listing of human studies of pertussis immune globulin, including several of the manufacturer's own product. Their own interpretation of these studies is that the product is efficacious. It is unfortunate that this conclusion is based on uncontrolled studies, and not on the controlled ones, which do not prove any statistically significant benefits.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product.

Pertussis Immune Globulin (Human) Manufactured by Travenol Laboratories, Inc., Hyland Division

1. *Description.* This product is a 16.5 (± 1.5) percent solution of the immunoglobulin fraction (Cohn Fraction II) of the serum of healthy adults hyperimmunized with pertussis vaccine. The solution is made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. Cryoprecipitate is removed by centrifugation and reserved for other use. Fraction II is obtained from Fraction I, II, III by the Cohn method with some modifications. Donors are given 3 doses (0.5 mL) of pertussis vaccine subcutaneously at weekly intervals, the fourth dose is given after 4 weeks, and later doses are given at 4-week intervals as long as the donor remains on the program. Plasmapheresis is performed twice weekly.

The product is available in 1.5 mL single dose vials.

2. *Labeling*—a. *Recommened use/indications.* In *prophylaxis,* one 1.5 mL dose of pertussis immune globulin (human) is recommended for a child as soon after exposure as possible. A second dose, 1 week after the first, is desirable. If use of the globulin is delayed more than 1 week after exposure, larger doses should be given at 1 to 2 week intervals.

In treatment, for children already showing symptoms of pertussis, one 1.5 mL dose should be given as soon as possible, with additonal doses at 2-day intervals until recovery has begun. For critically ill children, the initial dose might well be doubled. In cases of pertussis pneumonitis, the globulin treatment may be supplemented with suitable sulfonamide or antibiotic therapy.

It is clearly stated that the product should be given intramuscularly and not intravenously.

b. *Contraindications.* None are listed. Under reactions the remote possibility of serum sickness and anaphylaxis are mentioned, as well as local tenderness and stiffness. A warning againts intravenous infection is given.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* The manfacturer's submission to the Panel (Ref. 4) cites the literature of pertussis immune globulin, but they appear not to have conducted any field tests of their own product. The product is tested for potency by measurement of agglutination titers. The aggflutination titers of the lot under test, a house reference lot, and the starting plasma pool are determined, using as the antigen a commercially available licensed pertussis vaccine, always from the same manufacturer. The lot under test must show at least 16 times concentration of antibody over the starting plasma pool (i.e., 4 doubling dilutions difference) and the house reference lot must show the same titer as it showed in previous tests, plus or minus 1 doubling dilution. No referecnce or standard from the Bureau of Biologics is being utilized.

b. *Safety.* This product is tested for purity, residual moisture, pyrogens, electrophoretic purity, "general safety," and stability.

(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on human safety for this specific product were supplied other than from the general literature. No data from the manufacturer's complaint file were submitted.

c. *Benefit/risk ratio.* The benefits of this product both for use in prophylaxis and treatment are questionable. Serveral uncontrolled studies report beneficial results, but the controlled studies, even those investigating the prophylactic use (Morris (Ref. 5) and Place (Ref. 6)) report no significant differences between patients given pertussis immune globulin and other material. The risks are minimal, but allergic reactions and isoimmunization have to be considered.

4. *Critique.* The most difficult problem is to determine if the current literature supports the belief that the use of pertussis immune globulin is effective in prophylaxis, let alone treatment of pertussis. The manufacturer's own product has not been field tested; however, such a test would be very difficult to institute. Data from complaint files are lacking. The Bureau of Biologics does provide a U.S. standard antipertussis serum, and the provisional requirements state that each lot of pertussis immune globulin shall contain a pertussis antibody level of not less than 500 pertussis units per vial compared with this standard. Information on adverse reactions to repeated administration of pertussis vaccine in adults, a procedure utilized in the production of pertussis immune globuline (human), should be developed. This information should include data on the types of vaccine used. Because sulfonamides are not the first choice in treatment of pertussis, the advice regarding supplementary treatment should be reworded: substitute "sulfonamide or antibiotic therapy" with "antimicrobial therapy."

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product.

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Generic Statement on Tetanus Antitoxins

Tetanus is an acute disease of the nervous system caused by infection with the tetanus bacillus, *Clostridium tetani,* which produces an extremely potent neurotoxin that is lethal to man in miniscule amounts (approximately 7 millionths of a milligram). The tetanus bacillus also produces lesser reactive substances. The disease is of major importance, killing perhaps 1 million people worldwide annually. The tetanus bacillus is probably primarily a resident of the intestinal tract of various animals, but spores are widely distributed in soil and dirt, and when carried into devitalized injured human tissues that is low in oxygen, the spore form of the bacillus can germinate, liberate toxin, and hence cause the disease. The disease can be prevented by

immunization with tetanus toxoid. Immunization is indicated for everyone, since natural immunity, if it exists at all, is exceedingly rare in man; not even the disease itself produces immunity in those who recover from it.

In the 1890's, tetanus antitoxin was developed, primarily in horses, by hyperimmunization—first by injection of slowly increasing amounts of tetanus toxin, and later, when it became available, by sequential injections of tetanus toxoid. The serum from such animals contained varying amounts of antibody capable of neutralizing tetanus toxin in experimental animals; therefore it has been used on a worldwide basis ever since both for the prophylaxis of tetanus in unimmunized persons thought to be exposed to the disease, and for treatment of the disease.

Both the safety and efficacy of tetanus antitoxin of animal origin have been the subject of concern and disagreement ever since its introduction, because of the frequency of reactions—not infrequently severe and sometimes fatal—following the injection of horse serum in sensitive individuals, and because unequivocal data regarding its efficacy have never become available. Substitution of antiserum prepared in cattle or sheep did not solve either problem, and during the past 15 years attention has been turned to the preparation of concentrated antitetanus antibody solutions from immunized or hyperimmunized human donors. The human preparation, disignated tetanus immune globulin, has eliminated the problem of reactions to heterologous serum, but the problem of efficacy remains unsettled. Nevertheless, the theoretical considerations and the clinical impression that either or both of these products are of value have led to their very general use, for prophylaxis of tetanus in previously unimmunized persons incurring a risk of contracting tetanus, and in the treatment of clinical tetanus.

Nature of Product

Tetanus antitoxin consists of the partially purified globulin fraction from the serum of animals (generally horses) hyperimmunized with multiple sequential doses of tetanus toxoid and sometimes toxin as well. Potency in units is determined by reference to the U.S. standard antitoxin. Antitoxin of bovine or ovine origin is similar except for minor differences in the prodominant type of antitoxin-containing globulin.

Tetanus immune globulin is the gamma globulin fraction from a pool of human donors who have either been selected because they already posses a sufficiently high serum antitoxin level against tetanus toxin, or else have been hyperimmunized so that their serum antitoxin level is suitably high.

Production

For the production of tetanus antitoxin, the best responders are selected from a number of horses that have been given several properly spaced injections of tetanus toxoid and further immunized until test bleeding showed that their serum antitoxin level is high enough to yield a concentrated antitoxin of acceptably high titer, e.g., 1,500 units or more per mL. Present day harvesting of serum is done by plasmapheresis, collecting 8 to 9 liters of blood and retransfusing the separated cells, on a regular schedule such as every 2 weeks. The plasma is fractionated, unsually by precipitation of the antitoxic antibodies with ammonium or sodium sulfate, yielding a mixture of proteins that contains a high proportion of the antitoxic globulin which is, in the horse, largely a beta-globulin. The precipitate is reconsitituted, dialyzed, and ajusted to yield approximately a 20-percent concentration of serum proteins. Further purification of the original serum is usually carried out under specified conditions of pepsin digestion, which hydrolyses much of the nonglobin protein present, yielding a preparation with fewer nonspecific proteins and a higher ratio of beta-globulin, modified by digestion but still fully against toxin. In practice, the proportion of specific antitoxin in the usual product is probably about 1 or 2 percent.

The digested, fractionated, dialysed product is adjusted to a concentration suitable for filling (either as prophylactic doses of 1,500 units or therapeutic doses commonly furnished as 10,000 units per vial). It is then tested for identity, safety, and for potency in units per mL by mixture with toxin in graded dilutions and injection of each mixture into groups of guinea pigs. A preservative (usually thimerosal) is added, and the product is filled with a 20 percent excess or more, according to Federal regulations.

Tetanus immune globulin. Production from normal donors is based on availability of outdated blood from cooperating blood banks and selection of those with high tetanus antitoxin titers, commonly selecting those that show eight units or more by hemagglutination. Alternatively, selected hyperimmunized donors may be bled by plasmapheresis, yielding a human serum pool of higher titer than is obtainable from selected normal adult blood. In either case, the plasmas of at least 10 donors are pooled, and the pool is fractionated according to the alcohol method of Cohen et al., yielding a preparation with over 90 percent gammaglobulin and conforming to the limitations set by Federal regulations regarding the presence of other globulins. The immune globulin is stabilized with 0.3 M glycine, titrated for tetanus antitoxin content as with animal serums, and diluted before filling to contain approximately 16.5 percent globulin. A preservative (normally thimerosal 0.01 percent) is added. The usual preparation is distributed in 250-unit amounts (plus the standard excess required by regulations) in a volume normally ranging from 2 to 4 mL.

Use and Contraindications

Tetanus antitoxin, like tetanus immune globulin, may be used for the prevention of tetanus following tetanus-prone injuries in unimmunized individuals or those whose immunization status is uncertain or for the treatment of clinical tetanus. For prophylaxis of injuries, tetanus antitoxin is generally considered to be indicated, if tetanus immune globulin is unavailable, in individuals having suffered injuries, burns, etc., judged by the physician as potentially at risk of developing tetanus. Prior to the injection of this material, the patient must be carefully questioned regarding any history suggesting sensitivity to horses or horse serum and should be tested for such sensitivity by conjunctival (1:10 dilution) or intradermal (1:100 dilution) test with the serum for freedom from reactions. Some experts advocate instead a "tolerance test" with 0.1 mL of a 1:100 dilution given subcutaneously. No test system is totally reliable and the patient must be watched for at least 1 hour after the antitoxin has been injected. The minimum dose is 1,500 units, but most authorities agree that this is insufficient and recommend a minimum of 3,000 units; some give 10,000 units routinely. If the wound is more than 24 hours old, some clinicians recommend doubling the dose. Epinephrine must be at hand at all times during testing and injection.

Special attention is required for babies born to unimmunized mothers under conditions conducive to neonatal tetanus. Such babies should be injected with 1,500 units of tetanus antitoxin or, if it is available, 500 units of tetanus immune globulin (see below). Sometimes the mother is also at risk, in which case she should be given prophylaxis as outlined for any patient at risk of developing tetanus.

Tetanus antitoxin is contraindicated in individuals with a history of sensitivity to horses, horse dander, or

horse serum, and should be given with extreme caution to anyone who has previously received any injections containing horse serum. In the presence of clearcut evidence of hypersensitivity, tetanus immune globulin should be used for prophylaxis even if its procurement means a delay of 24 hours. Although some believe that antibiotics are of value in the prophylaxis of tetanus, the available data do not support this belief. Nevertheless, antibiotics represent the only alternative when antitoxin-containing preparations are unavailable.

Prophylaxis with tetanus immune globulin is carried out without previous testing for sensitivity, but epinephrine should be at hand. The indications are the same as with antitoxin, but the dose is ⅓ to ⅙ the dose with equine antitoxin (250 to 500 units) since tetanus immune globulin is homologous and the half-life in vivo is about 3 weeks.

For therapy of tetanus, some clinicians prefer equine tetanus antitoxin because unlike tetanus immune globulin it can, with caution, be given intravenously and because 80 years of clinical experience has indicated that it may be of value. There is no general agreement as to the dose required for effective therapy, because it is quite evident that recovery from tetanus depends on many factors (sedation, debridement, prevention of spasms, prevention of infection, maintenance of respiration, etc.). Theoretical considerations and certain studies support the view that little is gained by giving more than 5,000 to 10,000 units of antitoxin. Others advocate much larger doses. It is established that the only function of antitoxin is to neutralize freshly liberated toxin from the infected source, i.e., antitoxin does not neutralize toxin already fixed to tissues. It is customary to give ½ the selected dose intravenously, the other half intramuscularly, after following the test precautions outlined above for the use of the product in prophylaxis. An additional precaution is to give 0.1 mL intravenously and wait ½ hour. If this small dose is tolerated, the patient will generally tolerate the remainder, which should nevertheless be given extremely slowly since some patients react at higher thresholds than others.

There is no general agreement on the value of continued therapy with antitoxin after the initial dose. By 7 to 10 days after the first dose, the majority of patients are sensitized to the horse serum and rapidly eliminate the antiserum.

Therapy with tetanus immune globulin has not been practiced for about 15 years. With generally available preparations of tetanus immune globulin the product must be given intramuscularly (NOT intravenously) which delays absorption so that the peak titer of antitoxin in the patient's serum will not be reached for 2 to 3 days. However, some clinicians have found that tetanus immune globulin can be given very slowly by intravenous drip without untoward reactions. This practice requires further study before endorsement. No firm guidelines regarding dosage exist, a commonly selected dose being 3,000 units. On the other hand, experimental animal studies suggest that the therapeutic dose of antitoxin is the same whether the serum is homologous or heterologous in origin; on this basis, at least 5,000 to 10,000 units of tetanus immune globulin should be given.

Preliminary sensitivity tests are not needed prior to injection of tetanus immune globulin; however, since patients will on rare occasions be sensitive to the preservative, to a specific allotype of globulin in the preparation, etc., therefore epinephrine should be at hand when this product is given.

Safety

Like other animal sera, equine tetanus antitoxin can cause serious or fatal anaphylactic reactions in a small proportion of people and the discomfort of serum sickness in a much larger proportion of people. Therefore, its use always incurs at least a small risk. Parallel experience with prophylactic diphtheria antitoxin has disclosed about 1 death per 50,000 persons injected.

Being homologous in origin, tetanus immune globulin is almost reaction-free if given intramuscularly. However, it can cause alarming hypotensive reactions if given intravenously.

Efficacy

The use of tetanus antitoxin or tetanus immune globulin for the prophylaxis of tetanus is endorsed by most physicians on the basis of logic and clinical experience, although unequivocal proof of efficacy is not available. Both preparations can protect animals under experimental conditions against either toxin or spore challenges. Data from World War I suggested, but did not prove, that antitoxin prophylaxis was of significant value. On the other hand, 1 reviewer has collected reports of 5,000 failures of tetanus antitoxin to prevent tetanus and failures of prophylaxis have occurred with tetanus immune globulin as well. Such data do not prove that the product is ineffective, but they clearly show that there are limitations to its value. These may be due to inability to prevent fulminating tetanus, delay in prophylaxis, failure to prevent delayed tetanus, rapid metabolism of the antitoxin, and various other causes.

With regard to therepy, many reports have given conflicting results, but most reliable studies have tended to suggest that moderate doses of antitoxin are of some value, the optimal dose probably ranging between 10,000 and 20,000 units. However, as noted above, the role of antitoxin in the treatment of tetanus may be secondary to the crucial importance of sedation, maintenance of respiration, and control of infection. Likewise, deaths from tetanus have occurred following the therapeutic use of tetanus immune globulin. Except for its freedom from the danger of reactions and from rapid elimination from the circulation of the host, tetanus immune globulin is subject to the same limitations as tetanus antitoxins: it cannot reverse the effects of toxin already fixed to tissue, and the clinical management of tetanus is the same (except for serum reactions) with either agent. Clinicians will continue to use these products for treatment until they are fully evaluated despite incomplete evidence as to the efficacy of either agent for the treatment of tetanus.

The Panel believes that tetanus immune globulin and tetanus antitoxin (as an alternative) should be classified as Category I for prophylactic purposes. Although unequivocal proof of effectiveness for this purpose is not available, theoretical considerations and uncontrolled clinical experience support an assessment of probable effectiveness. Furthermore, it is unrealistic to expect that a study could be defended that would withhold tetanus immune globulin (or tetanus antitoxin) from a patient for whom it would be indicated under the Public Health Service Advisory Committee on Immunization Practices guidelines on wound management.

On the other hand, the therapeutic use of tetanus immune globulin and/or tetanus antitoxin is a somewhat different matter for the reasons discussed above. There is far less of a consensus among clinicians concerning the therapeutic effectiveness of these products in cases of tetanus. The number of years required to obtain additional data are indeterminate and the possiblity of controlled trials is very small because of the relatively low incidence of the disease and the probable low effect of the antitoxin. Although a Category IIIA was considered, the number of years required to obtain additional data are

indeterminant, and the possibility of controlled trials is very small. For this reason, a Category I classification for therapeutic use of tetanus immune globulin and/or tetanus antitoxin is recommended.

Special Problems

In the United States, tetanus immune globulin has virtually superseded equine antitoxin for prophylactic use, but the equine product is still used in therapy, presumably because of its acceptability for intravenous administration and possibly because of cost and availability. Clearly, if the problem of intravenous use of tetanus immune globulin could be surmounted, there would be little reason for maintaining supplies of equine antitoxin. Furthermore, a number of preparations of tetanus immune globulin have been made experimentally, either in the United States or Europe, which appear suitable for intravenous use. Therefore, it appears that the problem of developing a satisfactory intravenous tetanus immune globulin product may be soluble.

Further evidence for the prophylactic and therapeutic efficacy of tetanus immune globulin is needed, but for ethical reasons a controlled study in the United States cannot be easily done. However, one comparison between tetanus immune globulin and equine antitoxin (in neonatal tetanus) has already been conducted, and no difference was noted. As indicated earlier, such a result is inconclusive as to the effectiveness of either agent inasmuch as untreated controls were not included.

Recently the old but discarded practice of intrathecal administration of equine antitoxin has been revived and is under systematic study overseas, using preparations free of the irritating preservatives that in the past apparently caused severe reactions. Such studies should be watched with interest since they might have application to the similar use of appropriately modified tetanus immune globulin.

It should be noted that none of the above problems would exist if active immunization were universal.

Recommendations

1. Universal active immunization against tetanus should be promoted.

2. Support any studies necessary to establish the availability, safety, stability, and potency of tetanus immune globulin suitable for intravenous use.

3. Support studies, clinical or in animals, to provide further information of value in judging the value of tetanus immune globulin in prophylaxis and therapy of tetanus.

4. Review and follow the accumulating data on intrathecal therapy with a view to its possible applicability to treatment of human tetanus with tetanus immune globulin.

5. Further information should be obtained regarding the possibility of a significant reduction in the reactivity of animal serum.

Basis for Classification

In the absence of controlled studies, difficult to obtain with this now rare (in the United States) life-threatening disease, the Panel could not insist on such evidence of efficacy. There is a sufficient body of historical data suggesting that tetanus antitoxin is of some effect, albeit marginal, in the treatment and prophylaxis of tetanus to justify classification in Category I.

Bibliography

See Bibliography for tetanus toxoid.

SPECIFIC PRODUCT REVIEWS

Tetanus Antitoxin Manufactured by Istituto Sieroterapico Vaccinogeno Toscano Sclavo

1. *Description.* This antitoxin is a sterile aqueous solution of enzyme-refined and concentrated immunoglobulins obtained from the plasma of horses hyperimmunized with tetanus toxin and/or toxoid. The plasma is pepsin-digested and precipitated in ammonium sulfate. The precipitate is collected, dialyzed, made up to 0.85 percent sodium chloride and 0.3 percent metacresol at pH 6.4, and filtered for bulk chilled storage. It is tested for titer, pyrogens, pH, electrophoretic composition, protein concentration, preservative concentration, and sterility. These tests, plus tests for identity, potency, stability, and total solids, are done for each filling which may be in vials holding 1,500, 3,000, 5,000, or 25,000 units (plus excess for dating as may be required).

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for prevention and treatment of tetanus when tetanus immune globulin is not available. Prevention is indicated for individuals who have had two or fewer doses of tetanus toxoid and who have tetanus-prone injuries that are more than 24 hours old. Tetanus toxoid (plain or adsorbed) should be given in a different syringe at a different site, and the immunization completed later as per schedule.

Precautions include careful inquiries regarding allergies of any type and previous injections of serums. Skin tests (1:1,000, 0.1 mL intradermally) and eye tests (1 drop of 1:10 dilution into conjunctiva) are mandatory. Normal saline controls should be used. Interpretation of skin test results is described. Epinephrine 1:1,000 should be at hand in a syringe. In the event of a positive sensitivity test, a so-called "desensitization" sequence of injections is described.

Adverse reactions of the various types included under "serum sickness" are said to occur in about 10 percent of patients, more frequently with large doses. The usual dose is 1,500 to 5,000 units for prophylaxis, 50,000 to 100,000 for treatment.

b. *Contraindications.* Intravenous injections in patients showing positive sensitivity tests.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission to the Panel (Ref. 1) states that "The efficacy of the product has been confirmed by the good results obtained through the years in Italy and abroad" and cites 8 references including the American Academy of Pediatrics "Red Book"—but not Bianchi (Ref. 2) (who has collected reports of 5,000 prophylactic failures).

b. *Safety*—(1) *Animal.* Two thousand lots have been tested in guinea pigs and/or mice, with no unsatisfactory results. This product meets Federal requirements.

(2) *Human.* A few million vials have been marketed in the last 5 years without any "significant complaints" according to data submission.

c. *Benefit/risk ratio.* In the absence of tetanus immune globulin, the available evidence indicates that the benefit-to-risk assessment for this product would be satisfactory for the recommended uses.

4. *Critique.* This is a standard enzyme-purified antitoxin which appears to be prepared and tested with all necessary precautions and should be as safe and effective as any licensed tetanus antitoxins. The label does not explain the exclusion of this product from use in fresh wounds in the unimmunized.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for this product for which they were licensed at the time this

review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Massachusetts Public Health Biologic Laboratories

No data have been provided by the manufacturer for tetanus antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell Inc.

No data have been provided by the manufacturer for tetanus antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Parke Davis & Company

No data have been provided by the manufacturer for this product for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Swiss Serum and Vaccine Institute Berne

No data have been provided by the manufacturer for tetanus antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

References

(1) BER VOLUME 2112.

(2) Bianchi, R., "Zur Serumprophylaxe des Tetanus," *Helvetica Medica Acta*, 29:2, 101–142, May 1962.

Tetanus Immune Globulin (Human) Manufactured by Abbott Laboratories

1. *Description.* This is a 16.5 percent ±1.5 percent solution of immunoglobulin prepared by cold alcohol fractionation of plasma from donors hyperimmunized with tetanus toxoid. The product is stabilized with 0.3 M glycine and contains 0.01 percent thimerosal as a preservative. Plasma samples employed are nonreactive for hepatitis associated antigen.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization of patients with tetanus-prone injuries, especially when there is doubt of adequate immunity or if there is a history of severe reactions to tetanus toxoid. It is also indicated in the treatment of tetanus. It may be administered simultaneously with tetanus toxoid. The recommended prophylactic dose is 250 units; therapeutic dose data are not adequate although it is stated that doses ranging from 500 units in infants to 56,000 units in adults have been employed.

In general the labeling is rather vague and could be greatly improved by incorporating the Public Health Service Advisory Committee on Immunization Practices recommendations (or their equivalent) regarding wound management. The desirability of simultaneous active immunization with adsorbed toxoid should be stressed.

b. *Contraindications.* Avoid intravenous injection. Hypersensitivity reactions are rare, as with other immune globulins.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data relative to this manufacturer's product are given. Indeed it appears that Abbott Laboratories has marketed this product only as a partially processed material (dry globulin powder) for further manufacture. There are apparently no data available. The manufacturer's submission to the Panel (Ref. 2) cites the general literature on the subject in support of efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data relative to this product are given. Indeed no data are available even from marketing experience since the final product for which the license was granted has never been sold. Over a 5-year period, a few hundred Kg of the globulin power has been sold to other manufacturers.

c. *Benefit/risk ratio.* A benefit-to-risk assessment for this product cannot be determined.

4. *Critique.* Since there are actually no data at all on the safety and efficacy of the actual product for which a license was granted, and the licensed product per se has not been sold, there is no basis for any judgment. Theoretically, the product could be put through final processing and sold at any time, and there is no reason to think that it would be any less safe or effective than other marketed products.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Tetanus Immune Globulin (Human) Manufactured by Armour Pharmaceutical Company

1. *Description.* Tetanus immune globulin (human), as manufactured by the Armour Pharmaceutical Company, is a sterile 10 percent to 18 percent solution of the immunoglobulin fraction prepared from plasma of persons who have been hyperimmunized with tetanus toxoid. The solution is made isotonic with glycine and contains up to 0.1 percent sodium chloride. The pH is adjusted with either sodium bicarbonate or acetic acid, and 0.01 percent thimerosal is added as preservative. It is packaged in 250 unit vials.

Human plasma is pooled and fractionated to freeze-dried Fraction II powder, using the alcohol fractionation method of Cohn. Fraction II is reconstituted in water, stabilizers and preservative are added, and the solution further processed to the final dosage forms. An extensive description of the process is made part of the submission.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be indicated as a prophylactic agent in persons whose injuries are liable to tetanus infection. Although experience

is limited, tetanus immune globulin (human) in large doses is stated as being possibly useful in the therapy of clinical tetanus.

b. *Contraindications.* None are specified. A precaution against intravenous administration is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data supporting the efficacy in humans of this product is cited in the submission to the Panel (Ref. 1), but no specific data relative to the Armour Pharmaceutical Company's product are provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data relative to the Armour Pharmaceutical Company's product are provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The information supplied by the manufacturer, the animal tests that this product is required to pass, and the general body of data regarding the safety and efficacy of tetanus immune globulin (human) is sufficient to place this product in Category I. The labeling should be more specific about indications for tetanus immune globulin prophylaxis in humans. The recommendations of the Public Health Service Advisory Committee on Immunization Practices are quite specific on this point, and could well be reproduced in their entirety in the labeling. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* This globulin is prepared from outdated blood or plasma donated to the Bureau of Laboratories, Michigan Department of Public Health, from American Red Cross Regional Blood Centers, and Michigan Blood Banks affiliated with the Blood Salvage Program of the Michigan Department of Public Health. Outdated plasma containing significant amounts of tetanus antitoxin, as demonstrated by the hemagglutination test, is pooled and fractionated by the cold alcohol fractionation procedures of Cohn. The final product is prepared as a 15 to 18 percent protein solution to which 2.25 percent glycine has been added as a stabilizer, and 1:10,000 thimerosal is added as a preservative. It is distributed in 250 unit vials.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for use in injured persons who need the immediate protection offered by tetanus antitoxin. Persons who have received the basic course of tetanus immunization are recommended to receive a booster dose of tetanus toxoid in preference to tetanus immune globulin. It is rather emphatically stated that the use of this material should be based on specific recommendations from full time health officers and/or the Division of Epidemiology of the Michigan Department of Public Health. For that reason the Public Health Service Advisory Committee on Immunization Practices recommendations are not reprinted as such.

A separate product, tetanus immune globulin (human) for therapeutic use, containing 2,000 units of tetanus antitoxin per bottle is also produced by this laboratory. The product under consideration therefore is for prophylactic use only and contains 250 units of tetanus antitoxin to be given intramuscularly.

b. *Contraindications.* None are listed. A precaution against intravenous administration is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are provided. It is noted that thousands of doses of Michigan Department of Public Health's tetanus immune globulin have been distributed in Michigan since 1965 with no reports of adverse reactions having been received. There is no evidence that this particular product has been responsible for the transmission of hepatitis B virus.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears satisfactory.

4. *Critique.* This submission (Ref. 3) is brief, but generally complete and adequate. Information provided by the manufacturer, the animal tests the product is required to pass, together with the general body of data concerning tetanus immune globulin (human) are sufficient to determine this product to be safe and effective. The recommendations for use and indications should be clarified in the labeling. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Cutter Laboratories, Inc.

1. *Description.* Tetanus immune globulin (human), Hyper-Tet®, is a solution of immunoglobulin prepared from venous blood of humans hyperimmunized with tetanus toxoid. Hyper-Tet® contains 16.5 percent ±1.5 percent protein dissolved in 0.3 M glycine and preserved with 1:10,000 thimerosal. The pH is adjusted with sodium carbonate.

Antibodies of homologous origin (as this product) have been shown to have a half life in the blood stream of 3.5 to 4.5 weeks.

Vials are said to contain 250 units of tetanus immune globulin, but the volume in which this is contained is not given.

The plasma is obtained exclusively by plasmapheresis (4 percent sodium citrate) and only donors of sufficient titers are selected.

Informed consent is obtained before a donor is enrolled in the program and the donor's health appears to be adequately monitored by annual examination.

Only plasma from individual donors that is tested at each donation for hepatitis B antigen and is negative when tested by any one of the official Bureau of Biologics' methods is used. Outdated preserved whole blood is used for fractionation into the components of plasma. According to the Bureau of Biologics' directions, a minimum of 10 donors should be used. The Cohn cold alcohol fractionation method is used. No preservatives are added during the pooling of the plasma or fractionation.

The final product solution is sterilized by filtration. Sodium chloride U.S.P. is added to a final concentration of 0.45 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is indicated in those patients who require immediate immunity against tetanus toxin, especially those who have little or no active immunity against it. It is also indicated in the regimen of treatment of active cases of tetanus.

In cases where the injury is severe and where the risk of potential tetanus infection is higher, a dose in excess of that recommended may be indicated. Dosage: for adults, 250 units should be given by deep intramuscular injection. In small children the dose may be calculated by the body weight (4.0 units per kg) or it may be advisable to administer the entire contents of the vial. The Public Health Service Advisory

Committee on Immunization Practices is cited as a guide in would management.

b. *Contraindications.* This product is contraindicated in individuals who are known to have had an allergic response to immunoglobulin.

It is warned that the product should not be given intravenously, since such injections, on occasion, cause a precipitous fall in blood pressure, and a picture not unlike anaphylaxis. Skin tests should not be carried out because the product is known to cause a localized area of inflammation which can be misinterpreted as a positive allergic reaction.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several clinical studies consisting of measurement of antibody increase are reported in the submission to the Panel (Ref. 4) for this product. Twenty subjects were given 400 units of Hyper-Tet® and antibody levels compared with 15 subjects receiving 1,500 units of equine antitoxin. At first, serum levels were higher for those receiving the equine product in the high dosage, but after about 6 weeks higher levels of antitoxin remained among those receiving the human immunoglobulin.

Studies were also carried out measuring the response when subjects were given immunoglobulin alone or in combination with tetanus toxoid. Satisfactory (0.1) antitoxin levels were achieved with or without simultaneous administration of toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* References to safety reported in the literature are cited in the submission. The product is tested by several chemical tests as to content of protein, chloride, glycine, and for stability and pH, and electrophoretic identity.

c. *Benefit/risk ratio.* Although no human efficacy studies are available, on theoretical grounds the benefit-to-risk assessment should be satisfactory .

4. *Critique.* Labeling is satisfactory, although it may be desirable to give the approximate volume of plasma necessary to provide the recommended dose of 250 units. No data from the manufacturer's complaint files were provided. It is unclear how many donors are utilized for pooling of sera. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Dow Chemical Company

1. *Description.* Tetanus immune globulin (human), as produced by the Dow Chemical Company, is a sterile solution of immunoglobulin obtained from the pooled venous blood of humans hyperimmunized with tetanus toxiod. The contents of the vial or syringe are standardized to contain 250 units of tetanus antitoxin. It is prepared by Cohn cold alcohol fractionation, stabilized with 2.25 percent glycine, and preserved with 1:10,000 thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be indicated for passive immunization of persons incurring wounds other than clean, minor wounds only when the history of tetanus toxoid administration is uncertain, or if only one or no toxoid injection has been administered; or if the wound has been unattended for more than 24 hours even with the history of two toxoid injections.

b. *Contraindications.* None are listed. A precaution against intravenous use is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of literature supporting the efficacy of human tetanus immune globulin is cited in the submission (Ref. 5), but no specific data relative to the Dow Chemical Company's product are provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Ten human volunteers were given 250 units of tetanus immune globulin (human) intramuscularly, and observed immediately after the injection, and once daily at 24, 48, and 72 hours. No unusual untoward reactions were noted in these 10 volunteers. The general body of data supporting the human safety of tetanus immune globulin (human) is cited as well.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This submission is supported by a large number of reprints of data supporting the safety and efficacy of human tetanus immune globulin. Although little of the data applies directly to the Dow Chemical Company's product, the animal safety and efficacy tests, together with the general body of data supporting the safety and efficacy of human tetanus immune globulin, is sufficient to place this product in Category I. (See Generic Statement.)

In the labeling, the recommendations for use should be clarified.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by E.R. Squibb & Sons, Inc.

1. *Description.* This is a 16.5 percent solution of Cohn Fraction II obtained from plasma of selected donors immunized with tetanus toxoid. It is stabilized with 0.3 M glycine and contains 0.01 percent thimerosal as preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization against tetanus. It is recommended for prophylactic use (250 units) in patients lacking a recent (5 year) history of active immunization or in those never immunized or of uncertain status. Therapeutic doses of 3,000 units or more (up to 6,000 units) are recommended as part of the treatment of clinical tetanus. The narrative of the package insert is fairly adequate, but would be improved from the user's point-of-view by including the Public Health Service Advisory Committee on Immunization Practices wound management recommendations in tabular form. Also, the advisability of adsorbed tetanus toxoid for simultaneous active immunization needs to be stressed.

b. *Contraindications.* Essentially none, except avoidance of intravenous injections. Hypersensitivity reactions are rare.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on this product are given. The submission to the Panel (Ref. 6) refers to the American College of Surgeons 1972 recommendations and to a review by Heurich (Ref. 7) for prophylactic use of tetanus immune globulin and other aspects of management of tetanus.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data, not even the approximate number of doses distributed, are provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product cannot be determined.

4. *Critique.* The manufacturer has supplied no information on human safety and efficacy for this specific product. The product does not appear to

have been produced for a number of years.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked because this product has not been marketed for a number of years and there are insufficient data on labeling, safety, and effectiveness.

Tetanus Immune Globulin (Human) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This is a 10 to 18 percent solution of globulin derived from plasma of donors hyperimmunized with tetanus toxoid. The globulin is prepared by a modified Cohn alcohol fractionation process and is dissolved in 0.3 M glycine containing not more than 0.25 percent sodium chloride. The preservative is thimerosal, 0.01 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization against tetanus. For prophylactic use, a dose of 250 units is recommended in injured individuals who have not been previously immunized with tetanus toxoid or for those with vague histories or with lapses of many years since the last booster. Prophylactic use is also recommended when the risk is great from extensive contaminated wounds. Simultaneous active immunization is also recommended. For treatment purposes in the management of clinical tetanus, it is noted that experience is limited and that doses of 3,000 to 6,000 units have been used with mixed results. The instructions given are rather vague and could be improved by incorporation of the Public Health Service Advisory Committee on Immunization Practices recommendations on wound management with appropriate updating of the literature references. They should also specify adsorbed toxoid for use in simultaneous active immunization.

b. *Contraindications.* Essentially those for immunoglobulin, especially avoiding intravenous injection. Hypersensitivity reactions are extremely rare.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims for efficacy are based on the identity of the product and are supported by a review in the submission (Ref. 8) of a number of literature citations relevant to the use of tetanus immune globulin in general. No specific data on this particular product are given.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No significant reactions were reported for 1970 to 1974. A few hundred thousand doses were distributed over a 5-year period. Some mild local inflammatory reactions for immunoglobulin given for measles were seen in 1.2 percent of cases in 1969. In general, immune globulin is a product of proven safety which rarely presents a serious problem. There is no serious question of safety for this product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

4. *Critique.* There are no efficacy data in humans for this specific product. Tetanus immune globulin in a generic sense is an accepted product for the prophylaxis of tetanus where indicated. Its use along with other appropriate treatment is clearly accepted in cases of clinical tetanus although the appropriate dosage for this purpose is not clearly established. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is a 16.5 percent (±1.5 percent) solution of globulin prepared by cold ethanol fractionation of human plasma selected by hemagglutination tests to contain significant levels of tetanus antitoxin. It is stabilized by 0.3 M glycine and contains 0.01 percent thimerosal as a preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization in persons at risk of tetanus who lack a reliable history of active immunization. It is stated that a booster response to tetanus toxoid (even after 20 years) is preferred to tetanus antitoxin. Doses of 250 units given intramuscularly are recommended for prophylaxis. Simultaneous active immunization with adsorbed toxoid is always recommended. No specific recommendations on therapeutic use are given; in this case the use is advised to contact the producer. In general, the labeling is brief and to the point, although it is less easy to follow than the Public Health Service Advisory Committee on Immunization Practices guidelines.

b. *Contraindications.* Essentially none. Avoid intravenous injection. Hypersensitivity reactions are rare.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Publications from the manufacturer's laboratory relative to the use of the product are cited in the submission (Ref. 9). These pioneering and often cited papers document the recommended use of the 250 unit dose for prophylaxis as judged by maintenance of protective antitoxin levels. These studies document the feasibility and desirability of combined active-passive immunization, showing the superiority of adsorbed toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* From the years 1969 to 1973, thousands of 250 unit vials were distributed without incident. Considering the proven safety of immune globulin in general, there is no question of safety.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

4. *Critique.* This is a brief, but well-documented report from a laboratory that helped pioneer the concept of tetanus immune globulin. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This product is a solution of human immunoglobulin prepared by Cohn cold ethanol fractionation of plasma drawn from donors who have been hyperimmunized with tetanus toxoid. The solution is dissolved in 0.3 molar glycine and contains thimerosal 1:10,000 added as preservative. The protein content is given as 10 to 18 percent globulin and the antibody content is given as at least 250 units of tetanus antitoxin per dose.

The general procedure for immunization of donors is said to conform to the Federal regulations for source plasma, human.

2. *Labeling*—a. *Recommended use/indications.* This product is indicated in injured persons not actively immunized or in whom the immunization status is undetermined and who otherwise would be candidates for an injection of tetanus antitoxin for protection against the possibility of the development of tetanus. Passive protection need be considered only when the patient has had fewer than two previous injections of tetanus toxoid or when the wound has been untended for more than 24 hours.

The usual dosage for adults and children is 250 units (entire contents of one single-dose prefilled disposable syringe) regardless of body weight. The same dose is indicated for adults and children because theoretically the same amount of toxin will be produced in both.

More than 250 units may be indicated, together with antibiotics, when the risk of potential infection is great.

The advantages of using tetanus immune globulin rather than equine or bovine antitoxin are outlined. The product is also recommended for treatment of tetanus, but the dosage may vary, and it is said that 3,000 to 6,000 units have been used.

b. *Contraindications.* None are specifically given, but it is pointed out that the material should not be given intravenously, that local tenderness and stiffness of the muscles may occur after injection. Hypersensitivity to injections of immune serum globulin is mentioned as a possibility and in highly allergic individuals repeated injections may lead to anaphylactic shock or even death.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Pertinent human studies are cited in the submission (Ref. 10) but no serologic studies of the manufacturer's product appear to have been carried out.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No special testing of the manufacturer's product appears to have been carried out. However, between 1969 and 1974 a sizable number of doses have been distributed without any reports of adverse reactions having been received.

c. *Benefit/risk ratio.* Assuming this product is effective as discussed in the Generic Statement, the benefit-to-risk assessment should be satisfactory.

4. *Critique.* This is a rather brief application, which provides no specific data on the efficacy of the manufacturer's own product. The approximate volume containing one dose is not given. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Metabolic, Inc.

No data have been provided by the manufacturer for tetanus immune globulin, for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Immune Globulin (Human) Manufactured by Osterreichisches Institut fur Haemoderivate G.M.B.H.

1. *Description.* This is a tetanus immune globulin of human origin containing, per mL, 250 U.S. units of tetanus antitoxin, 100 to 160 mg of total protein, 22.5 mg glycine, 3.0 mg sodium chloride, and 1:10,000 thimerosal as preservative. The product is said to be prepared from blood of healthy donors who had been immunized against tetanus. A good description of the production process is provided, which basically consists of passage of a plasma pool through an adsorption column, followed by cold ethanol fractionation. The final protein concentration varies between 10 percent and 16 percent w/v.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be indicated in case of injury with risk of tetanus infection in instances in which adequate active immunity is not proven. "Adequate" active immunity is nowhere defined. Simultaneous active-passive vaccination is said to be indicated in cases of (1) lacking or inadequate active immunization or if definite history of immunization cannot be ascertained, (2) risk of antibody deficiency syndrome or reduced capacity of antibody formation, (3) risk of heavy contamination of the wound with tetanus bacilli, (4) injuries dating back longer than 3 days, and (5) serious burns.

b. *Contraindications.* The only contraindication listed is a previous severe reaction following the administration of tetanus immune globulin (human). A precaution against intravenous administration is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are provided. The submission (Ref. 11) contains an interesting report of one prophylactic failure in one case of a femur heavily injured by a slaughtering apparatus. The patient received active and passive immunization on the same day, but developed severe tetanus a few days later and died. The immunization history of this patient would have been considerable interest.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Radioimmunoassays for the determination of hepatitis B antigen are carried out on both the raw source plasma and the final product. The submission notes that no adverse reactions have been reported, and there have been no reports of transmission of hepatitis with this product. No prospective clinical data are presented, however.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The information provided by the manufacturer, the animal tests that this product is required to pass, and the general body of knowledge concerning the safety and efficacy of human tetanus immune globulin are sufficient to place this product in Category I for prophylactic use.

No labeling was provided in the sense of a package insert. Pages 3 through 9 of the submission appear to serve the same purpose, and suffer significantly in the translation from German to English. Extensive revision will be necessary to put the language into contemporary usage. "Adequate" active immunization must be defined, and reference should be made to official recommendations of advisory bodies such as the Public Health Service Advisory Committee on Immunization Practices. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Parke, Davis & Co.

1. *Description.* This product is a concentrated solution of tetanus antitoxin as immunoglobulin prepared from the blood of adults who have been hyperimmunized with tetanus toxoid. It is prepared from plasma, which was nonreactive when tested for hepatitis B antigen. The globulin is precipitated by the Cohn cold ethanol fractionation process and supplied as a sterile standardized solution containing 100 to 180 mg of protein per mL (10 to 18 percent). The globulin fraction is dissolved in a 2.25 percent solution of aminoacetic acid (glycine) containing approximately 0.2 percent sodium chloride. It is preserved with 0.01 percent thimerosal and adjusted to approximately pH 6.8 with sodium acetate buffer.

2. *Labeling*—a. *Recommended use/indications.* This product is

recommended for immediate passive immunization against tetanus as an emergency measure in persons sustaining other than clean minor wounds when immunization history is uncertain or when less than 2 doses of tetanus toxoid have been administered. When the wound is more than 24 hours old, however, the product should be given to patients who have received 2 doses of tetanus toxoid.

Tetanus immune globulin (human) is preferred over the similar product of equine or bovine origin.

The usual dosage for adults and children is 250 units regardless of body weight, although for children a dosage of 4 units per kg body weight may be adequate but larger doses are not harmful. The approximate volume necessary to supply the recommended dosage is not given; the material is supplied in a syringe.

Large doses (usually 3,000 to 6,000 units) of tetanus immune globulin (human) have been used therapeutically for treatment of clinical tetanus.

The use of combined active and passive immunization is discussed. If tetanus toxoid is not given immediately, active immunization with tetanus toxoid should be completed in all cases, either immediately or shortly after treatment.

b. *Contraindications.* None are stated, but it is mentioned under adverse reactions that reactions following intramuscular injections are infrequent and usually confined to the area of injection. Sensitization to repeated injections of tetanus immune globulin is said to be extremely unusual. As a precaution, the product should be administered intramuscularly, and not intravenously.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission to the Panel (Ref. 12) includes referral to the pertinent literature only. This specific product appears not to have been evaluated in any form in humans.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No adverse experiences have been reported in a 5-year span between 1969 and 1974 from the use of hundreds of thousands of doses distributed worldwide. The company has received 61 complaints in 51 reports. The tetanus immune globulin was cloudy in five of these cases, the remaining reports related to packaging defects.

c. *Benefit/risk ratio.* Assuming the product is effective as discussed in the Generic Statement, the benefit-to-risk assessment should be satisfactory.

4. *Critique.* The selection and monitoring of donors is not described, neither is the method of obtaining informed consent described. Labeling is generally satisfactory, except that the approximate volume of the dose should be stated. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Travenol Laboratories, Inc., Hyland Division

1. *Description.* Tetanus immune globulin (human), as produced by Travenol Laboratories, is a sterile 15 to 18 percent solution of immuno-globulin fraction of the plasma of persons who have been hyperimmunized with tetanus toxoid. The solution is made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. The globulin is precipitated by the alcohol fractionation technique of Cohn. It is packaged in 250-unit vials.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be useful in the treatment of injured persons at risk of tetanus and who need the immediate protection offered by tetanus antitoxin. Since it is of human origin, it offers two advantages over an antitoxin of nonhuman (equine) origin: (1) the risk of immediate or delayed sensitivity reactions is practically nonexistent; (2) fewer antitoxin units are required to produce a longer lasting effect. The labeling is quite specific in terms of who should receive tetanus immune globulin, containing not only the specific recommendations of the Public Health Service Advisory Committee on Immunization Practices, but also a rather cogent discussion of the recommendations.

b. *Contraindications.* No absolute contraindications are listed. A precaution against intravenous administrative is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data relative to the Travenol Laboratories' product are cited in the submission to the Panel (Ref. 13).

b. *Safety*—(1) *Animal.* This product meets Federal requirements

(2) *Human.* No specific data relative to this product are cited.

c. *benefit/risk ratio.* The benefit-to-risk assessment of this product appears to be satisfactory.

4. *Critique.* This submission, while brief, is quite to the point. Some specific details are provided relative to the testing for hepatitis B antigen, and to the hyperimmunization of donors. The information supplied by the manufacturer, the animal tests that the product is required to pass, and the general body of data regarding the safety and efficacy of tetanus immune globulin (human), as summarized in the Generic Statement on Tetanus Immune Globulin, are sufficient to place this product in Category I. For prophylactic use see Generic Statement.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* Tetanus immune globulin (human) is a sterile 16.5 (±1.5) percent solution of human immunoglobulin prepared by Cohn cold ethanol fractionation of plasma from donors hyperimmunized with tetanus toxoid. The final product contains 0.3 molar glycine as a diluent and stabilizer and 0.01 percent thimerosal as a preservative. This product was prepared from blood that was nonreactive when tested for hepatitis B antigen.

Wyeth Laboratories purchases from Cutter Laboratories sterile tetanus immune globulin in bulk volume that has been released by the Bureau of Biologics. The product is used in the TUBEX hypodermic syringe. The manufacturing procedure for the Cutter Laboratories' products, for which there is a separate application, thus applies also to the Wyeth Laboratories' product, and the reader is referred to the product review for the Cutter Laboratories' product. In summary, the Cutter Laboratories' manufacturing process appears satisfactory.

The Wyeth Laboratories' product is designed to contain not less than 175 antitoxin units per mL. The degree to which this minimal potency level is exceeded is a direct function of the degree of hyperimmunization reflected in the donor plasma pool.

2. *Labeling*—a. *Recommended use/indications.* Tetanus immune globulin (human) is indicated for passive immunization against tetanus in any person with an injury that might be contaminated with tetanus organisms, who has never been actively immunized with tetanus toxoid, or whose active immunity status is uncertain or of questionable validity and cannot be established. Passive immunization is probably also indicated for those

persons activily immunized with tetanus toxoid whose last recall (booster) dose or last dose of the basic immunizing series (reinforcing dose) was given more than 10 years prior to injury and if a delay of more than 24 hours has occurred between the time of injury and initiation of specific tetanus prophylaxis.

The need to initiate active immunization with tetanus toxoid adsorbed at the same time as the human immunoglobulin is clearly spelled out.

The recommended adult dose is 250 units intramuscularly. The dose for children may be calculated on the basis of body weight (4.0 units per kg) or the entire contents of the TUBEX may be injected regardless of body weight since theoretically the same amount of toxin would be produced by infecting tetanus organisms regardless of whether the infection is occurring in an adult or child.

The half-life of tetanus immune globulin is approximately 4 weeks. In situations where the threat of tetanus persists or for treatment of the disease, repeated doses may be administered.

b. *Contraindications.* None is specifically mentioned, but local and systemic reactions are said to be infrequent and usually mild. The risk of isoimmunization is ever present when immunoglobulin is administered to immunologically competent persons. Under precautions, it is warned that the product should not be given intravenously, because severe pyrogenic and fatal cardiovascular reactions have occurred following intravenous administrations. Tests for sensitivity should not be done.

3. *Analysis.* No specific analysis of efficacy or safety is outlined in this submission (Ref. 14). However, the product is purchased from Cutter Laboratories, for which a detailed separate submission is available. The reader is referred to the analysis of this product. Date on efficacy, based on studies of antitoxin in humans after administration of this product, are available. No field trials have been carried out, neither would such an undertaking be feasible at the present time. No data from the complaint file are available.

a. *Benefit/risk ratio.* Since the product produces satisfactory levels of antitoxin in human subjects with originally low antitoxin levels, and the product appears to be safe, the benefit-to-risk assessment should be satisfactory.

4. *Critique.* The efficacy and safety of this product is the same as for the Cutter Laboratories' product. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

References

(1) BER Volume 2108.
(2) BER Volume 2039.
(3) BER Volume 2071.
(4) BER Volume 2025.
(5) BER Volume 2087.
(6) "A Guide to Prophylaxis Against Tetanus in Wound Management," American College of Surgeons, 1972 Revision, pp. 32–33, December 1972.
(7) Heurich, A.E., J.C.M. Brust, and R.W. Richter, "Management of Urban Tetanus," *Medical Clinics of North America*, 57(6):1373–1381, 1973.
(8) BER Volume 2030.
(9) BER Volume 2055.
(10) BER Volume 2012.
(11) BER Volume 2115.
(12) BER Volume 2004.
(13) BER Volume 2107.
(14) BER Volume 2018.

MISCELLANEOUS PRODUCTS

Collagenase Manufactured by Advance Biofactures Corporation, Distributed by Knoll Pharmaceutical Corporation

1. *Description.* Collagenase ABC ointment and collagenase santyl ointment contains the enzyme collagenase extracted from cultures of *Clostridium histolyticum* suspended in a petrolatum base in a concentration of 250 units per gram. Collagenase is an enzyme which digests undenatured collagen fibers. Collagen is produced by fibroblasts and exists in the form of an interwoven fiber consisting of three strands which in turn are made up of a left-handed poly-1-proline type helix. The ropelike coiled structure then has an opposite (right handed) supertwist. The uniqueness of collagenases compared with other proteolytic enzymes is that they attack the intact helical structure of collagen. Although collagenase from other sources are described, only that from *Clostridium histolyticum* has been produced in significant amounts for therapeutic application.

Other proteolytic enzymes employed in debridement act on fibrin and on denatured collagen but do not break up native collagen fibers which anchor the eschars of large ulcers, particularly burns, to the wound.

Collagenase is prepared from the supernatant of broth cultures of a standard strain of *Clostridium histolyticum*. The enzyme is concentrated by ammonium sulphate precipitation and the concentrate is sterilized by x-radiation. It is mixed with white petrolatum U.S.P. and distributed in containers without preservatives. The potency of the enzyme is measured by an assay involving the digestion of bovine Achilles tendon and the subsequent measurement of liberated amino acids with ninhydrin reagent.

2. *Labeling*—a. *Recommended use/indications.* The ointment is recommended as a therapeutic debriding agent for dermal ulcers and burns and particularly to remove dense eschars which anchor necrotic tissue to the base of wounds and delay their epithelization. The enzyme is active at physiologic pH and temperature and loses activity rapidly at unfavorable conditions. The activity is also adversely affected by detergents, hexachlorophene, and heavy metals such as mercury and silver which are contained in certain antiseptic solutions (e.g., Burow's Solution). Lesions must be thoroughly washed with normal saline before applying collagenase. The ointment should be confined to the lesions and normal surrounding skin should be protected by dressings. Concurrent infection should be treated with topical antibiotics. Debilitated patients must be closely observed for the theoretical possibility of disseminated infection and bacteremia during the debridement. Crosshatching a thick eschar with a scalpel to increase penetration of the enzyme is helpful as is removing and loosening as much necrotic tissue as possible with forcepts and scissors. Excess ointment should be removed with each daily change of dressing. It is appropriately pointed out that treatment of necrotic lesions other than dermal ulcers and severly burned areas has been limited only to reports of clinical observations without controls.

b. *Contraindications.* Since the enzyme is a protein, sensitization may develop with prolonged use although none has been reported. Adverse reactions have not been noted when used as recommended.

3. *Analysis*—a. *Efficacy.* Five contolled and 12 partially controlled studies are cited in the submission to the Panel (Ref. 1) as supporting evidence of efficacy. The five controlled studies were double-blind and included placebos. The controlled studies involved a total of 79 patients with dermal ulcers or decubiti. Some of these studies employed inactivated enzyme as placebo, were randomized, and a relatively brief treatment period was evaluated to prevent obvious changes in the wounds from unblinding the study. Attempts were made to score the responses objectively by recording

wound size, using serial photographs, obtaining cultures, and recording estimates of the amount and character of pus, debris, odor, and inflammation. In all controlled studies there was a statistically significant difference in favor of collagenase over placebos in all measured parameters of wound healing (Table 1).

b. *Safety.* This product is well tolerated when used properly and no significant untoward effects have been reported except occasional erythema. Animal studies reveal a high level of tolerance and low toxicity in rabbits, mice, and guinea pigs by injection of enzyme powder subcutaneously, intramuscularly, and intravenously. Topical application in animals produces local erythema but no systemic toxicity. This product meets Federal requirements.

TABLE 1.—SUMMARY TABLE-EFFICACY

Number and investigator	Exhibit No.	Diagnosis	Patients treated	Lesions treated [1]	Satisfactory Response [2] E or G
1—Controlled studies:					
Varma				C-10	9
	34	Dermal ulcers; decubiti	20	P-10	1
German				C-32	31
	13	Decubiti	34	P+-22	5
Bardfeld				C-9	9
	2	Lower extremity ulcers	8	P+-5	0
Ambrus				C-17	11
	1	Decubiti	10	P-10	0
Boxer		Venous or arterial ulcers; decubiti		C-10	9
	7 and 8	dedubiti	7	P-7	1
2—Partially controlled and uncontrolled studies:					
German				C-15	12
	13	Decubiti	26	P-11	1
Boxer	7 and 8	P. V. ulcers and decubiti	40	C-62	58
Georgiev	12	Decubiti	21	C-21	17
Rein	31	Burns	6		6
Barrett				C-12	12
	3	Decubiti	12	P-4	0
Original submission				C-327	270
	33	Dermal ulcers, burns	268	P+-155	70
Lippmann	20	Dermal ulcers	40	C-40	34
Mixurek	24	Dermal ulcers, wounds; burns [4]	1,356	C-1,356	1,065
Zimmermann	37	Dermal ulcers	64	C-64	Not reported
Zimmermann	36	Burns	230	C-230	Not reported
Mahler	22	Extensive burns	59	C-59	Not reported
Blum	5	Dermal ulcers, decubiti; burns	71	C-71	59 Fair–Good

[1] Refers to Exhibit in manufacturer's submission to the Panel (Ref. 1).
[2] C=Collagenase, P=Placebo, P+=Controls consisted of either placebo or other active agents.
[3] E=Excellent, G=Good.
[4] Includes Zimmermann studies.

c. *Benefit/risk ratio.* For use in the treatment of dermal ulcers and burns, the ratio is satisfactory since the risk is small and with proper usage there is often significant improvement in the character of the wound without interference with antibiotic efficacy or other forms of treatment.

4. *Critique.* There is little question that this enzyme can digest intact collagen and that in large, eschared dermal ulcers described, such as those encountered in decubiti and burns, surface debridement can be enhanced, and that decrease in pus, inflammation, and odor is quite regularly observed; adverse reactions are few. The labeling is accurate and pertinent and clearly defines the limitations of the product and instructions for its use. It is not clear, however, why, in some labels, routine topical antibiotic treatment is insisted upon rather than advised when indicated by the degree of infection. Labeling for these products may have to be revised to discuss the possible interference of silver sulfadiazine or sulfamylon with the enzymatic activity of collagenase, an issue not fully resolved by the Fox, Sanford, and Sampath paper (Ref. 2).

5. *Recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued because there is satisfactory evidence of safety and effectiveness for the products when used as recommended, provided the labeling is revised in accordance with this Report.

References

(1) BER Volume 2119 and 2120.
(2) BER Volume 2118.

Bibliography

(1) Bardfeld, L. A., "Treatment of Dermal Ulcers of the Lower Extremity With Collagenase," *in* "Collagenase," Mandel, I. (editor), New York, Gordon and Beach, pp. 191–195, 1972.

(2) Boyer, A. M., N. Gottesman and H. Bernstein, "Debridement of Dermal Ulcers and Decubiti With Collagenase," *in* "Collagenase," Mandel, I. (editor), New York, Gordon and Breach, pp. 155–163, 1972.

(3) German, F. M., "Control of Dermal Ulcers With Collagenase," *in* "Collagenase," Mandel, I. (editor), New York, Gordon and Breach, pp. 165–169, 1972.

(4) Lee, L. K. and J. L. Ambrus, "Collagenase Therapy for Decubitus Ulcers," *Geriatrics*, 30(5):91–93, 97–98, 1975.

(5) Varma, A. O., E. Bugatch and F. M. German, "Debridement of Dermal Ulcers With Collagenase," *Surgery, Gynecology and Obstetrics*, 136:281–282, 1973.

Generic Statement

Streptokinase-Streptodornase

Streptokinase-Streptodornase is a mixture of extracellular enzyme activators and enzymes produced by some sero-groups of hemolytic streptococci. These agents liquify fibrin and nucleoproteins in purulent exudates. Streptokinase effects the conversion of plasminogen to plasmin, a proteolytic plasma enzyme. The latter digests fibrinogen and fibrin, resulting in fibrinolysis. Streptodornase is a group of enzymes that act in stages to liquify deoxyribonucleoprotein, the viscous cellular protein present in pus.

Tillett and Garner first described the fibrinolytic activity of hemolytic streptococci in 1933. By 1949 partial purification of the streptococcal extracellular enzymes that liquify pus was accomplished and the liquid

preparation of Streptokinase-Streptodornase was introduced into therapy by Tillett and Sherry who instilled it into the pleural cavity to accomplish lysis of thick exudates. Topical use of the preparation for "enzymatic debridement" of purulent exudates was widely employed by 1950 and by 1955 intramuscular injections were tried for the nonspecific suppression of inflammation and edema in certain local infections. In 1958, buccal administration of tablets was introduced as an alternative to intramuscular injections and by 1960 clinical investigation of the effectiveness of oral tablets began, followed by marketing in 1963.

Production

The mixture of Streptokinase-Streptodornase employed in topical therapy is an extracellular product of a Group C strain of streptococcus grown for about 18 hours in a medium consisting of acid-hydrolyzed casein fortified with sugar, minerals, vitamins, and a reducing substance. The culture filtrate is purified by the method of cold alcohol fractionation. A unit of streptokinase is the quantity required to produce from plasminogen an amount of plasmin sufficient to dissolve a standard fibrin clot in 10 minutes at 35 °C. A unit of streptodornase is the quantity necessary to cause a decrease of 1 viscosity unit in 10 minutes at 30 °C in a reaction mixture of 2.4 mL of deoxyribonucleic acid of a standard relative viscosity. The streptokinase-streptodornase mixture also includes a number of other streptococcal extracellular enzymes such as deoxyribonuclease, hyaluronidase, nucleotidase, and nucleosidase, all of which may contribute to the liquifying effect of the product on purulent exudates. The mixture is apparently free of streptolysin and proteinase. The solution is buffered with phosphate. Some preparations are mixed with carboxymethylcellulose 4.5 percent jelly. Mixtures are unstable at room temperature but retain full potency for 2 weeks when refrigerated at 2 to 10 °C.

Labeling

1. *Use and indications.* Compatibility with antibiotics is not yet clearly determined and it is recommended that antibiotics be administered separately. Streptokinase and streptodornase administered in solution either locally or parenterally are both antigenic and frequently elicit antienzyme antibodies. These antienzymes, antistreptokinase and antistreptococcal DNAses may also appear after hemolytic streptococcal infections. A high titer is not harmful but requires increasing dosage of streptokinase-streptodornase to exert an effect. No antigenic responses have been reported for the buccal or oral forms but it is likely that they may also occur.

The rationale for topical or local administration of streptokinase-streptodornase is the augmentation of liquefaction of fibrin and pus where such action is considered desirable to produce healing more rapidly and to prevent extensive adhesions and fibrosis. The product does not act upon mucoproteins, fibroblasts, fibrous tissues, or collagen in vivo although lysis in vitro has occasionally been reported.

Streptokinase is considered the most effective therapeutic agent available for enhancing the resolution of fibrin in closed body cavities containing inflammatory effusions (or clotted blood). It is superior to proteolytic enzymes for this purpose. Most inflammatory exudates contain plasminogen and the mechanism of fibrinolysis results from the diffusion of the plasminogen activator into the fibrinous substance resulting in production of plasmin within the fibrin network and thus rapid fibrinolysis. In addition, streptokinase is inactivated slowly (except by antistreptokinase) in contrast to proteolytic enzymes. On surface wounds, however, where proteolytic enzymes such as trypsin are not blocked by tissue inhibitors, plasmin is not as effective as other more widely active proteolytic enzymes. Thus, third degree burn eschars and necrotic connective tissues are not susceptible to plasmin digestion but are attacked by trypsin.

Except for the occasional presence of antistreptodornase, inflammatory exudates contain little which inhibits the activity of topically administered streptodornase. When streptodornase is administered systemically, however, its inactivation is rapid. For this reason, parenterally administered streptokinase-streptodornase owes whatever specific effect it may have exclusively to streptokinase.

A peculiar situation exists, therefore, whereby streptokinase-streptodornase has been licensed for parenteral as well as topical use although any claim for parenteral efficacy would have to be unrelated to the action of streptodornase. Moreover, purified streptokinase for intravenous use in the treatment of thromboembolism is now available commercially and two preparations have recently been licensed.

The administration of streptokinase-streptodornase intramuscularly in dosages of 5,000 units of streptokinase twice daily has been recommended in the treatment of edema associated with infection and trauma, particularly cellulitis and thrombophlebitis, rather than extensive tissue necrosis. Claims have been made for rapid reduction in inflammatory reactions within a few days of initiation of treatment. About 10 percent of treated patients develop fever thought to be attributable to streptokinase-streptodornase. The recommended doses do not produce fibrinolysis, hematomas, petechiae, or hemmorrhage.

Package inserts recommend that streptokinase-streptodornase intramuscularly be accompanied by the systemic administration of a broad spectrum antibiotic agent. It is also emphasized that in the treatment of abscesses, streptokinase-streptodornase, intramuscularly, may reduce accompanying cellulitis but should not replace sound surgical principles of drainage.

Administration (as recommended by current labeling). Streptokinase-streptodornase has been tried and recommended by the manufacturer for a long list of clinical applications. Appraisal of these is complicated and compounded by distinctions between topical application, local instillation into body cavities and abscesses, intramuscular administration, buccal tablets for parenteral administration, and oral tablets.

Topical administration may be achieved in a variety of ways including dressing with streptokinase-streptodornase solutions, or application of streptokinase-streptodornase in a carboxymethylcellulose jelly. Instillation and irrigation in body cavities are effected by repeated applications and drainage as exudates are thinned.

Intramuscular streptokinase-streptodornase is recommended by the manufacturers for treatment of inflammation in inaccessible areas. It is suggested that such intramuscular injections deep into the gluteal muscle induce a "fibrinolytic response in areas of inflammation of any site." This is alleged to result in rapid reversal of the inflammatory process presumably by the digestion of fibrin in the edema fluid and reduction of the viscosity of the fluid.

Buccal tablets are recommended to produce results comparable to intramuscular administration. The tablets are placed in the buccal pouch or under the tongue and allowed to dissolve slowly for 10 minutes or more.

Oral administration is also advised on the grounds that gastric juice contains a

considerable amount of "plasminogen proactivator," which reacts with streptokinase, and the product is supposedly absorbed without inactivation.

Clinical applications suggested by manufacturers include: treatment of abscesses (by topical application only—parenteral has not been considered effective), bronchopulmonary inflammation by aerosol or instillation, or by systemic administration; cellulitis, ulceration, and necrosis; gangrene from occlusive arterial disease (excluding dry gangrene); radiation necrosis; cervicitis; contusions, ecchymoses, and hematomas (topical, intramuscular, and oral); cystitis, bladder clots, ureteral calculi (all forms of administration); dental and oral disorders, dermatological conditions (e.g., cystic acne vulgaris); empyema and hemothorax; nontuberculous purulent meningitis; suppurative joint infections; osteomyelitis; pericarditis; ophthalmic inflammation; puerperal pelvic conditions; pulmonary hyaline membrane syndrome; sinusitis and many other inflammatory conditions.

Thrombophlebitis and thromboembolic disease require special comment. Purified products of streptokinase are now licensed for intravenous and intraarterial therapy. Several cooperative trials have been conducted on the effectiveness of intravenous urokinase and streptokinase in pulmonary embolism and deep vein thrombosis and in myocardial infarction and other forms of arterial thrombosis. These and other studies have been summarized in several excellent recent reviews.

2. *Contraindications and precautions recommended in current labeling*—a. *Topical and local use.* Should be used only in areas where adequate drainage is maintained or in closed spaces, such as the pleural cavity when adequate drainage or operation is possible. A local increase of exudation and leukocytosis occurs in the first 24 hours. Pyrogenic reactions are the most common untoward effect. Allergic reactions are rare but the physician should be alert to the possibility of such reactions. Streptokinase-streptodornase is antigenic, which limits the effectiveness of prolonged and repeated use.

b. *Intramuscular use.* Administration of broad spectrum antibiotics is advised concomitantly with the use of streptokinase-streptodornase intramuscularly. Appropriate surgical drainage is also urged. Defects in blood coagulation of liver disease are contraindications to parenteral use.

c. *Buccal tablets.* Buccal tablets are contraindicated in patients with reduced plasminogen or fibrinogen. Urticaria and rashes have been reported.

d. *Oral tablets.* Oral tablets are also contraindicated in patients with reduced plasminogen and fibrinogen.

Safety

No reactions have been reported from 1969 through April 1974 for the use of topical streptokinase-streptodornase produced by Lederle Laboratories.

Efficacy

To clarify considerations of safety and efficacy, the recommended uses of streptokinase-streptodornase should be clearly separated into three general categories: (i) Debridement, (ii) anti-inflammation, and (iii) thrombolysis; and the effectiveness of each product should be considered in relation to these categories. (See Table 1.)

1. *Debridement.* On theoretical grounds, by in vitro studies, and by clinical observations, topical and local use of streptokinase-streptodornase can be expected to liquefy pus and blood clots in vivo in several conditions and under appropriate methods of application. Topical and local use of streptokinase-streptodornase may have efficacy in some situations where enhanced liquefaction of pus and fibrin is beneficial and where the products of inflammation can be properly drained. Such uses are clearly only adjunctive to other medical and surgical procedures. The effectiveness of streptokinase-streptodornase can only be assessed, therefore, as a supportive rather than primary therapeutic agent. Furthermore, instruction for its usage must clearly define its major limitations as a topical agent—its substrates must be available and accessible and the enzymes and activators must be in continued contract with their substrates under physiological conditions of temperature and pH. For these reasons, instructions for the local and topical uses should be clearly subdivided into topographical categories, such as: (i) body cavities, (ii) wounds and fistulae, and (iii) the lumina of body passages (bronchi, urethra, external auditory canal, etc.). Extensive lists of clinical conditions for which streptokinase-streptodornase is recommended by the manufacturer do not offer critical guidance to the selection of the appropriate clinical indications.

Body cavities. Streptokinase-streptodornase may be effective in liquefying pus and fibrin in certain body cavities as in the case of treatment of the appropriate stages of empyema or hemothorax, provided that adequate drainage is maintained. Lysis of inflammatory products and the local irritative effect of streptokinase-streptodornase cause an increased volume of fluid to accumulate in a closed cavity and the ease with which a cavity can be drained should be considered before employing the product. The use of streptokinase-streptodornase intrathecally is not generally recommended for primary forms of meningitis because of the severe local reactions it produces. The irrigation of neurosurgical drainage systems in certain cases of chronic obstruction of the cerebrospinal circulation may not be contraindicated, however, but would depend upon well-informed clinical judgment as to its value. Instillation of streptokinase-streptodornase into body cavities probably offers the best opportunities to maintain local contact of the product with its substrates and yet it is not extensively employed in current practice because of other effective medical and surgical approaches to drainage of such cavities.

Wounds and fistulae. Topical therapy with streptokinase-streptodornase may also have adjunctive effectiveness in the treatment of wounds and fistulae by enhancing debridement, but the need for maintaining continuous contact with the surface of these lesions must be emphasized. Suspension of streptokinase-streptodornase in a jelly (such as carboxymethylcellulose) may facilitate such application, but again efficacy would depend upon the ingenuity with which would contact is maintained with either solutions or pastes. There seem not to be significant reactions or contraindications to such topical use.

Luminal applications. The same issues, discussed above, apply to the efficacy of debridement of such tracts as the bronchi, urethra, auditory canals, etc. The clinical investigative evidence for the effectiveness of streptokinase-streptodornase in the debridement of these areas is even more difficult to assess than debridgement of body cavities and wounds. So many variables are included in attempts to maintain good drainage of the respiratory, urinary, and other tracts, that the design of an effective investigative protocol to demonstrate clear adjunctive efficacy of streptokinase-streptodornase would be very difficult if not impossible. Some degree of efficacy could be assumed, however, if the recommendations for topical use are followed closely.

2. *Anti-inflammatory effects of streptokinase-streptodornase.* The evidence of the parenteral use of

streptokinase-streptodornase, either intramuscularly or by buccal tablets, or the use of oral tablets, is inadequate to establish these products as effective agents for reducing inflammatory reactions. The criteria of physiologic responses by which the systemic dose can be monitored are vague since the doses are below the threshold of fibrinolysis. The empirical criteria for beneficial responses are subjective and anecdotal and based on such observations as "improved" or "excellent" response in complex multifactorial diseases. Because streptodornase is inactive when given parenterally, the alleged anti-inflammatory effect should be due either to streptokinase activity or to the nonspecific effects of streptococcal proteins on host defenses. Because streptokinase activity by the dose and methods given cannot be demonstrated to be fibrinolytic, the remaining rationale for streptokinase-streptodornase as an anti-inflammatory agent might be its nonspecific effect as a foreign protein. The latter does not constitute an adequate rationale for the use of streptokinase-streptodornase as an anti-inflammatory agent.

3. *Thrombolysis.* In contrast to the intramuscular use of streptokinase-streptodornase, recent clinical investigation of highly purified and potent preparations of streptokinase and urokinase have been carried out in the treatment of thromboembolic diseases. Two purified streptokinase preparations have recently been licensed by FDA. An appraisal of clinical efficacy should be considered separately for each of the following indications:

a. *Pulmonary embolism and deep vein thrombosis.* It is difficult to separate these two indications because pulmonary embolism that does not arise from thrombi in the right heart is almost always associated with deep vein thrombosis. In pulmonary embolism the diagnostic tools of angiography ventilation-perfusion lung scans, and selective vascular catheterization have permitted quantification of the effects of thrombolytic agents on pulmonary emboli to an extent not possible with many other lesions. Although all recent studies were not always completely controlled, the universal observation has been more rapid resolution of the embolus than expected with conventional treatment and the parameters of improved functions measured were frequently statistically significant.

Similarly, it has been well demonstrated by venous angiograms in a statistically significant number of selected cases that thrombi in the deep veins of the lower extremity can be lysed and blood flow restored, at least temporarily.

In life-threatening pulmonary embolization, wherein obstruction of the pulmonary circulation is of a severe degree, intravenous streptokinase clearly improves blood flow. What is not yet proven by adequate clinical data is whether such use reduces mortality significantly, reduces subsequent embolization, or reduces damage to the lungs. Similarly, the demonstrated lysis of venous thrombi in the lower extremities does not yet establish that normal venous function has been restored, vascular damage avoided reduced, pulmonaryemboli reduced, or chronic venous insufficiency prevented. Further experience will be necessary to determine the degree of efficacy of intravenous streptokinase in this form of thromboembolic disease. Meanwhile, however, the Panel considers intravenous streptokinase with the licensed products to be effective to the extent described and within the limitations expressed.

b. *Arterial thrombosis*—(1) *Myocardial infarction.* Of nine recent controlled clinical trials (Refs. 3 through 12), three early European trials showed a statistically significant decrease in mortality in patients treated with streptokinase for 18 to 24 hours as compared to controls. In general, trials which only a minority of patients were studied in coronary care units suggested reduced mortality in patients treated with fibrinolytic agents; whereas four controlled randomized trials done entirely in coronary care units failed to verify these findings. Further trials are needed to clarify whether there are true benefits to be derived from treatment of myocardial infarctions with intravenous fibrinolytic agents.

(2) *Peripheral arterial thrombosis.* Although data for efficacy in acute arterial occlusion suggest some effect, especially in the more distal vessels of the lower extremity, the critical and urgent nature of such problems usually demands a surgical approach. Use of thrombolytic agents for peripheral arterial occlusion should probably be limited to clinically important lesions in patients who either are poor surgical candidates or in whom the indications for surgery are not absolute. Adequate data to establish efficacy are not yet available, however.

c. *Retinal diseases.* The reported experience of patients with retinal vascular disease treated with thrombolytic agents is generally anecdotal and insufficient to establish efficacy. Controlled studies with objective, double-blind measurements are, however, underway.

d. *Complications of intravenous thrombolytic therapy.* Fever appears to be a common reaction. A single dose of 100 mg of hydrocortisone intravenously has been administered routinely in several investigative protocols presumably to reduce the febrile and "allergic" responses. No clear evidence for the value of corticosteriods administered this way is available. The nature of the pyrogenic reaction is also not clear. It may be hyperimmune or an endotoxin-like reaction to the streptococcal protein or it may be the result of rapid fibrinolysis. Skin testing in man to determine the local reactivity of the highly purified streptokinase products has not been done systematically.

Clearly allergic reactions (other than fever) have been remarkably few and have been more annoying than serious. A few cases have been reported wherein shock-like reactions resembling sublethal anaphylaxis have occurred. The nature of these are difficult to establish, but on theoretical grounds a rare truly anaphylactic reaction may be anticipated.

Bleeding is common from puncture sites, but serious hemorrhage occurs only occasionally and usually is due to underlying predisposing causes.

Antibodies to streptokinase are stimulated and they may increase refractoriness to repeated doses. More careful studies of these responses and their possible relation to untoward reactions involving immune complexes should be made.

e. *Contraindications of thrombolytic therapy.* These are similar to contraindications of anticoagulant therapy—bleeding disorders, recent surgery, severe hypertension, gastrointestinal ulcers, diabetic retinopathy, and recent cerebrovascular accidents.

Recommendations

For the sake of clarity, the following table relates the recommendations by major category of usage to the licensed products available.

1. *Topical products.* Category I is recommended for the topical use of streptokinase-streptodornase but only if the current labeling is revised to conform with the recommendations detailed above. The value of the suspension of the topical product in carboxymethylcellulose should be documented by further clinical evidence of effectiveness (Category IIIA).

2. The streptokinase-streptodornase products for intramuscular and oral use, including buccal tablets, have not been proved to be effective thrombolytic or anti-inflammatory agents. Category II is recommended for these.

3. The Panel considers the intravenous use of streptokinase with the licensed products to be effective to the extent described and within the limitations expressed. Further intensive investigation of streptokinase and urokinase in thromboembolic disease should be encouraged, bearing in mind that risk-benefit assessments will vary greatly in individual clinical conditions and circumstances.

Efforts to purify or synthesize urokinase should also be encouraged in order to substitute a naturally synthesized human product for a streptococcal protein.

TABLE 1.—STREPTOKINASE-STREPTODORNASE

Indications	Topical		Tablets			Intravenous
	Topical	Jelly	Intramuscular	Buccal	Oral	
1. Debridement:						
a. Body cavities	I (1)					
b. Wounds and fistulae	I (1)	III A				
c. Luminal	I (1)					
2. Anti-inflammatory			II	II	II	
3. Thrombolytic			II	II	II	I

I = Effective.
II = Ineffective.
IIIA = More clinical data required before efficacy can be determined.
— = Not applicable.
(1) = Revise labeling.

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Streptokinase-Streptodornase (Varidase) Buccal Tablets Manufactured by Lederle Laboratories Division, American Cyanamid Co.

The manufacturer did not submit specific information for streptokinase-streptodornase buccal tablets. In its generic review of buccally administered streptokinase-streptodornase, the Panel found no evidence that this product is effective.

Recommendations. The Panel recommends that this product be placed in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

Varidase, Intramuscular, Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Each vial for intramuscular injection contains 20,000 units of streptokinase and at least 5,000 units of streptodornase with thimerosal 0.2 mL per vial added as a preservative. The production of streptokinase-streptodornase is as described in the Generic Statement. Two milliliters of sterile water for injection of sterile physiologic saline is added to the contents of a vial to make a solution containing 5,000 units of streptokinase per 0.5 mL for intramuscular injection. Procedures employed in the manufacture of Varidase include standards tests for pyrogenicity in animals and sterility.

2. *Labeling*—a. *Recommended use/indications.* Intramuscular use of Varidase is recommended in the treatment of edema associated with infection and trauma. The best results are claimed in infections that do not produce necrosis of tissue such as thrombophlebitis, epididymitis, and cellulitis. A beneficial effect of inflammation and edema with the use of this product is expected in all patients within 2 days after the start of treatment and in a small number of patients within a period of hours. An aggravation of the infection has not been observed in any of the patients but a rise in temperature attributable to streptokinase has been noted in about 10 percent of these patients. No significant change in prothrombin time nor in fibrinolysis can be detected at usual doses recommended. It is recommended that intramuscular use of Varidase be accompanied by the administration systemically of a broad-spectrum antibiotic. The use of the product in patients with abscesses is not a substitute for sound surgical principles.

b. *Contraindications.* Varidase should never be administered intravenously. Varidase should not be injected intramuscularly when there is evidence of a defect in blood coagulation, or where liver function is depressed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* Upon intramuscular injection, the mechanism by which streptokinase produces a reversal of the inflammatory process is not known. The streptodornase in the product is inactive when administered systemically. Parenteral administration has not been considered effective in the treatment of abscesses but is claimed to be effective in a wide variety of inflammatory lesions including bronchopulmonary inflammation (by either aerosol or systemic administration), gangrene from occlusive arterial disease, radiation necrosis, cervicitis, cystitis, pericarditis, osteomyelitis, etc.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No significant untoward reactions reported. Streptokinase and streptodornase are antigenic but allergic reactions are rare. The antibody response may require higher dosage to overcome inhibition of enzyme action but is not harmful.

c. *Benefit/risk ratio.* There is little risk in the use of the product but efficacy has not been demonstrated.

4. *Critique.* The criteria of physiologic responses by which the systemic dose of streptokinase can be monitored are vague since the doses are below the threshold of fibrinolysis. The empirical criteria for beneficial responses are subjective and anecdotal and based on such observations as "improved" or "excellent response" in complex multifactorial disease and unmatched control series. Because streptodornase is inactive when given parenterally and streptokinase activity in the dose given cannot be demonstrated to be fibrinolytic or clearly antithrombotic, the only remaining rationale for streptokinase-streptodornase as anti-inflammatory therapy might be its nonspecific effect as a foreign protein. The latter does not constitute an adequate rationale for the use of

streptokinase-streptodornase as an anti-inflammatory agent.

5. *Recommendations.* The Panal recommends that this product be placed in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

Varidase, Oral Tablets, Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Desciption.* Each tablet contains 1,000 units of streptokinase and 2,500 units of streptodornase. Tablets are marketed as peach-colored, round, flat-faced, beveled tablets scored in half and 1 1/32 inches in diameter. The enzymes are prepared as described in the Generic Statement.

2. *Labeling*—a. *Recommended use/indications.* Varidase oral tablets are recommended for the same indications as the intramuscular preparation and for the reduction of edema and inflammation in the conditions mentioned in the Generic Statement. The average oral dose is 1 tablets (10,000 units of streptokinase) 4 times daily. In acute situations higher doses may be advisable. Normally treatment is continued for 4 to 6 days. Streptodornase is not believed to have therapeutic benefit in oral therapy.

b. *Contraindications.* Contraindicated in patients with reduced plasminogen or fibrinogen.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* Only streptokinase is involved in bringing about the desired clinical effect. The rationale for the use of tablets appears to be twofold: (i) Buccal absorption: Streptokinase is supposed to combine with salivary plasminogen and then to be absorbed by the buccal mucosa in quantities sufficient to convert plasminogen to plasmin. (ii) Intestinal absorption: Gastic juice contains considerable quantities of plasminogen that appears to be activated by streptokinase and absorbed. Claims for clinical efficacy have been discussed in the Generic Statement on streptokinase-streptodornase.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* During the past 5 years there has been only one complaint of a reaction.

c. *Benefit/risk ratio.* There is little risk in the use of the product but benefit has not been demonstrated.

4. *Critique.* In addition to the lack of clear evidence that Varidase is absorbed from the gastrointestinal tract in a form that can produce the physiologic activity of streptokinase, the claims for significant clinical benefit from this route of clinical administration, as in the case of intramuscular therapy, are subjective and anecdotal and do not constitute adequate proof of efficacy.

5. *Recommendations.* The Panel recommends that this product be place in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

Varidase, Topical Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Desciption.* This product is a partially purified mixture of extracelluar enzymes produced from a culture of Group C streptococci grown for about 18 hours in a medium consisting of acid-hydrolyzed casein fortified with sugar, minerals, vitamins, and a reducing substance. The enzymatic actions on fibrin and pus are described in the Generic Statement. Each vial contains 100,000 units of streptokinase and 25,000 units of streptodornase and less than 100 units of streptolysin. The powder is dissolved in 10 to 20 mL of sterile water or normal saline. This dilution gives a solution containing approximately 5,000 to 10,000 units of streptokinase and 1,000 to 2,000 units of streptodornase per mL.

The identical product is available in a mixture with 4.5 percent carboxymethylcellulose jelly.

Procedures employed in the manufacture of topical Varidase include standard tests for pyrogenicity in animals and sterility.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended wherever clotted blood, fibrinous, or purulent accumulations are undesirably present following trauma or infectious processes which have led to ulceration or abscess formation. The action of the enzymes results in the liquefaction of the two main viscous substances in inflammatory and purulent exudates, fibrin, and nucleoprotein. A long list of suppurative conditions are suggested for topical treatment (see Generic Statement) on wounds or by installation in body cavities such as the pleura, pericardium, bladder, sinuses, bronchi, and joints.

b. *Contraindications.* Varidase should not be used in the presence of active hemorrhage and is not intended for and cannot act upon fibrous tissue, mucoproteins, or collagens.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* May be effective for topical and local use in some situations where enhanced liquefaction of pus and fibrin is beneficial and where the products of inflammation can be drained. Such uses are only adjunctive to other medical and surgical procedures. Its substrates must be available and accessible and the enzymes and activators must be in continued contact with their substrates under physiologic conditions of temperature and pH. Its use in body cavities, wounds and fistulae, and luminal areas should be effective only under conditions defined in the Generic Statement.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No reactions have been reported from 1969 through April of 1974 for the use of topical streptokinase-streptodornase by Lederle Laboratories.

c. *Benefit/risk ratio.* Aside from the potential dangers of using this product in closed body cavities without adequate drainage, there is little risk in its topical use and the product is effective when its use is limited to well-defined situations.

4. *Critique.* The local and topical use of streptokinase-streptodornase has some limited efficacy as a method adjunctive to other medical and surgical procedures but only when used strictly in accord with the specific conditions that make the enzymes active—particularly the presence of the proper substrates and the use of a technique adequate to keep the solution in contact with pus and fibrinous exudates for adequate periods of time.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued provided that labeling is revised in accordance with the recommendations in this Report.

Varidase With Carboxymethylcellulose Jelly Topical Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product is identical to Varidase, topical, produced by Lederle Laboratories except for the addition of carboxymethylcellulose jelly, 4.5 percent. The mixture is then packaged in jars of jelly and vials of streptokinase-streptodornase with instructions to prepare a mixture by dissolving the contents of the vial in 5 milliliters of sterile water or normal saline and mixing this volume with the jar of jelly supplied.

2. *Labeling*—a. *Recommended use/indications.* The indications are the same as described for the use of Varidase, topical, when surface applications are made and when the use

of jelly will enhance maintenance of contact between the enzymes and the surface substrates. For application to the hands the jelly containing Varidase may be placed inside a loose rubber glove fastened at the wrist.

b. *Contraindications.* No specific contraindications are noted for the addition of the jelly to topical varidase when used on surfaces as a debridement aid.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* May be effective for topical use in some situations where enhanced liquefaction of pus and fibrin is an aid to debridement and where the maintenance of contact between the enzymes and the substrates on the wounds may be enhanced by the use of a jelly.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No reactions have been reported through April of 1974 for the topical use of streptokinase-streptodornase.

c. *Benefit/risk ratio.* There is no apparent risk to the topical use of this product and the issue of efficacy is limited to its use in well-defined situations and to the method of maintaining the product in contact to the surface to which it is applied.

4. *Critique.* The topical use of this product may be of some use in the specific situations defined in the Generic Statement when the addition of jelly to the mixture will assist in maintaining enzyme-substrate contact. No clear clinical evidence has been presented, however, that specifically pertains to the advantages of the addition of the jelly to topical solutions of Varidase.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall provide evidence for the effectiveness of this product, provided that the labeling is revised in accordance with the recommendations in this Report.

FDA's Responses to the Panel's Recommendations

A. Regulatory Categories

1. The Panel recommended that bacterial vaccines and toxoids be grouped into regulatory categories as follows:

a. *Category I.*—(1) *Licensed biological products determined to be safe and effective and not misbranded* [and may continue in interstate commerce]: Collagenase, Advance Biofactures Corp., License No. 383; Tetanus Immune Globulin (Human), Armour Pharmaceutical Co., License No. 149; BCG Vaccine, Botulism Antitoxin (Types A, B, and E), Botulism Antitoxin (Type E), Tetanus Toxoid, Connaught Laboratories, Ltd., License No. 73; Plague Vaccine, Tetanus Immune Globulin (Human), Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Eli Lilly & Co., License No. 56; BCG Vaccine, Glaxo Laboratories, Ltd., License No. 337; Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Cholera Vaccine, Tetanus Immune Globulin (Human), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Immune Globulin (Human), Tetanus Toxoid Adsorbed, Typhoid Vaccine, Massachusetts Public Health Biologic Laboratories, License No. 64; Tetanus Immune Globulin (Human), Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Anthrax Vaccine Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Typhoid Vaccine, Michigan Department of Public Health, License No. 99; Tetanus Immune Globulin (Human), Parke-Davis, Division of Warner-Lambert Co., License No. 1; Tetanus Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140; BCG Vaccine, University of Illinois, License No. 188; and Cholera Vaccine, Tetanus Immune Globulin (Human), Typhoid Vaccine (acetone inactivated), Typhoid Vaccine (heat-phenol inactivated), Wyeth Laboratories, Inc., License No. 3.

(2) *Biological products also recommended for Category I but for which the product license has been revoked at the manufacturer's request subsequent to the Panel's review.* Diphtheria Toxoid, Connaught Laboratories, Ltd., License No. 73; Tetanus Toxoid, Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (with aluminum phosphate), Tetanus Immune Globulin (Human), Dow Chemical Co., License No. 110; Cholera Vaccine, Pertussis Vaccine, Typhoid Vaccine, Eli Lilly & Co., License No. 56; Streptokinase-Streptodornase (Varidase, Topical), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Antitoxin, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Tetanus Immune Globulin (Human), Michigan Department of Public Health, License No. 99; Tetanus Immune Globulin (Human), Oesterreichisches Institut Fuer Haemoderivate GmbH, License No. 258; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Parke-Davis, Division of Warner-Lambert Co., License No. 1; and Pertussis Vaccine, Typhoid Vaccine, Texas Department of Health Resources, License No. 121.

A list of all voluntarily revoked products reviewed by the Panel, with the date of license revocation, is on file with FDA's Dockets Management Branch (address above). No further regulatory or administrative action is necessary for these products.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsobted, and Diphtheria Antitoxin to Connaught Laboratories, Inc. Connaught Laboratories was issued License No. 711 on January 3, 1978. FDA advises that all comments and recommendations directed to the Merrell-National products apply equally to the products as now manufactured by Connaught Laboratories, Inc.

FDA agrees with the Panel's findings and recommendations for these products, and hereby proposes to adopt its conclusions, including proposed labeling revisions concerning the intended use of the products. Comments or additional data on this classification are invited.

b. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:* Streptokinase-Streptodornase (Varidase-buccal tablet, intramuscular, and oral tablet dosage forms), Lederle Laboratories, Division American Cyanamid Co., License No. 17.

Lederle Laboratories was licensed for the manfacture and sale of five forms of Streptokinase-Streptodornase: topical, topical jelly, buccal tablet, intramuscular, and oral tablet. The topical form was recommended for Category I, the topical jelly for Category IIIA, and the buccal tablet, intramuscular, and oral tablet for Category IIIB. At the request of the manufacturer, the product license for the

manufacture and sale of all forms of Streptokinase-Streptodornase has been revoked. Accordingly, no further FDA action is necessary.

c. *Category IIIA.* The Category IIIA classification is a determination that there are concerns about whether the data are sufficient to support an action by the agency to reaffirm or revoke a product license and that, based on an assessment of the present evidence of safety and effectiveness of a product, the potential benefits outweigh the potential risks likely to result from the continued use of a product for a limited period of time. See § 601.25(f)(3).

Under the original procedures for the review of biological products FDA could permit the continued interim marketing of products classified in Category IIIA, provided the manufacturer undertook the necessary additional studies to determine fully the safety and effectiveness of the product. FDA has, however, revised these procedures. The agency decided that it is in the best interest of the public health to reclassify those biologics previously classified in Category IIIA and to proceed either to reaffirm, or to initiate proceedings to revoke, the license for each product. The procedures for implementing this policy were codified under § 601.26 (21 CFR 601.26) by final rulemaking of October 5, 1982 (47 FR 44062).

Under the new procedures, the data for each product classified in Category IIIA will be reviewed by an expert panel to recommend whether:

(i) The product is safe, effective, and not misbranded (Category I) and may remain licensed;

(ii) The product is unsafe, ineffective, or misbranded (Category II) due to the lack of sufficient supportive evidence and for which the product license shall be revoked; or

(iii) The product lacks sufficient supportive evidence of effectiveness (also administratively identified as Category II) but should remain on the market pending the completion of further testing. Such a recommendation may be made only when there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent is available in sufficient quantity to meet current needs.

Accordingly, FDA has submitted for review by the Vaccines and Related Biological Products Advisory Committee the available data for those licensed products recommended for Category IIIA by the Panel, including those recommended for Category I for booster immunization and Category IIIA for primary immunization. Upon completion of its review, the Advisory Committee will submit a report to FDA containing its conclusions and recommendations for reclassification of the affected products. FDA will respond with a proposal to implement the Advisory Committee's recommendations and will provide an opportunity for public comment at that time. The products classified in Category IIIA are listed below.

(1) *Licensed biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce pending completion of testing:* Pertussis Immune Globulin (Human), Cutter Laboratories, Inc., License No. 8; Pertussis Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140.

FDA will submit data and information on the two currently licensed Pertussis Immune Globulin (Human) products recommended for Category IIIA to the Vaccines and Related Biological Products Advisory Committee for review and reclassification in accordance with procedures under § 601.26 (21 CFR 601.26).

(2) *Biological product also recommended for Category IIIA but for which the product license has been revoked at the manufacturer's request subsequent to the Panel's review:* Streptokinase-Streptodornase (Varidase, Jelly), Lederle Laboratories, Division of American Cyanamid Co., License No. 17.

d. *Category I and Category IIIA.*

(1) *Licensed biological products recommended by the Panel for Category I when used for booster immunization and for Category IIIA when used for primary immunization:* Tetanus Toxiod, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxiods and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Lederle Laboratories, Division American Cyanamid Co., License No. 17; Tetanus Toxoid Adsorbed, Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Diphtheria and Tetanus Toxoids Adsorbed, Tetanus Toxoid Adsorbed, Michigan Department of Public Health, License No. 99; Tetanus Toxoid Adsorbed, Swiss Serum and Vaccine Institute Berne, License No. 21; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Wyeth Laboratories, Inc., License No. 3.

(2) *Biological products also recommended for Category I when used for booster immunization and for Category IIIA when used for primary immunization but for which the product licenses have been revoked at the manufacturer's request subsequent to the Panel's Review.* Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (with potassium alum), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Dow Chemical Co., License No. 110; Diphtheria and Tetanus Toxoids, Diphtheria and Tetanus Toxoids Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Eli Lilly and Co., License No. 56; Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Diphtheria and Tetanus Toxoids, Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Tetanus Toxoid, Tetanus Toxoid Adsorbed, Parke-Davis, Division of Warner-Lambert Co., License No. 1; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Toxoid, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Texas Department of Health Resources, License No. 121.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, and Tetanus Toxoid Adsorbed to Connaught Laboratories, Inc. (The facilities and processes for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine also were transferred but the license for this product subsequently was revoked voluntarily at the request of Connaught Laboratories, Inc.) FDA issued Connaught Laboratories, Inc., License No. 711 on January 3, 1978. All comments and recommendations concerning these products remain applicable.

The Panel found that until laboratory potency tests for Diphtheria Toxoid and Tetanus Toxoid could be adequately correlated with effectiveness for primary immunization, clincial testing of the toxoid was necessary to demonstrate effectiveness for primary

immunization. Accordingly, the Panel recommended that those products containing a diphtheria or tetanus toxoid component for which there were inadequate clinical data be placed in Category I for booster use and Category IIIA for primary immunization. Since the Panel completed its review, additional clincial data applicable to both primary and booster immunization have been made available to FDA. These additional data are applicable to the clinical response elicited by several toxoid containing products. Data have been provided both for products which were licensed after 1972 and for some licensed products reviewed by the Panel. The products all met the existing animal potency requirements of FDA as well as other requirements for release. Not all clinical data completely meet the criteria of the sample protocol described by the Panel for assaying the efficacy of tetanus toxoid in humans, e.g., number of subjects, percent with titers greater than 0.01 units, or method used for antitoxin assay.

FDA has submitted additional clinical data for review by the Advisory Committee for the following products: Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, and Tetanus Toxoid Adsorbed, Connaught Laboratories, Inc., License No. 711; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), (tetanus toxoid component only), Wyeth Laboratories, Inc., License No. 3.

FDA is not aware of additional serologic data applicable to the use of the following licensed products for primary immunization: Diphtheria and Tetanus Toxoids Adsorbed, and Tetanus Toxoid Adsorbed, Michigan Department of Public Health, License No. 99; Tetanus Toxoid, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Tetanus Toxoid Adsorbed, Swiss Serum and Vaccine Institute Berne, License No. 21; Diphtheria and Tetanus Toxoids Adsorbed, Tetanus Toxoid, Tetanus Toxoid Adsorbed, and the diphtheria component of Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Wyeth Laboratories, Inc., License No. 3.

FDA is not at this time judging the adequacy of the data cited above and is not proposing a regulatory classification for those products recommended for Category IIIA by the Panel. All data for these products are under review by the Advisory Committee and will be reclassified in either Category I or II. FDA will announce its evaluation of the data in a proposed rule after consideration of the Advisory Committee's recommendations.

e. *Category IIIB. Biological product for which available data are insufficient to classify its safety and effectiveness and should not continue in interstate commerce:* Gas Gangrene Polyvalent Antitoxin, Lederle Laboratories, Division American Cyanamid Co., License No. 17.

FDA agrees with the Panel's findings; however, because the license for Gas Gangrene Polyvalent Antitoxin was revoked at the manufacturer's request on March 12, 1981, no further FDA action is necessary.

f. *Category IIIC.* A Category "IIIC" designation is not defined in § 601.25, pursuant to which the review process for biological products is established. FDA appreciates that in establishing a Category "IIIC" the Panel wished to make explicit its opinion that certain of its recommendations for revocation of licenses were based on administrative and procedural problems and were not judgments derived from a scientific evaluation of the products. For example, some licenses are held for products which the manufacturer has not produced or marketed for many years. Other licenses are held for products for which there is no labeling, and which are manufactured only for combination with other biologically active components. As a result, the manufacturers submitted incomplete or outdated information and labeling, if any, for the Panel's review. The concerns of the Panel regarding these issues were properly transmitted to the agency. However, these issues can be resolved within the mechanisms already provided in § 601.25, and the use by FDA of new Category IIIC is unnecessary FDA finds that Category IIIB (biological products for which available data for a product are insufficient to classify their safety and effectiveness and should not continue in interstate commerce), is appropriate regardless of whether the data for a product are scientifically insufficient or insufficient due to administrative and procedural deficiencies. Accordingly, with the exception of several antitoxin and immune globulin products noted below, the agency agrees with the Panel's recommendation that licenses for these biological drugs should be revoked because the available data are insufficient to classify their safety and effectiveness. Accordingly, FDA proposes to classify the products listed below in Category IIIB. In accordance with §§ 601.5 and 601.25(f)(2), the agency intends to publish a notice of opportunity for hearing (NOH) to revoke the licenses for these biological drugs.

(1) *Licensed biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce and for which the insufficient data are due to essentially administrative and procedural problems rather than scientific factors:* Tetanus Immune Globulin (Human), Abbott Laboratories, License No. 43; Diphtheria Toxoid, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Diphtheria Antitoxin, Tetanus Antitoxin, Tetanus Toxoid, Massachusetts Public Health Biologic Laboratories, License No. 64; Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Typhoid Vaccine, Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Michigan Department of Public Health, License No. 99; Tetanus Antitoxin, Swiss Serum and Vaccine Institute Berne, License No. 21; Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, Pertussis Vaccine, Wyeth Laboratories, Inc., License No. 3.

(2) *Biological products also recommended for Category IIIC but for which the product licenses have been revoked at the manufacturer's request subsequent to the Panel's review:* Diphtheria Toxoid, Diphtheria Toxoid and Pertussis Vaccine Adsorbed, Pertussis Vaccine, Dow Chemical Co., License No. 110; Tetanus Immune Globulin (Human), E.R. Squibb & Sons, Inc., License No. 52; Botulism Antitoxin, Diphtheria Antitoxin, Pertussis Vaccine, Tetanus and Gas Gangrene Polyvalent Antitoxin, Tetanus Antitoxin, Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria Toxoid, Massachusetts Public Health Biologics Laboratories, License No. 64; Diphtheria Toxoid, Pertussis Vaccine, Tetanus Antitoxin, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Tetanus Immune Globulin (Human), Metabolic Inc., License No. 415; Pertussis Vaccine, Michigan Department of Public Health, License No. 99; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and

Poliomyelitis Vaccine, Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccine Adsorbed, Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, Pertussis Vaccine, Pertussis Vaccine Adsorbed, Tetanus Antitoxin, Parke-Davis, Division of Warner-Lambert Co., License No. 1.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria Toxoid, and Pertussis Vaccine to Connaught Laboratories, Inc. Connaught was issued License No. 771 on January 3, 1978.

Abbott Laboratories transfered its manufacturing process and facilities for manufacturing Tetanus Immune Globulin (Human) to Alpha Therapeutic Corp. for whom License No. 744 was issued on August 15, 1978.

The possible revocation of the licenses for the individual vaccines listed above will not jeopardize the availability or license of combination products which contain the individual vaccine.

The regulation on permissible combinations, § 610.17 (21 CFR 610.17), requires that a manufacturer of a combination biological product be licenses for the combination product. In addition, to assure that the individual therapeutic, prophylactic, or diagnostic products in the combination products are compatible, safe, potent, and effective, it was previously the agency's policy to require the manufacturer of a combination product to obtain a license for each product in the combination. Although FDA has not enforced this policy for a number of years, some manufacturers continue to retain licenses for individual vaccines, even though the manufacturer does not intend to market the product in that form. In addition, some vaccines were initially prepared as monovalent products, but subsequently such products were no longer marketed. As announced for viral and rickettsial vaccines in the **Federal Register** of April 15, 1980 (45 FR 25652), FDA has revised its policy to permit the licensing of combination vaccines without requiring the licensure of the individual component vaccines, provided appropriate data are submitted showing the compatibility, safety, and effectiveness of the combination product. In the event a component vaccine is purchased from another licensee, the manufacturer of each purchased vaccine must be identified in the package insert for the combination product, in accordance with the requirements for divided manufacture (21 CFR 610.83). Thus, FDA may revoke the licenses for many of the individual vaccines or toxoids listed above without jeopardizing the availability or license of the combination products in which they are incorporated.

FDA disagrees with the Panel's recommendations concerning Diphtheria Antitoxin and Tetanus Antitoxin manufactured by Massachusetts Public Health Laboratories and Tetanus Antitoxin manufactured by Swiss Serum and Vaccine Institute Berne. The Panel recommended that each of these products be placed in Category IIIC because no information or labeling for the products was submitted by the manufacturers for the Panel's review. FDA proposes that the products be placed in Category I.

After the Panel had completed review of Diphtheria Antitoxin and Tetanus Antitoxin, FDA accepted amendments from Massachusetts Public Health Laboratories and Swiss Serum and Vaccine Institute Berne to update the licenses for their antitoxin products to reflect current good manufacturing practices. No clincial data concerning the effectiveness of the products were submitted with the amendments; however, limited clinical data are available in support of the safety and effectiveness of Tetanus Antitoxin manufactured by Massachusetts Public Health Laboratories. FDA concurs with the Panel's finding that there is a sufficient body of evidence suggesting that Diphtheria Antitoxin and Tetanus Antitoxin are of some effect, albeit marginal, in the prophylaxis and treatment of diphtheria and tetanus, respectively. The available data do not demonstrate unequivocally the effectiveness of any licensed Diphtheria or Tetanus Antitoxin. However, FDA recognizes the difficulties in constructing controlled clinical studies to prove the effectiveness of these antitoxins for the prevention and treatment of these rare, life-threatening diseases. Accordingly, FDA finds that the existing clinical evidence, as corroborated by the long history of diphtheria and tetanus antitoxins' successful use, are adequate to find Diphtheria Antitoxin and Tetanus Antitoxin manufactured by Massachusetts Public Health Laboratories and Tetanus Antitoxin manufactured by Swiss Serum and Vaccine Institute Berne safe and effective for their intended uses.

FDA disagrees with the Panel's recommendation that the product license for Tetanus Immune Globulin (Human) (TIG), formerly manufactured by Abbott Laboratories and now by Alpha Therapeutic Corp., be revoked. As noted by the Panel, this product is manufactured only as a partially processed material (dry globulin powder) and is intended only for export into foreign commerce for further manufacture. The agency does not object to this practice. Several other manufacturers of plasma derivatives are engaged in similar activities. Consistent with the agency's policy on such matters, the product license has been suitably amended to provide for the export of the partially manufactured product and complete export labeling has been approved. The manufacturer is also retaining on file a written agreement with each consignee for the product which includes the specifications required for further processing, labeling, or repackaging of the final product. The agency advises that, if Alpha Therapeutic Corp. should decide to manufacture TIG as a final product for sale in the United States, suitable labeling to accompany the final product must be approved by the agency and the manufacturer must demonstrate the ability to manufacture a safe and effective final product in conformance with the standards set in the regulations before the agency would permit the release of the final product for sale in the United States. Accordingly, FDA is proposing that Tetanus Immune Globulin (Human) manufactured by Alpha Therapeutic Corp. be classified in Category I as safe and effective.

B. General Recommendations

In the following paragraphs, FDA is responding to the Panel's general recommendations regarding the products under review and to the procedures involved in their manufacture and regulation.

2. The Panel recommended changes in the labeling of the biological products under review. The Panel also recommended a generic order and wording for information in the labeling of bacterial vaccines.

FDA agrees with the labeling changes recommended by the Panel. The labeling recommendations applicable to a group of products, rather than an individual licensed product, are summarized in paragraphs 13, 19, and 24 of this response. Those labeling recommendations concerning product use will be discussed with the Public Health Service's Immunization Practices Advisory Committee (formerly known as the Advisory Committee on Immunization Practices and still identified as ACIP). In the preamble to the final rule, FDA intends to advise the licensed manufacturers of products generically reviewed in this report, including products licensed after July 1, 1972, to submit appropriately revised

draft labeling to the Center for Drugs and Biologics (CDB), FDA for review and approval according to the schedule given at the end of this paragraph. FDA proposes that such draft labeling shall conform with the Panel's recommendations, as modified as a result of public comment and FDA's evaluation of the Report. FDA finds the Panel's recommended labeling content and format consistent with the current regulations and recommends that it be used as a general guideline for the revision of bacterial vaccine and toxoid labeling. FDA notes that two additional sections not mentioned by the Panel, entitled *Animal Pharmacology* and/or *Animal Toxicology* and *Clinical Studies*, may be included in product labeling.

The draft labeling shall also be consistent with the regulations governing the content and format for labeling of human prescription drugs (21 CFR 201.56 and 201.57). The effective dates for implementation of the labeling content and format regulations are codified under § 201.59 (21 CFR 201.59). Consistent with § 201.59, FDA proposes that draft labeling, revised in conformance with this report and with the content and format regulations, should be submitted for FDA review no later than 6 months after the date of publication of the final rule based on this proposal. FDA is also proposing to require that such revised labeling accompany all products initially introduced or initially delivered for introduction into interstate commerce no later than 30 months after the date of publication of the final rule.

3. The Panel noted a number of labeling deficiencies (discussed in detail in the Panel's review of products) and expressed its belief that substantial improvement should be made in the labeling for biological products. To implement these improvements, the Panel recommended that labeling be reviewed and revised as necessary at intervals of no more than every 2 years.

FDA agrees that labeling for biological products should be improved; however, FDA believes the current system of labeling review will adequately assure accurate labeling. One of the important objectives of each advisory panel's review of biological products is to ensure that the labeling for the products under review is revised and updated according to the most recent scientific knowledge. As described elsewhere in this response, many products have not been manufactured for many years and, as a result, may have outdated labeling. The licenses for these products are either being proposed for revocation or have already been revoked; the labeling for the remaining products will be revised consistent with the Panel's recommendations and the current regulations.

It is the agency's policy to request that labeling be revised as indicated by current scientific knowledge and when the recommendations for the use of a given product have been significantly revised by ACIP or another responsible public organization. Revised draft labeling is then submitted by the manufacturer(s) for review and approval by FDA. FDA's Office of Biologics Research and Review also monitors the revision dates for the labeling for each licensed biological product. If a significant period of time has elapsed since the last labeling revision and it appears that the labeling may be outdated, the manufacturer of the product is asked to inform the agency of the status of the product, including its labeling. From the manufacturer's response, the agency can determine whether revision of the labeling may be appropriate.

In some cases, labeling must be revised as a result of changes in the regulations. In such circumstances, the agency sets an effective date by which time labeling revised in accordance with the regulations must accompany the product. In instances where, for routine updating purposes, the manufacturer has submitted updated draft labeling for agency approval, the manufacturer is asked to notify the agency when the new labeling is put into use.
If the labeling revision would significantly affect a product's use, the Office of Biologics Research and Review may request at the time of approval of the draft labeling that the new labeling be put into use by a specified date. Otherwise, FDA requests the manufacturer to notify the agency of the date the new labeling is put into use, to provide the identifying number of the product the approved labeling first accompanied, and to submit a copy of the approved final labeling for the agency's files. Thus, the agency is able to monitor continually the labeling in use for each licensed product, assuring that the labeling is consistent with current scientific knowledge and regulations. Accordingly, FDA believes it is unnecessary to specify a time interval, such as every 2 years, for the review and revision of labeling for biological products.

4. The Panel recommended that actions be taken to improve the reporting and documentation of adverse reactions to biological products. The Panel particularly noted the need to improve the surveillance systems to identify adverse reactions to pertussis vaccine.

Manufacturers voluntarily submit individual and/or periodic summaries of the reaction reports they have received to CDB. FDA receives reports from consumers both directly and through the United States Pharmacopeia (U.S.P.) Problem Reporting Program, the Drug Experience Reporting System, and the Government-Wide Quality Assurance Program. All of these reaction reports for biologics are reviewed at CDB, entered in a computer data base, and appropriate action taken. FDA investigators also routinely review complaint files maintained by biological product manufacturers.

The Centers for Disease Control (CDC) maintain another product surveillance system and receive adverse reaction reports primarily from local and State health departments. FDA and CDC frequently exchange information regarding reactions to biological products.

FDA recently supported a study to determine the incidence of reactions associated with DTP and DT immunization (Ref. 1). This study provided information similar to other reports since 1978 (Refs. 2 and 3).

A case-control study of neurological damage attributable to pertussis vaccine has been completed in the United Kingdom (National Encephalopathy Study). These data provide information which may be applicable to estimating the predicted incidence of local and systemic reactions to pertussis vaccine, including the incidence of severe neurological disorders.

The agency's systems for reporting of adverse reactions are continually under review by FDA. However, FDA believes that a discussion of FDA's systems for reporting and processing of adverse reactions to biological products is outside the scope of this rulemaking.

5. The Panel recommended that all licensed vaccines be periodically reviewed to assure that the data concerning the safety and effectiveness of these products are kept current and that the licenses be revoked for products which have not been marketed for years or which have never been marketed in the licensed form. The Panel noted that some standards of purity, immunogenicity, and immune responses for older well-established vaccines are based upon methods that should be updated by more sophisticated techniques made possible by advancing scientific knowledge. The Panel noted that by limiting the period for which specific vaccines may be licensed, older products would be assured periodic

review and new products for which additional efficacy data are required could be provisionally licensed for only a limited period of time within which additional data can be generated.

The agency believes it would be unnecessary and burdensome to review comprehensively at defined intervals the data held in the license applications for each biological product. It is the continuing agency policy to require product standards consistent with current biomedical knowledge and technology and to revise such standards whenever sound and substantiated laboratory and clinical data demonstrate that changes in methods of production and testing would result in a better product. Under § 601.12(a) (21 CFR 601.12(a)), licensees are required to report any important changes in manufacturing procedures to FDA. Some important changes in manufacturing processes may require submission of additional supporting clinical data prior to the agency's approval. Through these means, the agency believes that the data, standards, and manufacturing process for actively manufactured biological products are kept consistent with current biomedical knowledge.

The majority of the instances where data or manufacturing processes appeared outdated to the Panel were for products that have not been marketed in many years or were never marketed in the licensed form. The licenses for these products are proposed for revocation as part of the implementation of this efficacy review.

The Panel's recommendation that some new vaccines be provisionally licensed for only limited periods of time while additional required data on effectiveness are generated cannot be implemented under present law which requires that a biological product be determined to be safe, pure, and potent before it is licensed.

6. The Panel recommended that compensation from public funds be provided to individuals suffering injury from vaccinations that were recommended by competent authorities, carried out with vaccines which passed official safety and efficacy requirements, and when the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccine.

A similar recommendation concerning a public compensation system was made at the National Immunization Conference held in April 1977. Such a public compensation system has been under study by the Department of Health and Human Services. The Department has testified before the Senate and House during the 98th Session of Congress regarding two bills (S. 2117 and H.R. 5810), which would establish a Federal vaccine compensation program. Both bills have laudable goals and reflect many of the recommendations that have been made to the Department over the past several years by different groups. These bills, however, also have major weaknesses which made them impossible for the Department to support and which interrelate to provide a significant disincentive to vaccine programs.

The vaccine compensation issue is a very complicated area and one in which there may be no single simple solution. The Department is analyzing the position of the American Medical Association and the American College of Physicians and will soon review the report of the Institute of Medicine. A thorough analysis of these proposals is important to the development of a position on this complex issue of compensation.

7. The Panel recommended that both FDA and the public support widespread immunization programs for tetanus, diphtheria, and pertussis.

FDA agrees that the immunization of children for tetanus, diphtheria, and pertussis should continue to be emphasized. Such immunization programs are part of national policy. In April 1977, the Department announced a plan to achieve immunization of the 3 million infants born in the United States each year as well as those already born who had not been immunized. The target diseases included tetanus, diphtheria, pertussis (under age 7), measles, mumps (under age 7), rubella, and polio. The national program successfully raised immunization levels from a range of 66 to 75 percent in 1977 to immunization levels of 95 percent or greater for these diseases in children entering school for the school year 1981–1982. The Department has affirmed that the immunization program will continue to be emphasized (Ref. 4).

8. The Panel recommended that the agency work closely with the CDC and other appropriate groups to ensure that adequate supplies of vaccines and passive immunization products continue to be available. The Panel was especially concerned about products that are available solely from foreign firms; products for which there is only a single domestic manufacturer; and products for which discontinuation of production is possible or probable for commercial reasons, despite current or potential needs. The Panel recommended establishment of a national vaccine commission to address such issues.

FDA agrees that the government should cooperate with industry, the health professions, and the public to ensure adequate production and supply of vaccines and other immunization products. The agency believes that the establishment of such a commission is unnecessary because the government is already extensively involved in production and supply issues through such efforts as the National Institutes of Health (NIH) research program, FDA's release of products shown to be safe and effective, and CDC's epidemiological/surveillance programs which help to predict future needs. These agencies now cooperate extensively.

9. The Panel recommended that the protocols for efficacy studies should be reasonably consistent throughout the industry for any generic product. To achieve this goal, the Panel recommended the development of industry guidelines that provide standardized methodology for adducing required information.

The agency believes that the development of general guidelines for conducting studies on vaccine products is not practical at this time. Most study protocols are uniquely designed to meet the individual objectives of each clinical study and to accommodate the characteristics of the vaccine and the size and qualifications of the test population available for the study. In addition, it is rare that a significant number of manufacturers will initiate clinical studies on similar biological products within a reasonably short period of time; the situation where guidelines would be most useful. Accordingly, the agency intends to continue its policy of cooperating with manufacturers on an ad hoc basis in discussing possible clinical studies and to comment on proposed protocols for studies to demonstrate clinical potency (efficacy) and safety of vaccine products. FDA scientists generally review and comment upon protocols for FDA required clinical studies on vaccines before studies are initiated. FDA believes that the current system allows the manufacturer maximum flexibility in selecting the appropriate tests and procedures for a clinical study while assuring that the necessary data are generated to fulfill the intended objectives of the study.

10. The Panel expressed concern that regulations governing informed consent and the protection of human subjects involved in clinical investigations should not establish unnecessary impediments to the equally worthwhile goal of obtaining adequate evidence for

the safety and effectiveness of a product.

FDA believes that the Panel's concerns are unwarranted. FDA does not believe that the regulations governing informed consent and the protection of human subjects involved in research activities (21 CFR Parts 50 and 56) impose unnecessary impediments to obtaining adequate evidence for the safety and effectiveness of the products under the agency's jurisdiction. The Panel's report was prepared before the publication of the proposed and final rules clarifying the requirements governing informed consent and the protection of human subjects. The final rule concerning these matters (46 FR 8942; January 27, 1981) requires the informed consent of all human subjects, or their legal guardian, involved in research activities under FDA's jurisdiction. The regulations also require that the research activities be reviewed and approved by an institutional review board (IRB) to assure the adequate protection of the human research subjects. FDA is unaware, through public comment or the agency's own investigations, of these requirements having hindered the gathering of a suitable subject population for a research activity.

C. Response to Recommendations Concerning Specific Products

In the following paragraphs, FDA is responding to those Panel recommendations relating to specific licensed products.

11. The Panel recommended that FDA encourage further studies on the use of adjuvants in bacterial vaccines and toxoids.

FDA agrees that further investigation is appropriate on the use of adjuvants in biological products. Since the Panel completed its review, further data from the Connecticut Tumor Registry show that no changes in the incidence of soft tissue sarcomas of the upper arm were observed which could be attributed to the use of alum (Ref. 5). These data were directly related to introduction of alum adsorbed allergens but are also relevant to the use of aluminum adjuvants in topical vaccines. FDA continues to monitor information regarding the use of adjuvants in all types of products. In collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), and NIH, the Bureau of Biologics (now the Office of Biologics Research and Review, CDB) sponsored an International Symposium on Adjuvants on February 20 to 21, 1979 (Ref. 6).

12. The Panel recommended that standards should be established for purity of both diphtheria and tetanus toxoids in terms of Limit of flocculation (Lf) content per milligram (mg) of nitrogen.

FDA agrees with the recommendation. The agency is currently developing information needed to propose additional standards for these two bacterial products, which would include proposed minimum purity requirements expressed in Lf content per milligram of nitrogen. The agency notes that the requirements of the World Health Organization (WHO) provide a minimum purity requirement of 1000 Lf/mg nitrogen for Tetanus Toxoid and 1500 Lf/mg nitrogen for Diphtheria Toxoid (Ref. 7). FDA invites comment on appropriate purity requirements for Tetanus and Diphtheria Toxoids licensed in the United States.

13 The Panel recommended that the immunogenic superiority of the adsorbed diphtheria and tetanus toxoids over the fluid (plain) preparations be strongly emphasized in product labeling, especially with regard to the duration of protection.

FDA agrees with the recommendation. The apparent immunogenic superiority of adsorbed toxoid over plain toxoid should be emphasized in product labeling. FDA notes that most toxoid products are already labeled consistent with this recommendation. FDA intends to require that the remaining applicable labeling be appropriately revised according to the schedule announced elsewhere in this proposal. The comparative immunogenic superiority of the adsorbed toxoids over the fluid toxoids was emphasized by ACIP in its most recent guidelines for vaccine prophylaxis of diphtheria, tetanus, and pertussis (Ref. 8).

14. The Panel noted a need for further studies with tetanus toxoids on a WHO sponsored quantitative potency test in animals to establish the conditions under which the test results are reproducible, and to relate these results more closely to those obtained in immunization of humans. The Panel also recommended the development of an animal or laboratory testing system for diphtheria toxoid that correlates consistently, and with acceptable precision, with primary immunogenicity in humans.

FDA agrees with the recommendations. For several years, FDA has participated in collaborative studies with WHO to evaluate international standards in terms of International Units per milliliter (IU/mL) for toxoids in animals. For tetanus toxoid, FDA has participated in collaborative studies with WHO to apply a quantitative potency test in both mice and guinea pigs (Refs. 9 and 10) and has compared the response to toxoids in women to that of guinea pigs and mice (Ref. 11). The Office of Biologics Research and Review, CDB, has assayed the IU/mL of many toxoids in both animal species in efforts to establish reference toxoids suitable for routine lot control. In addition, the potency (IU/mL) of many types of licensed tetanus toxoids has been assayed. CDB staff has recently completed a study in monkeys in which the relationship of the antitoxin response and the potency of several of these toxoids, as expressed in IU/mL, was examined. Some of these data have been published. (Ref. 12).

Only a few studies in man are available that utilized diphtheria toxoids with potencies defined in IU/mL by this procedure. As described below, FDA intends to continue to evaluate this procedure and is taking steps to provide suitable reference standards.

The Panel indicated that the potency tests now required for diphtheria and tetanus toxoids are suitable for determining the acceptability of the toxoids for booster use, but not for primary immunization. The agency is aware that the Panel was provided with a limited amount of data from studies of primary immunization. Both monovalent and combined products containing these toxoids, which passed the current potency tests for adsorbed toxoids, have been shown by manufacturers to induce adequate antitoxin responses when used as recommended for primary immunization. The products meeting the current potency tests yield satisfactory booster responses. Thus, FDA considers the current animal potency assays suitable for routine potency determinations. The agency agrees that limited data support the use of the current potency tests for evaluating the fluid toxoids for use in primary immunization. However, the limited available data do support the efficacy of fluid tetanus toxoid. No Diphtheria Toxoid fluid is currently being marketed.

In addition to meeting the current potency requirements, the agency recommends that the potency of toxoids administered in future clinical studies be assayed for IU/mL using appropriate protocols and references. In this manner, the response in humans could be compared to that of guinea pigs and/or mice, so that eventually the correlation between laboratory data and clinical effectiveness can be firmly established. In evaluating such studies, host responses may require evaluation as well, e.g., effect of age, sex, or

nutritional status of the host population (Ref. 13).

Until the results of additional clincial studies can be better correlated with the IU/mL content of the products containing these toxoids, FDA will retain the current potency tests for the release of each lot of products containing diphtheria toxoid or tetanus toxoid.

15. The Panel recommended that the agency require potency testing after combination of the individual toxoid components in Diphtheria and Tetanus Toxoids (DT) for pediatric use.

FDA agrees with the recommendation. This procedure is followed by all manufacturers and FDA on products submitted to the agency for release.

16. The Panel recommended that regulations concerning the maximum pertussis vaccine dose should be updated to reflect current recommendations and practices. The Panel recommended that pertussis vaccine should have a potency of 4 protective units per single human dose and that the upper estimate of a single human dose should not exceed 8 protective units. The Panel also recommended that the total immunizing dose should be defined as 4 doses of 4 units each compared to the 3 doses of 4 units each now defined in the biologics regulations.

FDA agrees with part of the Panel's recommendations. Currently, ACIP and the Committee on Infectious Diseases of the American Academy of Pediatrics recommended as an immunization schedule for pertussis vaccine a primary series of three doses given at 4- to 8-week intervals, a fourth "reinforcing" dose given 1 year later, and a booster dose administered when the child enters school. FDA agrees that with available vaccines the first four doses are necessary for primary immunization and therefore may be considered as the "total immunizing dose." At the time the additional standards for Pertussis Vaccine were codified (21 CFR 620 Subpart A), the first three doses were defined as the "total immunizing dose" and the potency requirements prescribed in §§ 610.21 and 620.4(g) were set accordingly. FDA did not intend, however, to prescribe in the regulations a specific immunization schedule for administration of the vaccine. Manufacturers of pertussis vaccines are responsible for recommending in their labeling an immunization schedule consistent with the recommendations of ACIP and the Committee on Infectious Diseases. FDA intends to revise and update the additional standards for Pertussis Vaccine. One objective of this revision would be to prescribe potency standards on the basis of a single human dose, rather than the total immunizing dose, thereby removing the existing difference in terminology.

Section 620.4(g) requires that the potency be 12 units per total immunizing dose (3 doses with an estimate of 4 units each) with a minimum acceptable potency of 8 units (or 3 doses of approximately 2.7 units each) and a maximum acceptable potency of 36 units (3 doses of 12 units each). FDA agrees with the objective of establishing 4 units as the minimum potency per single dose and invites submission of further information and comments on this question. All pertussis vaccines tested and released by FDA now meet or exceed the recommended minimum potency, and there is no indication that the vaccines being marketed are not effective.

FDA is unaware of existing data to support a reduction in the upper estimate of potency from 12 to 8 units per single human dose. Unitl such supporting information is provided, FDA disagrees with the Panel's recommendation that maximum potency should not exceed 8 units per single dose.

17. The Panel recommended that the weight-gain test in mice used to determine toxicity of pertussis vaccines be revised to include a reference standard and specifications regarding mouse strain(s) to be used. The Panel also recommended that studies be undertaken to develop assays other than the mouse weight-gain test to predict human reactivity.

FDA does not believe that the use of a standardized mouse strain should be required by regulation. The agency believes that the weight-gain freedom from toxicity mouse test as provided in § 620.5 (21 CFR 620.5) continues to be adequate for ensuring that overtly toxic vaccines are not marketed. There are currently no specifications regarding the mouse strains used for pertussis vaccine testing. A standardized mouse strain, the HSFS/N mouse, has been developed by the Office of Biologics Research and Review, for use in bioassays in general and pertussis vaccine assays in particular. The standardized strain is available for distribution. Every lot of vaccine containing a pertussis component must pass both the manufacturer's and the agency's toxicity and potency assays. FDA believes that confirmatory testing in agency laboratories is an effective method for controlling the variable in pertussis vaccine toxicity assays.

FDA believes that elucidation of the immunochemistry of *Bordetella pertussis* and the development of sensitive and specific tests for protective and reactogenic components of pertussis vaccine are the most productive approaches to provide safe and effective vaccines. Recent studies have defined two potential vaccine components and proposed several other candidate antigens for inclusion in new acellular pertussis vaccines. Pharmacologic, immunologic, and chemical tests, as well as animal tests, are being developed to identify and quantitate these immunogens.

18. The Panel recommended that the agglutination test used to determine pertussis vaccine response in humans should be standardized and that a reference serum should be used for comparison. Also, a reference laboratory should be available at FDA.

FDA agrees with the recommendations. The agency advises that the agglutination test to determine vaccine response in humans has been developed, standardized, and published by agency scientists (Ref. 14). A reference serum and diagnostic antigen are available and a reference laboratory has been established in the Division of Bacterial Products, Office of Biologics Research and Review. In addition, sensitive and specific enzyme-linked immunosobrent assays (ELISA) have been developed to measure *B. pertussis* antigens and quantitate total and individual immunoglobulin responses to human and animal sera and colostrum. The ELISA equipment is automated, has been computer-linked, and is capable of processing large numbers of specimens.

19. The Panel recommended that the pertussis vaccine label should warn that if shock, encephalopathic symptoms, convulsions, or thrombocytopenia follow a vaccine injection, no additional injections with pertussis antigens should be given. The Panel also requested that the label include a cautionary statement about fever, excessive screaming, and somnolence.

FDA agrees with the recommendation, except that the agency believes it is more appropriate to include the information above in the package insert (labeling) rather than on the container or package label.

The recommendations of ACIP (1981) and the Committee on Innfectious Diseases (1982) (Refs. 8 and 15) state that collapse or shock, persistent crying or screaming episodes, temperatures of 40.5 °C or more, and/or convulsions with or without fever following the administration of pertussis vaccine are contraindications to further injections with vaccines that contain a pertussis vaccine component. An evolving

neurologic disorder is a contraindication to the use of pertussis vaccine. In addition, current ACIP recommendations state that severe alterations in consciousness, generalized or focal neurologic signs, system allergic reactions, thrombocytopenia, and hemolytic anemia are contraindications to the continued use of pertussis vaccine. Labeling for products containing a pertussis vaccine component is being revised in accordance with these recommendations.

20. The Panel recommended that any fractionated pertussis vaccine which differs from the original whole cell vaccine should be field tested until better laboratory methods for evaluating immunogenicity are developed; field testing should include agglutination testing and, if possible, evaluation of clinical effectiveness.

FDA agrees with the recommendation. No vaccine containing a fractionated pertussis component is currently being manufactured under license in the United States; however, FDA agrees with the Panel that clinical trials of candidate fractionated pertussis vaccines should provide evidence that disease is prevented as proof of efficacy until better laboratory methods are developed for evaluating immunogenicity in humans. The propriety of agglutination testing will be considered on an ad hoc basis.

Research to develop a new generation of acellular pertussis vaccines is in a dynamic state; thus, it is difficult to predict what tests would be necessary to demonstrate the effectiveness of a newly developed acellular pertussis vaccine. The problems associated with the clinical evaluation of such vaccines were discussed at a workshop, "New Pertussis Vaccines—Laboratory and Clinical Evaluation", sponsored by FDA's former Bureau of Biologics, NIAID, and CDC on February 11 and 12, 1982.

21. The Panel recommended that adequate public support be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization.

FDA agrees with the recommendations. Support should be provided for both the extramural and intramural basic research necessary to develop the definitive pertussis vaccine. FDA's efforts to assess the variety and extent of adverse reactions to pertussis vaccine are discussed elsewhere in this response.

Several laboratories, including those at CDB and NIAID in NIH, have been involved in studies that have resulted in the isolation, purification, and characterization of two vaccine candidates; lymphocytosis promoting toxin and filamentous hemagglutinin (Ref. 16). Several in vivo and in vitro models for research on the infectious process and its prevention have been established (Refs. 17, 18, and 19). A contract for basic studies on the biochemical and genetic characterization of *Bordetella pertussis* has been completed (Refs. 20 through 25).

The need for research on *Bordetella pertussis*, pertussis, and pertussis vaccine was emphasized in an *International Symposium on Pertussis* sponsored by FDA's former Bureau of Biologics, NIAID, CDC, the International Association of Biological Standardization, and The Fogarty International Center in 1978. The proceedings of the symposium have been published and widely distributed (Ref. 26).

The International Symposium on Bacterial Vaccines was covened at the National Institutes of Health in 1980. The conference was sponsored by NIH, FDA, Walter Reed Army Institute of Research, CDC, and the Department of Agriculture. Recent findings from research on bacterial vaccines, including pertussis vaccine, were reported. The proceedings of the meeting have been published (Ref. 27).

In February 1982, a workshop on "New Pertussis Vaccines—Laboratory and Clinical Evaluation" was held to discuss the technical, legal, logistical, and ethical problems associated with the clinical testing of the new acellular pertussis vaccines. The workshop was sponored by FDA, NIH, and CDC and was attended by scientists from 11 foreign countries and WHO.

In the **Federal Register** on June 1, 1984 (49 FR 22873), FDA announced an opportunity for the public to participate in collaborative laboratory tests on a proposed new lot of U.S. Standard Pertussis Vaccine and submit to FDA the results of the tests. FDA will consider any test data that are submitted concerning potency, stability, ampoule-to-ampoule variation, and toxicity during its final evaluation of the suitability of the proposed new lot. If its final evaluation is satisfactory, FDA intends to use the new lot of vaccine as the U.S. Standard Pertussis Vaccine, when the current lot of the standard vaccine is depleted. The biologics regulations (21 CFR 610.20) require that manufacturers must assure that each new lot of Pertussis Vaccine sold commercially is equivalent to the U.S. Standard Pertussis Vaccine.

22. The Panel recommended that the results of a WHO field trial in India to evaluate BCG vaccines be evaluated when the data become available, and that consideration be given to recommending that all BCG vaccines distributed in the United States be prepared from the same seed lot strain with demonstrated efficacy, if the data justify such an action.

The results of the WHO field trial in India have become available since the Panel's report was submitted (Refs. 28, 29, and 30). For the specific region of India in which the vaccine trial was conducted, the evidence indicates that BCG vaccine did not protect against bacillary pulmonary tuberculosis. The results should not be interpreted to mean that BCG vaccine would be ineffective for other populations of the world. Indeed, a prevalence of nontuberculous mycobacteria has been demonstrated in the trial region (Chinglepat, South India). Infection with such generally nonpathogenic mycobacteria is capable of conveying immunity and use of BCG vaccine may not have been able to increase this immunity significantly. The South India trial did not provide sufficient information on the effects of BCG vaccine in infants and young children. Continued followup should provide more information.

Because there is no conclusive evidence from the WHO BCG vaccine trial as to which strain is efficacious, it is not possible to implement the Panel's recommendation that all U.S. licensed BCG strains be prepared from the same seed lot strain with demonstrated efficacy.

23. The Panel recommended public support for development of an improved cholera vaccine, believing that such support is warranted because unsatisfactory sanitary conditions in many countries make is clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

FDA agrees with the recommendation. Other government agencies have been involved in programs to develop and to evaluate new types of vaccines and to study the pathogenesis of cholera. CDB has participated in selected aspects of these programs. Cholera is not an important disease in the U.S. at the present time, although a number of cases have been identified in the U.S. recently (Ref. 31). The major risk for cholera is to travelers to certain countries and to citizens of countries where the disease is endemic. Toxigenic

E. Coli disease is also an important cause of enteric disease in travelers. The recognition of the immunochemical simiarities and of the apparently identical mechanism of action of cholera toxin and the heat labile toxin of *E. coli* (Ref. 32) have resulted in increased research toward developing vaccines for these types of toxins. The Office of Biologics Research and Review will continue to monitor progress in these areas and will develop programs as necessary to evaluate these products.

24. The Panel recommended that the following plague vaccine immunization schedule should be considered: (a) a primary series of 3 intramuscular injections (1 mL, 0.2 mL, and 02 mL) 1 and 6 months apart, respectivly; (b) booster intramuscular inoculations of 0.2 mL at 12, 18, and 24 months; and (c) for persons achieving a titer of 1:128 after the third and fifth inoculation, further booster doses should be administered under the following circumstances: (i) When the passive hemagglutination titer falls below 1:32; (ii) empirically every 2 years when the patient cannot be tested serologically.

The agency agrees with the Panel's recommended immunization schedule for plague vaccine and notes that the current product labeling (since 1975) and the current ACIP recommendations (1982, Ref. 33) follow this schedule. The Panel had completed its review of plague vaccine before the revised package insert became available for its review. The Panel's recommendation and the current labeling are based on studies done by the U.S. Army with a plague vaccine manufactured exclusively for military use; however, the vaccine formulation for civilian use is now the same as that used the U.S. military and the labeling has been revised accordingly.

25. Regarding typhoid vaccine, the Panel recommended that (a) appropriate support should be given to studies aimed at clarifying the immune mechanism(s) in typhoid fever; (b) field or volunteer studies designed to test promising vaccines or their fractions for protection against typhoid fever should be supported; and (c) a search for laboratory tests of potency that correlate well with results of vaccination in humans should be conducted.

FDA agrees with the recommendations. However, ACIP has reported that "the incidence of typhoid fever has declined steadily in the U.S. in the last half century * * * The continuing downward trend is due largely to better sanitation and other control measures; vaccine is not deemed to have played a significant role * * * Routine typhoid vaccination is no longer recommended for persons in the U.S. * * *" (Ref. 34). Typhoid fever is decreasing in the U.S. civilian population, but the need is recognized for the ability to immunize selected personnel against enteric disease, including typhoid. In addition, typhoid fever remains a problem in other parts of the world. Although FDA itself is not prepared at this time to allocated significant resources to studies aimed at clarifying the immune mechanisms in typhoid, other government agencies are providing support for such studies. Field and volunteer studies are being supported by both government and private institutes. A new type of live oral vaccine has been field tested in Egypt (Ref. 35).

The agency will continue to review and evaluate laboratory procedures that may be suitable for correlating with the immune response of humans following vaccination. New methods for evaluating potency may be required for oral vaccines.

26. FDA proposes to amend § 610.21 (21 CFR 610.21) by requiring a minimum potency of not less than 250 units of tetanus antitoxin per container for Tetanus Immune Globulin (Human) (TIG).

The Panel noted that TIG is usually marketed in 250 unit amounts. Indeed, all currently licensed TIG is marketed with a labeled potency of 250 units per container. The specific antitoxin activity of the globulin is such that in the final product, 250 units has been contained in anywhere from approximately 0.6 to 4.0 mL of fluid, depending on the manufacturer's specifications, the starting potency of the purified globulin, and the type of container (vial or syringe) in which the product is to be marketed.

Under current § 601.21, the minimum potency of TIG must be not less than 50 units of tetanus antitoxin per milliliter (μ/mL). Because the volume of the final product has varied without any apparent effect on the performance of the product, FDA has determined that it is inappropriate to regulate the potency of TIG on a per volume (mL) basis. However, FDA notes that TIG currently is manufactured consistently at a concentration of 170 μ/mL or greater. FDA believes that TIG should continue to be manufactured at a comparable concentration, although not specifically required by regulation. The Panel found TIG to be effective based on the historical evidence of the clinical use of TIG for the prevention and treatment of tetanus. TIG has consistently been administered at doses of 250 units or larger. FDA believes that TIG should continue to be marketed at a potency no less than the potency of the minimum dose (250) units) which historically has been shown to be effective.

The 250 units per container would represent the minimum potency of TIG permitted throughout the dating period of the product. Under § 610.53(a) (21 CFR 610.53(a)), TIG is prescribed a dating period of 3 years, provided three is an initial 10 percent excess of potency. Accordingly, a potency of 275 units per container (250 units plus 10 percent excess) would be required at the date of manufacture. FDA advises that in this discussion and the proposed regulation "per container" is interpreted to be that amount of the contents of the container that is deliverable to the patient in normal use. All current manufacturers of licensed TIG already conform to the proposed requirement by marketing the product in 250 unit amounts, plus an excess of at least 10 percent. Thus, FDA believes the proposed amendment would make the regulations consistent with current practices.

D. Response to General Research Recommendations

27. Throughout its Final Report, the Panel identified many areas in which there should be further investigation, beyond that immediately required of a manufacturer for a safe, effective, and properly labeled licensed product. Included were recommendations to monitor the population for its immune status against several bacterial diseases, suggestions for improving existing bacterial products and developing new products, and recommendations for developing laboratory tests and animal models correlated with the clinical potency of certain bacterial products.

FDA agrees with the recommendations. There are many areas surrounding the manufacture, testing, and use of bacterial vaccines, toxoids, and other bacterial products that require further investigation. FDA, through its Office of Biological Research and Review, continues to participate in these efforts. In this response, the agency has responded to several specific recommendations to initiate further investigations to help assure the safety, purity, and potency of currently licensed products. FDA will continue to consider the Panel's findings and recommendations when initiating or supporting investigative studies.

The agency notes that some of the investigations recommended by the Panel, such as monitoring the immune status of the population, are primarily

the responsibility of other agencies. To aid in the development of new or improved vaccines, FDA continues to participate in basic research to gain a better understanding of disease mechanisms and the physiology of the causative organisms. FDA also supports vaccine development by reviewing study protocols and data and by aiding in the development of laboratory tests suitable for assuring the safety, purity, and potency of the product. Many of the organizations involved in the study of bacterial disease and the development of bacterial products already are aware of the Panel's recommendations through their attendance at Panel deliberations. Through the publication and broad dissemination of the Panel's Report, FDA is encouraging the cooperation of public and private organizations to achieve the research objectives recommended by the Panel.

In several cases, the Panel recommended the development of a new biological product for the prevention or cure of a rare disease. FDA believes that these products may not have been developed in the past because of insufficient commercial incentive to justify the considerable expense for manufacturers involved in the development and clinical testing of new drug products. Drugs intended for rare disease are commonly called "orphan drugs."

The Orphan Drug Act (Pub. L. 97–414) became law on January 4, 1983. The Orphan Drug Act establishes a number of incentives to facilitate the development and marketing of drugs, including biological drugs, for rare diseases or conditions. FDA has created an Office of Orphan Products Development to coordinate FDA's efforts to assist manufacturers in the development of orphan drugs. FDA has announced in the **Federal Register** the availability of interim procedures to implement the Orphan Drug Act (48 FR 40784; September 9, 1983).

In the following paragraphs FDA is summarizing its response to those Panel recommendations that require further investigations for developing or improving biological products.

a. *Animal models and laboratory tests for demonstrating vaccine efficacy.* The Panel recommended that the public support the development of animal models that accurately predict vaccine responses in humans. The Panel specifically mentioned animal models for diphtheria toxoid, tetanus toxoid, BCG vaccine, plague vaccine, and pertussis vaccine as needing further development. The Panel also found that increased emphasis is needed on the development of laboratory tests and procedures that would reflect vaccine efficacy with sufficient accuracy so as to minimize the need for field trials.

FDA agrees that there are needs for assay systems that predict primary immunogenicity in humans, especially in view of the increasing difficulty in finding suitable populations for conducting clinical studies for many types of vaccines.

The development of animal models and laboratory procedures that accurately reflect vaccine responses and effectiveness in humans require that vaccines of varying potency or strength be administered to humans so that accurate correlations can later be made with the animal and laboratory models being developed. DHHS is actively involved in fundamental programs requisite to such studies, particularly as previously discussed for toxoids and pertussis vaccine. The agency is involved in the operation of primate breeding colonies to assure a sufficient number of primates for research, including vaccine testing. Monkeys have been used by the Office of Biologics Research and Review for studies of toxoid potency. Laboratory techniques are modified to meet changing technical advances applicable to all products.

The agency is currently funding work directed, in part, toward the development of a radioimmune assay method for the sensitive evaluation of serologic responses of animals and man to plague vaccine, which may eliminate the need for expensive, time-consuming, and less precise animal challenge experiments.

The following factors make it unlikely that the development and evaluation of BCG vaccines in animal model systems will have high priority at this time: (1) the low incidence of tuberculosis in this country; (2) the availability of effective drugs for treating the disease; (3) the need for unassailable evidence for the clinical effectiveness of a specific vaccine in protecting humans against the disease; and (4) limited Federal resources.

b. *Unmet needs for vaccines.* The Panel found research is needed to fulfill unmet needs in protection against bacterial diseases such as streptococcal, staphylococcal, gonococcal, *Haemophilus influenzae*, and pseudomonas infections.

The Office of Biologics Research and Reviews investigating the immune response to selected encapsulated bacteria and the development of methods of providing safe and effective vaccines to prevent diseases caused by such bacteria. The purified capsular polysaccharides of these organisms have been shown to be inadequate immunogens because most of them elicit a poor immune response in infants less than 2 years of age, the age at which diseases caused by these organisms are most prevalent. Further, reinjection of these polysaccharides is unsuccessful in providing protection as they exert no booster effect. A field trial of *Haemophilus influenzae* type b polysaccharide vaccine, conducted in Mecklenberg County, was supported by FDA. The Office of Biologics Research and Review has investigated covalent binding of bacterial polysaccharides, especially *H. influenzae* type b, Pneumococcus type 6, and *E. coli* K13 and K1 to immunogenic and T-dependent carrier proteins.

The Office of Biologics Research and Review has studied *N. meningitidis* serotype proteins and lipopolysaccharides as serological and epidemiological tools for characterizing *N. meningitidis* strains. The Office of Biologicals Research and Review is investigating as a vaccine candidate serotype 2 protein (found in over 50 percent of the group B strains and in group C strains) in combination with the group B capsular polysaccharide.

Collaborative studies were initiated to defined the structural character of staphylococcal capsules. To date, 10 capsular types have been serologically defined, 2 of which were found to be associated with human disease. The studies were performed to purify and analyze the structure of these polysaccharides, which may provide protection staphlococcal antigens (see Ref. 41 below).

c. *Bacterial toxins.* The Panel recommended support for research on the mechanism of action of bacterial toxins, specifically botulism and histotoxic clostridia toxins.

FDA recognizes the need for studies on the mechanism of action of bacterial toxins. FDA has supported work on other aspects of botulism toxins and is actively engaged in research on the mechanisms of actions of several other bacterial toxins, including tetanus toxin. This latter work may prove relevant to botulism toxin because both toxins appear to inhibit neurotransmitter relase. Other government agencies are supporting work on botulism (see Ref. 39 below).

At this time, FDA does not intend to undertake studies of the histotoxic clostridia. The acceptable mode of therapy of gas gangrene is surgery, antibiotics, and other supportive therapy; the use of passive immunization with the polyvalent gas gangrene antitoxin has been, at most, adjunctive. As noted in the Panel's

review, there is no evidence that the antitoxin product available in this country is effective and there is general agreement that such products are not effective for prophylactic use. FDA is aware of the emergence of clostridia as pathogens in enteric diseases. FDA will reevaluate the need for increased effort in this area as new data become available. The agency is supplying antitoxins to investigators for studies in this area.

d. *Immune globulins.* In a number of instances, the Panel recommended support of research and testing for the improvement of currently licensed immune globulin products or the development of new products conferring passive immunity. Specifically the Panel recommended that:

(1) The development of botulism and diphtheria immune globulin preparation of human origin be considered;

(2) Studies be supported to provide further information in judging the prophylactic and therapeutic value of Tetanus Immune Globulin (Human) (TIG) and to establish the availability, safety, potency, and stability of TIG for intravenous use;

(3) The accumulating data on intrathecal therapy be reviewed and followed to determine its possible application in treating human tetanus with TIG;

(4) The protective antibodies in the currently available Pertussis Immune Globulin (Human) be identified and characterized and that other immunoglobulin preparations be studied to determine their efficacy in conferring passive immunity to pertussis; and

(5) Further informtion be obtained regarding the possibility or reducing the reactivity of animal serum used in tetanus and diphtheria antitoxins.

FDA agrees with these recommendations. On October 31, 1979, in conjunction with the National Heart, Lung, and Blood Institute, FDA held a public workshop to discuss the characteristics and current and potential development and use of immunoglobulins. Some of the topics discussed at the workshop were: The European experience with the use of I.V. preparations, the current and potential uses of I.M. and I.V. preparations, and the causes and prevention of clinical reactions to these products. The information provided at this workshop will aid interested manufactures and FDA in developing and assessing new immunoglobulins, including those for I.V. administation. In late 1981, Immune Globulin Intravenous manufactured by Cutter Laboratories, Inc., was licensed for sale in the United States.

Researchers have shown it is possible to prepare a diphtheria immune globulin (Ref. 36 and 37). The effectiveness of this type of preparation for either prophylaxis or therapy has not been demonstrated, but FDA is encouraging the development of such a product.

Development of a botulism immune globulin is in progress (Ref. 38 and 39). The agency supports further efforts to develop such a product.

FDA agrees with the Panel's observations that more information on the value of TIG in prophylaxis and therapy is needed. The Panel and FDA have both observed, however, that it would be difficult for ethical and epidemiological reasons to do controlled clinical trials of this product in te United States. The agency discusses elsewhere in this response the problem of developing animal models that accurately predict human response to biologicals, including TIG. The agency is aware of the growing body of conflicting data regarding the intrathecal administration of TIG and will continue to monitor information regarding this use.

The Office of Biologics Research and Review has an active research program directed at identifying and purifying the bacterial components necessary for prevention of pertussis (Ref. 16, 17, and 18). Animal models to study the infection and its prevention by active and passive immunization have been developed (Ref. 19). As indicated previously, FDA's former Bureau of Biologics has sponsored several symposia and/or workshops regarding pertussis. These meetings have provided forums for discussion of this disease and its prevention and treatment. FDA will continue to support the development of new or improved products for the prevention and treatment of pertussis.

FDA believes that priority should be given to developing suitable homologous antitoxins unless experimental data can be provided to show that antitoxins developed in animals have superior immunologic of therapeutic properties compared to that of human immune globulin and are potentially less reactive than current equine antitoxins. However, the agency is interested in manufacturing procedures which may reduce the reactivity of animal serum products because animal sera are more available throughout the world. Methods to immunopurify equine antitoxin have been reported (Ref. 40) and may have expanded application. The ability to produce monoclonal antibodies utilizing cell cluture techniques can be expected to provide new types of antitoxins in the future. The Office of Biologics Research and Review is engaged in research in this area and is willing to evaluate new products generated by this important technology.

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The agency has determined pursuant to 21 CFR 25.24(d) (2) and (10) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

FDA has examined the regulatory impact and regulatory flexibility implications of the proposed regulation in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The agency concludes that 18 manufacturers of bacterial vaccines and toxoids and related products will be affected by these requirements, of whom approximately 3 are small. No additional costs are expected to be incurred as a result of this rulemaking. The anticipated costs are insufficient to warrant designation of this proposal as a major rule under any of the criteria specified under section 1(b) of Executive Order 12291 or to require a regulatory flexibility analysis. Accordingly, under section 605(b) of the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rulemaking, if promulgated, will not have a significant economic impact on a substantial number of small entities. A copy of the threshold assessment supporting this determination is on file with the Docket Management Branch, FDA (address above).

List of Subjects in 21 CFR Part 610

Biologics, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and the Administrative Procedure Act and under 21 CFR 5.11, it is proposed that Part 610 be amended as follows:

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

1. The authority citation for 21 CFR Part 610 continues to read as follows:

Authority: Sec. 215, 58 Stat. 690 as amended, 42 U.S.C. 216, sec. 351, 58 Stat. 702 as amended, 42 U.S.C. 262; 21 CFR 5.10 and 5.11.

2. In § 610.21 by revising the item "Tetanus Immune Globulin (Human)" under the heading "ANTIBODIES" to read as follows:

§ 610.21 Limits of potency.

* * * * *

Antibodies

* * * * *

Tetanus Immune Globulin (Human), 250 units of tetanus antitoxin per container.

* * * * *

Interested persons may, on or before March 13, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the

heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 11, 1985.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 29206 Filed 12-12-85; 8:45 am]

BILLING CODE 4160-01-M

Federal Register

Friday
December 13, 1985

Part III

Department of Labor

Occupational Safety and Health Administration

29 CFR Part 1910

Occupational Exposure to Cotton Dust; Final Rule

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Part 1910

Occupational Exposure to Cotton Dust

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Final rule.

SUMMARY: OSHA is amending its occupational health standard for cotton dust issued in 1978 (29 CFR 1910.1043). The revisions for the textile industry will improve the cost-effectiveness and performance-orientation of the standard while maintaining full health protection. The American Textile Manufacturers Institute (ATMI) and the Amalgamated Clothing and Textile Workers Union (ACTWU) submitted many identical recommendations to OSHA. They generally support the final revisions for the textile industry. These revisions include incorporation of an action level; modification of exposure monitoring requirements; extension of compliance deadlines for ring spinning of coarse count yarn with a high cotton content; addition of a protocol for determining equivalency to the vertical elutriator; incorporation of a wage retention provision; exclusion of oil mist from the definition of cotton dust; clarification of scope of coverage; and substantial changes to the washed cotton provisions reflecting current research. The standard's permissible exposure limits (PELs) of 200 micrograms per cubic meter (200 $\mu g/m^3$) for yarn production and 750 $\mu g/m^3$ for slashing and weaving operations and methods of compliance provisions with preference for engineering controls remain unchanged. This reflects the success of the industry in already achieving these levels with more productive modern equipment at less cost than initially predicted and the significantly improved level of health of textile workers resulting from compliance with the standard. Both ATMI and ACTWU agree that no changes are appropriate in these provisions.

The 1978 cotton dust standard in general has not taken effect in the nontextile industries because of judicial and administrative stays and because OSHA has been awaiting the completion of additional research, but it would eventually take effect absent action by OSHA. These segments are currently covered by the 1000 $\mu g/m^3$ limit of 29 CFR 1910.1000. OSHA is deregulating knitting, classing and warehousing operations by exempting them from all provisions of the 1978 cotton dust standard and by exempting them from all provisions of 29 CFR 1910.1000 (the cotton dust standard adopted in 1971). New research does not demonstrate a significant health risk at current exposures for these segments which could be substantially reduced by exposure limits and other provisions nor does it indicate that significant risk would exist if all exposure limits are eliminated. NIOSH will perform a further study of the health of the workers in those operations to check on the corrections of those conclusions. OSHA is also deregulating cotton seed processing operations for similar reasons except that it is retaining medical surveillance because the research indicates medical surveillance is needed to assure the continuing health of employees in this sector.

OSHA is exempting waste processing and garnetting operations from all except the medical provisions of § 1910.1043 and retaining the 1000 $\mu g/m^3$ exposure limit of § 1910.1000 interpreted as a respirable dust limit. Health studies in waste processing indicate that uncontrolled exposure leads to a risk of byssinosis. At current exposure levels, there is evidence of chronic bronchitis and pulmonary function reductions but no evidence of byssinosis. However, there is not sufficient evidence demonstrating a significant risk at current exposures which would be eliminated or substantially decreased by lowering the PEL to justify a lower exposure limit in waste processing operations.

These changes in textiles and nontextiles will result in cost savings of $57.3 million in capital expenditures and $28.9 million per year in annual operating costs. They will maintain health protection for employees.

EFFECTIVE DATE: These amendments take effect February 11, 1986; except for § 1910.1043 which contain information collection requirements that have been submitted to the Office of Management and Budget for approval.

ADDRESS: For additional copies of this document contact: OSHA Office of Publications, Room N4101, U.S. Department of Labor, 200 Constitution Ave., NW., Washington, DC 20210. Telephone (202) 523-9667.

FOR FURTHER INFORMATION CONTACT: Mr. James F. Foster, OSHA Office of Information and Consumer Affairs, Room N3637, U.S. Department of Labor, 200 Constitution Ave., NW., Washington, DC 20210. Telephone: (202) 523-8148.

SUPPLEMENTARY INFORMATION:

I. Introduction

A. The Format of This Document (The Preamble).

The preamble accompanying this final standard is divided into eight parts, numbered I through VIII. The following is a table of contents:

References to the rulemaking record are in the text of the preamble and the following abbreviations have been used: number in Docket H–052.

1. Ex.: Exhibit Docket H–052 is located in Room N3670 at the Department of Labor.

2. Tr.: Transcript page number (All citations are from the 1983 hearings unless otherwise noted).

B. Recordkeeping Requirements

The recordkeeping requirements in this standard are being considered by the Office of Management and Budget under the Paperwork Reduction Act of 1980, Pub. L. 96–511, 44 U.S.C. 3501, *et seq.* They will not take effect until approved.

C. Summary

Pursuant to sections 6(b), 8(c) and 8(g) of the Occupational Safety and Health Act of 1970 (the Act) (84 Stat. 1593, 1599; 29 U.S.C. 655, 657), Secretary of Labor's Order No. 9–83 (48 FR 35736) and 29 CFR Part 1911, OSHA is amending some paragraphs of 29 CFR 1910.1043 (the new cotton dust standard issued in 1978 pursuant to section 6(b) of the OSH Act). It is also issuing an interpretation to and amending the exposure limit for cotton dust contained in 29 CFR 1910.1000, Table Z–1 (the pre-existing standard for cotton dust issued pursuant to 6(a) of the OSH Act).

OSHA proposed amendments to the cotton dust standards (§ 1910.1043 and § 1910.1000) on June 10, 1983 (48 FR 26962). The proposal included an extensive explanatory preamble. Public comments were solicited and public hearings took place in Washington, DC, Dallas, Texas and Columbia, South Carolina. The final amendments are based on an extensive record and are explained in this preamble.

Together the final amendments result in substantial deregulation while maintaining health protection for employees. The changes result in cost savings of $57.3 million in capital expenditures and $28.9 million per year in annual operating costs.

Changes are being made to the cotton dust standard in textiles to make it more cost effective and performance oriented. Basic provisions are being retained because they have been achieved and have improved the health of cotton textile workers. Both the American Textile Manufacturers Institutes and Amalgamated Clothing and Textile Workers Union generally approve of the cotton dust standard as amended.

No changes are being made in the permissible exposure limit (PEL) and compliance strategy for the textile industry. The PELs remain 200 $\mu g/m^3$ for yarn production, 750 $\mu g/m^3$ for slashing and weaving and 500 $\mu g/m^3$ for wastehouses in textile mills. The studies by Imbus and ELB indicate that the standard has substantially reduced the incidence of byssinosis and declines in lung function from the levels of the early 1970's, a greater reduction than had been previously predicted. The Beck study confirms and expands on the prior studies by Merchant that the higher exposures of the early seventies and earlier lead not only to significant risk of acute byssinotic symptoms but also to chronic lung disease. OSHA expects that the much lower levels now in effect will substantially reduce and could possibly eliminate this chronic disease for newer employees. Both the American Textile Manufacturers Institute (ATMI) and the Amalgamated Clothing and Textile Workers Union (ACTWU) agree to the retention of the exposure limits. OSHA commends both the industry and the union whose efforts along with OSHA's have led to this substantial improvement in the health of workers currently employed in the cotton textile industry.

Current studies by Centaur and others show that it has been technically and economically feasible to comply with the standard in the textile industry. Virtually the entire industry has come into compliance utilizing modern production equipment in conjunction with increased ventilation (except for certain operations, discussed below). Such new equipment (chute fed cards, projectile looms, open end spinning, etc.) has substantially increased industry productivity while lowering both cotton dust and noise levels. The cost of the standard has proven to be half of the cost predicted by OSHA in 1978 and has proven to be economically feasible for the industry. Therefore, OSHA finds no basis for changing the compliance strategy. Again, both ATMI and ACTWU agree with this conclusion.

A number of amendments are being made to § 1910.1043 for the textile industry reflecting evidence in the record. These changes improve cost-effectiveness and performance-orientation while maintaining full health protection. Some represent new technological developments such as improved monitoring devices and advances in washed cotton. Most of these changes are supported by both ACTWU and ATMI.

The terms "blow off" and "blow down," applicable to the use of compressed air for cleaning, have been clarified. This is being done to indicate when employees must vacate an area and what protective equipment is needed.

Lubricating oils are being excluded from the definition of cotton dust. This decision is based on extensive evidence in the record indicating that lubricating oil mist generated by Sulzer looms was not part of the cotton dust samples measured in the Merchant studies, and thus was not a part of the dose-response calculations. Therefore, this exclusion will not raise risk rates. Some types of modern looms, which were not used in the early seventies, produce a mist composed of lubricating oil. This oil is captured by the vertical elutriator thereby increasing the reported weight of cotton dust present.

The definition of cotton dust continues to include mineral and synthetic dusts present in the atmosphere. They were present in the samples measured in the Merchant and other studies, and were part of the dose-response curve. Excluding these elements from the definition of cotton dust would increase the risk rate of byssinosis at any given exposure limit set. OSHA has no substantial evidentiary base to justify making such a change.

An action level is incorporated into the standard at one-half the PEL. Employers may reduce medical examination frequencies if they develop methods to reduce exposures below the action level. This improves the health of the employees through lower exposures while saving medical costs for the employer, thereby increasing the cost effectiveness of the standard. Medical experts stated that the reduced frequency at lower exposures will be protective for employees.

The amendments set forth a statistically valid method for determining whether alternate exposure monitoring devices are equivalent to the vertical elutriator, the method upon which the standard was based. This will encourage the development and use of alternative devices which are lighter, less labor intensive and easier to use than the vertical elutriator.

Monitoring frequencies are reduced to yearly when worker exposure is less than the PEL because the large data base recently developed means that less frequent monitoring will be as protective at these levels. The time to notify employees of exposures has been

increased from 5 days to 20 days because the shorter notification period created feasibility problems.

The standard is changed to give employers wider discretion in checking ventilation equipment to improve the performance-orientation of the standard and reduce the paperwork burden. Respirator provisions are basically unchanged, but some clarifications are made reflecting current terminology and field practice.

The wage retention provision is incorporated into the standard as recommended both by the ATMI and ACTWU. The existing standard provides that if an employee is working in an area with exposures above the PEL and a medical condition prevents the employee from wearing any type of respirator, the employee is to be transferred to an area where respirator use is not needed if a job is available. The amendment requires that the employer not reduce the employee's pay if such a transfer is made. Of course, if no such job is available, this provision is inoperable.

The Supreme Court had initially invalidated a similar provision in the 1978 standard because OSHA had not clearly explained a health related need for the provision. At the hearing, evidence was introduced that some employees are unwilling to submit to medical examinations because of fear of being transferred to lower-paying jobs. As a result, medical conditions that could be diagnosed and reversed may develop into chronic conditions. This is a special problem for older workers who fear the loss of both current pay and a reduction in their pension and social security benefits which are based on their final few years of pay. In view of the evidence indicating a health need for this provision and the recommendation of the parties with the most direct interest, the ATMI and the ACTWU, OSHA is amending the standard.

The standard is being changed to grant a two-year extension of the requirement to achieve compliance with engineering controls for ring spinning and auxiliary operations of coarse, high cotton content yarns. The record indicates that there are some technical feasibility problems in complying with add-on ventilation at the present time. However, open-end spinning equipment is rapidly being improved to meet the needs of customers and will be able to achieve the exposure limit while substantially increasing productivity. The extension will permit compliance using more efficient new equipment without the major inefficiency of an expensive intermediate stage of limited usefulness.

Based on successful recent research, major changes are being made to the washed cotton provisions. Merchant's studies indicated that cotton washed in a caustic and water solution at high temperatures did not create byssinotic symptoms. However, such cotton could not be processed into usable yarn and cloth. A Washed Cotton Task Force was set up with representatives of ACTWU, ATMI, the National Cotton Council, Cotton Incorporated, NIOSH and the Department of Agriculture and its activities were funded by the Department of Agriculture and Cotton, Inc. Under the direction of the Task Force, various washing methods were tested. The cotton produced was then tested under carefully controlled conditions to determine if it caused any reduction in lung function. Several washing methods were devised which appear to be commercially viable and which result in cotton fibers which can be processed. Most importantly, exposure to dust from cotton washed in certain manners does not result in any acute changes in pulmonary function.

Based on this research, the Task Force made recommendations as to the types of washed cotton that could safely be removed from regulation by some or most provisions of the cotton dust standard. Based on the test results, the recommendations of the Task Force and the evidence in the record, OSHA has broadened the definitions of the type of washed cotton exempt from regulation. These changes, more fully explained elsewhere in this preamble, should increase the cost-effectiveness of the standard, and employees exposed to washed cotton as defined will remain fully protected.

The cotton dust standards (§ 1910.1043 and § 1910.1000) are being substantially changed as to scope of coverage for the nontextile segments of the industry. The nontextile segments are knitting including hosiery manufacturing, classing, warehousing, cotton seed processing and waste processing operations. (Knitting has consistently been included with the nontextile industries in the cotton dust regulatory proceedings and that terminology is maintained in this document.)

The 1978 cotton dust standard, § 1910.1043, was intended to cover the nontextile operations and included a 500 $\mu g/m^3$ exposure limit for those operations. Substantially less health data were available on these segments. The standard is not in effect in any of these segments because of various judicial and administrative stays. However, the standard would take effect eventually if OSHA did not revoke coverage. The nontextile segments are currently covered by the 1000 $\mu g/m^3$ limit of § 1910.1000 Table Z-1 which would remain in effect unless replaced by a 6(b) standard or revoked. The specific legal history of each segment is complex and detailed below. Essentially, each industry segment has been remanded to the Agency by the Court of Appeals for further consideration. This review is pursuant to those remand orders.

Since the issuance of § 1910.1043 in 1978, a number of new studies on these segments have been completed by NIOSH and others. OSHA has reviewed these newer studies in conjunction with the older studies in making its final determinations for the nontextile industries. However, because the exact etiologic agent of byssinosis is not known and because the content of cotton dust may vary from one segment to another, the Agency is not extrapolating the results of the studies conducted in the textile industries to the nontextile industries.

In 1983, Drs. Boehlecke and Battigelli completed an extensive and high quality study of knitting employees. They indicated that there was no difference in pulmonary function between knitters and appropriate controls, and that there was no increased prevalence of byssinotic symptoms. There was some decline in lung function measured over the shift similar to that seen in control groups in woolen mills. Virtually all the employees studied were exposed to less than 500 $\mu g/m^3$. This is the only major study available of the knitting industry. Based on this study and the extensive reviews and comments about it, OSHA concludes that the evidence now available indicates no significant risk of byssinosis existed for the workers studied and that the workers in the industry will remain free of byssinosis without the need for extensive regulation. Therefore, OSHA is excluding the knitting segment from all coverage of § 1910.1043.

OSHA concludes, based on the same data, that it will better effectuate the purposes of the Act also to remove this industry from the PEL specified in § 1910.1000 and the evidence currently available indicates this will not lead to the development of significant risk. NIOSH will perform an additional study to confirm these conclusions.

NIOSH completed studies of classing employees in 1982. The study of classing workers concluded there were no acute or chronic respiratory problems among these workers, but that dust levels had been reduced from earlier levels and were quite low. The NIOSH study of

warehouse workers indicates there was some reduction in pulmonary function compared to controls. However, this was inversely related to cotton dust exposure level and therefore probably related to exposure to vehicle exhaust emissions or other noncotton dust factors.

Based on these studies and on its analysis of the record, OSHA concludes that the evidence now available in the classing and warehousing industries does not support a finding of significant risk from cotton dust exposure in these segments and that the employees will remain free of byssinotic symptoms when the industry is exempted from regulations. Accordingly, OSHA is exempting these segments from all provisions of § 1910.1043. OSHA further concludes that it will better effectuate the purposes of the Act to remove these segments from the PEL specified in § 1910.1000 and the evidence currently available indicates this will not lead to the development of significant risk. NISOH will perform an additional study to confirm these conclusions.

There are a series of post-1978 studies on cottonseed processing employees by NIOSH and by a group of investigators at Tulane University. These studies indicate that a portion of cottonseed processing workers experience an acute pulmonary reaction to cotton dust. The dust has some biologic activity but that activity is substantially less than that seen in the textile industry. There is no clear dose-response relationship and a very low prevalence of byssinosis.

Based on the lack of a dose-response relationship, the low prevalence of byssinosis and the views expressed in the record, OSHA concludes that the evidence now available does not establish the need for a permissible exposure limit. Accordingly, OSHA is exempting cottonseed processing from all except the medical surveillance provisions of § 1910.1043. The Agency finds for the same reasons that it will better effectuate the purposes of the Act to remove this segment from coverage of § 1910.1000 and that the evidence currently indicates that this deletion, in conjunction with the retention of medical surveillance, will not lead to the development of significant risk.

OSHA is retaining the requirement for medical examinations for cottonseed processing. There is a reduction in overshift FEV_1 in some current employees. The examinations will identify and provide protection for those employees. All medically qualified experts testifying on this matter recommended retaining medical surveillance for this reason. This will also serve as a backstop to assure that the health of employees not covered by any exposure limit does not decline. It also carries out the Supreme Court's analysis in *IUD* v. *API* that medical examinations may be used as a "back stop" to assure that the health of workers for whom an exposure limit is eliminated does not deteriorate.

NIOSH completed an extensive study of the waste processing industry in 1982. This study indicated an excess prevalence of chronic bronchitis and decreases in pulmonary function but no statistically significant prevalence of byssinosis or clear dose-response relationship. Based on this and other studies and the extensive comments, OSHA concludes that the evidence now available does not support the finding that a reduction of the current exposure limit of 1000 $\mu g/m^3$ total dust would result in a reduction or elimination of a significant risk. Accordingly, OSHA is exempting this sector from all except the medical provisions of § 1910.1043.

Other studies indicate that high, uncontrolled exposures, which may occur if there is no dust control, lead to byssinosis and chronic bronchitis and the NIOSH study indicates that employees currently are not free of cotton dust-related pulmonary dysfunction and chronic bronchitis. Accordingly, the evidence does not justify OSHA concluding that eliminating the § 1910.1000 exposure limit of 1000 $\mu g/m^3$ (the national consensus limit) will better effectuate the purpose of the Act. In addition, in light of the possibility of operations in the waste processing industry leading to high exposures, eliminating all exposure limits would likely lead to the development of a significant risk in this segment.

OSHA is retaining the medical provisions of § 1910.1043 for this segment to assure that cases of bronchitis and reductions in pulmonary function are diagnosed and in conjunction with the exposure limit to protect these employees. Based on the recommendation of medical experts, the 1000 $\mu g/m^3$ limit is being changed from a total dust limit to a respirable dust limit because this is a more appropriate measure of the type of dust that leads to the development of byssinosis and bronchitis. Therefore, this interpretation better relates to improving health. A 1000 $\mu g/m^3$ respirable dust limit also presents substantially fewer feasibility problems.

Miscellaneous segments where there is no evidence of risk such as bedding assembly, furniture assembly and construction are being removed from all cotton dust regulation. Knitting, classing and warehousing are being removed from all cotton dust regulation.

D. State Plans Revisions

The 25 States with their own OSHA-approved occupational safety and health plans must revise their existing standard within six months of this publication date or show OSHA why there is no need for action, e.g., because an existing State standard covering this area is already "at least as effective" as the revised Federal standard. These States are: Alaska, Arizona, California, Connecticut, Hawaii, Indiana, Iowa, Kentucky, Maryland, Michigan, Minnesota, Nevada, New Mexico, New York, North Carolina, Oregon, Puerto Rico, South Carolina, Tennessee, Utah, Vermont, Virginia, Virgin Islands, Washington, Wyoming. (In Connecticut and New York, the plan covers only State and local government employees.)

E. History of the Regulation

Regulatory steps to address health problems in the cotton textile industry began when Great Britain legislated requirements for medical inspection of workplaces, compulsory reporting of industrial diseases, and compensation for disabled and diseased workers. By 1942, British law recognized byssinosis as an occupational disease.

In the United States, the American Conference of Government Industrial Hygienists (ACGIH) placed cotton dust on its tentative list of Threshold Limit Values (TLVs) in 1964. In 1966, ACGIH adopted 1 $\mu g/m^3$ (1000 $\mu g/m^3$ of total cotton dust as a recommended upper limit for exposure. This TLV was based upon the work of Roach and Schilling in the Lancashire cotton mills (Ex. 6–1).

Exposure to cotton dust was first regulated in the United States in 1968, when the Secretary of Labor, acting under the authority of the Walsh-Healey Act (41 U.S.C. 35 *et seq.*), promulgated the 1968 ACGIH list of Threshold Limit Values which included 1000 $\mu g/m^3$ for "Cotton dust (raw)." This Threshold Limit Value was subsequently adopted as an established Federal standard under section 6(a) of the Occupational Safety and Health Act of 1970. On September 26, 1974, pursuant to section 20(a)(3) of the Act, the Director of the National Institute for Occupational Safety and Health (NIOSH) submitted to the Secretary of Labor a criteria document which contained NIOSH's recommendations for a new cotton dust standard.

On December 28, 1976, at 41 FR 56498, OSHA proposed a revised cotton dust standard that would set a permissible exposure limit of 200 $\mu g/m^3$ averaged

over an eight hour period. An extensive record of documentary and testimonial evidence was compiled over a period of more than nine months. Among the witnesses were large corporate and small business employers, manufacturers, representatives from the affected workforce, experts in every relevant field including physicians, scientists, statisticians, economists, industrial hygienists, representatives from agriculture, and other interested parties. Virtually the entire "cotton community" participated in this rulemaking.

On June 23, 1978, at 43 FR 27350, OSHA promulgated 29 CFR 1910.1043 and set permissible exposure limits of 200 $\mu g/m^3$ of lint-free respirable cotton dust, averaged over eight hours, for yarn manufacturing; 750 $\mu g/m^3$ for slashing and weaving operations; and 500 $\mu g/m^3$ for knitting and nontextile industries which used cotton. Petitions for review were promptly filed by interested parties with United States Courts of Appeals.

In *AFL–CIO* v. *Marshall,* 617 F.2d (D.C. 1979), the District of Columbia Circuit upheld the standard for the textile industry (yarn manufacturing, slashing and weaving) and the nontextile processes of warehousing and classing. The Court held that OSHA had demonstrated that the standard would result in a substantial reduction in a significant risk, and that OSHA had demonstrated technical and economic feasibility. The Court vacated the standard for the cottonseed oil industry, finding that OSHA had failed to demonstrate economic flexibility, but it upheld OSHA's determinations of health risk and technological feasibility. The Court then remanded the record on the cottonseed oil industry to the Agency for reconsideration. The Court did not consider the validity of the standard for waste processing and waste utilization, having severed the industry representatives' petitions for review because of an administrative stay issued by OSHA for those segments of the industry (43 FR 39087, September 1, 1978). Although OSHA later lifted the administrative stay, the judicial stay remains in effect (44 FR 5438, January 26, 1979).

Representatives of the textile industry and warehousing and classing industries sought review of the Court of Appeals decision in the Supreme Court. Except for the wage retention provision, the Supreme Court upheld the standard for the textile industry (yarn manufacturing, slashing and weaving). *American Textile Manufacturers Institute, Inc.* v. *Donovan,* 452 U.S. 490 (1981). The Supreme Court upheld OSHA's conclusion that the cotton dust standard in textiles would substantially reduce a significant risk of byssinosis. The Court stated as to this issue: "It is difficult to imagine what else the agency could do to comply with the Courts' decision in *Industrial Union Department* v. *American Petroleum Institute*" (The "Benzene Decision," 448 U.S. 607 (1980) where the Supreme Court set forth the significant risk requirement). The Supreme Court also upheld the Court of Appeals finding that the standard was technically and economically feasible for the textile industry. The Court also rejected the contention that the Agency is to perform cost-benefit analyses in setting permissible exposure limits.

Earlier, on October 6, 1980, the Court at the request of OSHA and the industry had granted a petition for writ of certiorari and vacated the decision of the Court of Appeals with respect to the warehousing and classing segments of the industry. *Cotton Warehouse Association* v. *Marshall,* 449 U.S. 809 (1980). The Supreme Court instructed the Court of Appeals to reconsider the standard for these industries in light of the Supreme Court's decision in *Industrial Union Department AFL–CIO* v. *American Petroleum Institute,* 448 U.S. 607 (1980). On joint motion of the parties, the Court of Appeals then remanded the record to OSHA for the warehousing and classing segments of the industry. Order of February 3, 1981, in No. 78–1562. On July 29, 1980, OSHA issued an administrative stay of the standard to re-evaluate its applicability to warehousing and classing industries in view of *IUD* v. *API,* supra.

In its most recent action, the D.C. Circuit, at the request of OSHA, ordered that the records in the cases brought by the waste processing utilization industries, which it had previously stayed, be remanded to the Agency for further consideration. Order of March 30, 1983, in Nos. 78–1784, and consolidated cases Nos. 78–1796, 78–1985, 78–2015, and 78–2017. In addition, the Court noted that its prior remand orders for the cottonseed oil, warehousing, and classing industries remain in effect. Finally, the Agency was ordered to provide the Court with status reports of proceedings on reconsideration at 120 day intervals. These have been filed. It should be noted that the Court retained jurisdiction of the cases and remanded only the record.

A separate standard for the cotton ginning industry (43 FR 27418, June 23, 1978; 29 CFR 1910.1046) was vacated by the United States Court of Appeals for the Fifth Circuit in *Texas Independent Ginners Association* v. *Marshall,* 630 F.2d 398 (5th Cir. 1980). The Court found that the record did not demonstrate a significant risk of adverse health effects as required by the benzene decision. In response to the court's decision, OSHA deleted the cotton ginning standard from the CFR and no further action in this area is required.

The knitting industry never challenged the standard in court. Based on available data, however, OSHA temporarily stayed the standard for the knitting industry until the completion of this review of the standard (48 FR 5267, February 4, 1983).

In view of these court and Agency actions, the 1978 cotton dust standard is currently in effect only for the textile industry, yarn production and slashing and weaving operations. All provisions of the standard except the engineering controls provision took effect in 1981 for the textile industry. Compliance with the PEL using engineering controls was required by March 27, 1984. On February 23, 1984 (49 FR 6717), OSHA extended that deadline until September 27, 1984 (subsequently extended to March 27, 1986 at 50 FR 14698 on April 15, 1985), *only* for ring spinning, spooling, winding, twisting, beaming and warping of coarse count, high cotton content yarns as defined. With that limited exception, all provisions of the cotton dust standard are now in full force and effect for the textile industry.

For all segments of the nontextile industry, including knitwear and hosiery manufacturing, the 1978 standard has been stayed and the record is before OSHA for reconsideration in light of the benzene decision, or for other relevant factors. All the nontextile industries' court challenges to the standard have been placed in abeyance pending OSHA's reconsideration. Therefore, it was necessary for OSHA to have this rulemaking to reconsider the application of the standard for the nontextile segments of the cotton industry.

In light of these judicial and administrative actions, OSHA published an Advance Notice of Proposed Rulemaking (ANPR) on February 9, 1982 (47 FR 5906). Extensive comments were received in response to the ANPR and will be referenced throughout this discussion. In addition, OSHA contracted with Centaur Associates to survey the existing published data and to conduct a detailed survey of textile manufacturing establishments, including site visits, the actual cost and technical and economic feasibility of achieving compliance with the standard, productivity effects and the feasibility

and cost-effectiveness of alternative regulatory approaches. References to the Centaur study will be made throughout this discussion.

On June 10, 1983 (48 FR 26962–26984) OSHA proposed a number of amendments to the cotton dust standard for textiles but did not propose changes to the permissible exposure limits or methods of compliance for the textile industry. OSHA proposed deleting the nontextile segments from coverage of 29 CFR 1910.1043. Further, it proposed retaining coverage of waste processing, garnetting and mattress manufacturing under the exposure limit of § 1910.1000, Table Z–1, but deleting the other nontextile segments from that exposure limit. The preamble contained an extensive discussion of the reasoning in support of these proposals. Of course, OSHA made it clear that no final decisions would be made until all public comments and new evidence had been considered and that the evidence might lead OSHA to make new proposals on matters not covered by the notice.

OSHA had received comments on the proposal from 33 individuals and groups when the comment period closed on August 9, 1983. Public hearings held in Washington, DC on September 19–23, in Dallas, Texas on September 28–29, and in Columbia, South Carolina on October 4–6, 1983 generated over 1500 pages of testimony from 70 witnesses. Testimony was received from scientists, physicians, industrial hygienists, directors of state occupational safety and health programs, economists, industry executives, union officials, textile workers and other interested persons testified at the hearings, and all witnesses were available for questioning. In addition, 35 exhibits were entered into the record at the hearings. Following the close of hearing, 58 post hearing comments were filed.

Post hearing evidence was due on October 28, 1983. Post hearing briefs were originally due on November 29, 1983, but the date for submitting them was extended until December 16, 1983 at the request of several parties. The record was certified by the presiding administrative law judge on January 12, 1984.

OSHA has carefully considered all the information submitted into the record including the studies, comments, and testimony. OSHA's final decisions are based on this evidence and all the evidence, comments and data submitted to earlier rulemaking proceedings on cotton dust and in response to prior advance notices on cotton dust, all of which have been incorporated into the record of this proceeding.

II. Occupational Health Implications and Significant Risk Analysis From Exposure to Cotton Dust in the Textile Industry

While lung disease associated with exposure to dust from cotton or flax was described over 200 years ago (Ex. 7), the formal acknowledgment of the relationship has been relatively recent. In 1942, the British recognized this relationship by incorporating into law compensation for pulmonary disabilities due to cotton or flax dust exposure (41 FR 56499). In the United States, it was not until 1964 that ACGIH placed cotton dust on its tentative list of threshold limit values (TLVs). The TLV of 1000 $\mu g/m^3$ was not adopted until 1966 (Ex. 5).

When the Occupational Safety and Health Administration proposed to issue a new standard for occupational exposure to cotton dust in 1976, there was already a substantial amount of evidence linking exposure to cotton dust, particularly in the textile industry, with respiratory disease in exposed workers (41 FR 56500–56502). Byssinosis is the respiratory disease most commonly associated with exposure to cotton dust, but other diseases such as chronic bronchitis, mill fever, weavers' cough, and mattress makers' fever have also been associated with cotton dust exposure. These diseases have been described and their association with cotton dust exposure has been documented extensively in previous **Federal Register** publications. (41 FR 56500–56502; 42 FR 27352–27354; 48 FR 26964–26968.)

OSHA concluded that workers in both the textile and the nontextile industries were at a significant risk of byssinosis and other respiratory diseases including chronic bronchitis, as a result of their exposure to cotton dust and in 1978 issued a final standard for cotton dust that covered both the textile and the nontextile industries (43 FR 27350). The 1978 final standard set two permissible exposure limits for the cotton textile industry. For yarn manufacturing operations, the PEL is 200 $\mu g/m^3$ lint-free respirable cotton dust as an 8-hour TWA and for weaving operations, the PEL is 750 $\mu g/m^3$ lint-free respirable cotton dust as an 8-hour TWA.

On review, the U.S. Court of Appeals for the District of Columbia Circuit upheld the standard as it applied to the textile industry and approved the extensive analysis of health data set forth in the preamble to the standard (*AFL–CIO* v. *Marshall, supra*). OSHA's findings of significant risk of adverse health effects due to exposure to cotton dust in the textile industry have been upheld by the Supreme Court. Specifically, the Supreme Court noted that OSHA relied on dose-response curve data from the work of Merchant and his colleagues that showed 25% of employees suffered at least Grade ½ byssinosis at 500 $\mu g/m^3$ and that 12.7% of all employees would suffer byssinosis at 200 $\mu g/m^3$. The Supreme Court commented on the acceptability of OSHA's effort to provide a reliable assessment of health risk in compiance with the Court's decision in *Industrial Union Department* v. *American Petroleum Institute* as follows: "It is difficult to imagine what else the agency could do to comply with this Court's decision . . .". (*ATMI* v. *Donovan, supra* footnote 25.)

Byssinosis, sometimes referred to as "Brown lung" is characterized by coughing, breathlessness or tightness of the chest experienced on the first day of the work week. A grading scheme for byssinosis reflects the differences in duration of the Monday morning symptoms. These may extend into other days of the work week ultimately leading to permanent incapacitation. In addition to the symptoms, byssinosis is often characterized by reductions in pulmonary function and presence of respiratory airway obstruction. These symptoms initially are reversible through removal from exposure but later may become chronic. Substantial reductions in lung function limit physical activity and place stress on other systems such as the cardiovascular system. Pulmonary function can be evaluated through tests such as forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC) which are frequently used to indicate reduction of normal respiratory function.

Other occupational illnesses besides byssinosis have been noted in workers exposed to cotton dust. Some examples of these illnesses are weaver's cough which may be attributed to airborne exposure to fungus from mildewed thread (Ex. 36 and 37) and mill fever which sometimes developed in those unaccustomed to or previously unexposed to cotton dust, followed by a tolerance to the dust after a few days (Ex. 20). The final standard was designed to reduce the incidence of byssinosis and pulmonary dysfunction in affected industries.

British studies published in the 1960's established a dose-response relationship between exposure to cotton dust and prevalence of byssinosis (Exs. 6–1, 6–55, 6–56, 6–66). Studies conducted in the United States documented that byssinosis, bronchitis and lung function abnormalities were also present in

American textile workers (Exs. 6–14, 6–15, 6–18, 6–24).

Beginning in the early 1970's, the North Carolina State Board of Health and researchers from Duke University conducted a study of 3000 textile workers. This study, conducted in cooperation with Burlington Industries, examined the respiratory health, dust, and exposures of workers in cotton, synthetic, wool and blend operations. The results of this study were summarized at the 1983 hearing by Dr. James Merchant, one of the investigators.

The results of this study agreed closely with the findings of Roach and Schilling and with Molyneaux in regard to dose-response relationships. Again a linear dose-response relationship without a clear threshold was observed in preparation in yarn processing areas. It was clear that cotton dust was an important risk factor not only for byssinosis, but also for bronchitis. Similarly cotton dust was found to be associated with decline in pre-shift FEV_1 over a work shift. Smoking was also found to be an important risk factor for byssinosis, for bronchitis, and for a pre-shift FEV_1 and FVC. Evidence of an interaction between smoking and cotton dust was found for byssinosis prevalence and to a lesser extent for bronchitis prevalence when the severity of respiratory symptoms was taken into account. The vertical elutriator was judged, not only from the epidemiological data, but from an industrial hygiene standpoint to be a satisfactory area sampling instrument for this industry. (Ex. 192–9)

The permissible exposure limits for yarn manufacturing and slashing and weaving were based in part on the linear dose-response relationship demonstrated by the Merchant study. It should be noted that OSHA recognized that dust control alone, even to the PEL, would not adequately protect exposed workers. The Merchant study showed the prevalence of byssinosis in yarn areas was 26% at 500 μg^3, 13% at the PEL (200 $\mu g/m^3$) and in weaving areas was 15% at 1000 $\mu g/m^3$ and 5% at 500 $\mu g/m^3$ (Ex. 6–51; 43 FR 27355) when no other provisions were in effect. Therefore, the standard required that dust control be combined with other protective measures such as medical surveillance and job transfer. OSHA predicted that the medical surveillance and other provisions would further reduce byssinosis prevalence (43 FR 27359, col. 3). The Merchant and other earlier health studies are discussed at great length at 43 FR 27352–60 (June 23, 1978). That discussion is not repeated here.

Since the promulgation of the final standard in 1978, additional reports on the effect of exposure to cotton dust in the textile industry have been published or otherwise made available to OSHA and have been made a part of this record (Ex. 177, 170–9, 175–60, 187–17, 271).

At the hearing, Dr. Gerald Beck discussed the results of the study that he coauthored, "Follow-Up of Active and Retired Textile Workers." This 1979 study, sometimes called the "Yale Study", was initiated by the late Dr. Arend Bouhuys. It analyzed the health data on a group of active and retired cotton textile workers in Columbia, SC who had first been examined in 1973. Since all the workers had been employed in the mills for at least 3 years prior to 1955, the study focused on older workers with long work histories in the mills. The study was unique because it included a group of retired cotton textile workers. The data on cotton textile workers were compared to data obtained from community-wide respiratory health surveys of individuals in Lebanon, Connecticut.

Of the 646 cotton textile workers who participated in the initial 1973 survey, 383 participated in the follow-up in 1979. These workers had a higher prevalence (18%) of byssinosis than controls (1%). This difference held true when nonsmokers (12%) as well as smokers (26%) were compared to controls (smokers and non smokers 1%). The cotton textile workers also had a higher prevalence of chronic bronchitis (17%) as opposed to controls (3%). Over the six year interval between the initial study and the follow-up, there was a greater loss of lung function as measured by FEV_1 in the textile workers than in controls.

Work status, active or retired, could also be correlated with respiratory health. Significant differences in prevalence of respiratory symptoms were found among the three work status groups of cotton textile workers: (1) These who were active at both surveys (A–A), (2) those who had retired since the initial survey (A–R), and (3) those who were retired at both surveys (R–R). The prevalence symptoms was lowest in the A–A group, intermediate in the A–R group, and highest in the R–R group. Symptoms for which significant differences were found included chronic bronchitis, phlegm production, dyspnea, cough, and wheeze.

Dr. Merchant commented on the findings of this study and found them "fully consistent with the historical record." He went on to say that the hazard has been clearly established and that the continued use of controls is necessary. He said:

> Therefore, it is reasonable to conclude that cotton dust, if uncontrolled, will result in chronic obstructive lung disease among those with prolonged occupational exposure. This was the conclusion of the World Health Organization in their Recommended Health Based Occupational Exposure Limits for Selected Vegetable Dusts (1983). Although the National Research Council report on byssinosis questioned whether there was enough evidence to conclude that the cotton dust by itself caused chronic obstructive lung disease, they found that this was probable and stated clearly that it was important to regulate cotton dust exposure (Tr. 284–285).

As part of its comments in response to the ANPR, the ATMI submitted a critique of the Yale study prepared by Epidemiology Resources, Inc. This analysis criticized the study on several points including the method of selecting and expanding the cohort; the incomplete follow-up of the original cohort and controls; the use of controls from a separate geographical location; and the lack of dose-response calculations. OSHA concludes that Dr. Beck gave valid responses to many of these criticisms during his testimony and during the question and answer session that followed his testimony (Tr. 1097–1134). He commented on the reasons why all of the individuals eligible for the original cohort were not included; the validity of the controls used; the effect on follow-up when workers die or move from the area; the lack of assistance from the employers; and the difficulties in determining a dose-response when exact exposure levels are unknown.

During the hearings, however, the point was made that the workers studied were exposed to cotton dust in the 1930's, 1940's, 1950's, and 1960's when dust levels were much higher than they are today and when there was little or no medical surveillance. Many witnesses in addition to Dr. Beck were questioned on this point and the consensus was that the conditions in the mills have improved dramatically (Tr. 537–38, Tr. 96, Tr. 517). They agreed that as a result of dust controls, medical surveillance and other protective measures, workers employed in cotton textile mills, particularly new workers, are much better protected and substantially less likely to suffer from the long term as well as short term adverse effects of cotton dust exposure than the workers in the Yale study.

In 1982, the National Academy of Sciences published a report by the National Research Council's Committee on Byssinosis (Ex. 177). The Committee

investigated the scientific literature and reported on the complex nature of cotton dust, the search for an etiological agent, the definition of byssinosis, the identification of risk factors, and the need for additional research. The Committee agreed that the evidence clearly demonstrated an acute response to the dust, but called for additional research to clarify the relationship between cotton dust and chronic lung disease. Although the Committee identified additional research needs relating to the problem of respiratory disease in cotton textile workers, it did not question the appropriateness of or need for the cotton dust standard. Also included was a minority report which expressed disagreement with several of the Committee's findings on the relationship between acute and chronic disease and the definition of byssinosis.

At the public hearing, Dr. Hans Weill, a member of the Committee, discussed the findings of the Committee as they related to the standard. He said:

> The NAS Committee on Byssinosis considered that its primary responsibility was to evaluate the scientific evidence regarding the respiratory health effects of cotton dust exposure. This in no way leads to the conclusion that the important social issues which relate to occupational health must not often be addressed in the absence of convincing scientific evidence. The committee felt that they must indeed be dealt with in a timely and equitable way. The need for additional studies to clarify the dust-chronic airways effect relationship or the findings of some investigators that uncharacterized mill factors may influence byssinosis risk are *not* attacks on the present or, for that matter, any cotton dust standard. We specifically stated that "The committee does not intend to imply that the need for such studies precludes the need for maintenance of adequate dust controls in the working environment". As regards chronic pulmonary disease, we said that such a disease outcome is plausible and may have been a consequence of the exposure. We simply find that the evidence needs strengthening.
>
> Rational public policy must be based *in part* on valid scientific evidence while consideration is given to nonscientific issues. The process is appropriately a phased one, accomplished without losing the necessary rigor of the scientific evaluation. Once done, social decisions are made in the broader context, with input from all interested parties. Worker interests are best served when the acquisition of knowledge (research) and analysis and interpretation of results are free of pressures resulting from these wider public concerns since understanding and prevention of workplace-induced diseases depends on this unencumbered process. (Ex. 192-7)

The issue of disease prevention programs in the face of information gaps was also addressed by Dr. Harold Imbus. Dr. Imbus, testifying at OSHA's request, also attested to the benefits of acting to prevent lung impairment even though some questions remain to be answered. He stated:

> • • • I agree with those who say that we do not need to have all the answers in order to set up prevention programs. Nothing illustrates this more dramatically than the cotton dust issue.
>
> Here we have a substance capable of causing lung disease. We do not even know what the agent in the substance is.
>
> • • • However, by establishing preventive programs with the philosophy that we will try to prevent all lung disease irregardless of its cause, we have been able to show a remarkable reduction in prevalence of lung disease in the cotton textile industry. This has offered a great deal of protection for employees from both occupational and non-occupational lung disease. (Tr. 89-90)

Dr. Merchant is one of the world's leading experts on cotton dust-related disease. Dr. Weill is a recognized expert on occupationally-related pulmonary disease. Dr. Imbus was medical director of Burlington Industries for many years and was responsible for programs of medical surveillance and dust control which substantially improved the health of Burlington employees in the 1970's.

OSHA also received reports from the ATMI summarizing medical surveillance data from a large number of textile workers. The "Imbus Report", prepared by Dr. Harold Imbus of Health and Hygiene, Inc., (Ex. 175-60) covered approximately 41,000 workers and the summary prepared by ELB Associates (Ex. 187-17) covered 52,000 employees. In addition to their summary, ELB Associates also provided the raw data on workers from 23 of the companies (Ex. 271).

These data indicated that the prevalences of byssinosis and bronchitis have been dramatically reduced in the textile industry. The overall prevalence rate for byssinosis was less than 1.0%, and the bronchitis prevalence rate ranged from 6.0% to 7.0%. In their testimony, Dr. Merchant and Dr. Imbus attributed the reduction in respiratory disease in these workers to a combination of dust control and medical surveillance (Exs. 192-9, 192-2). In addition, Dr. Merchant pointed to the prescreening of new employees and the retirement of older employees as factors contributing to the decreased prevalence of respiratory disease (Ex. 192-9). He stated:

> It is my opinion that at least three processes have played an important role in reducing the prevalence of health effects in the textile industry. First, and most important, is improved dust control through improved machine design, plant design, use of effective exhaust ventilation. Technological feasibility was demonstrated at the time of the original cotton dust hearing, and these observations have now been largely validated by the record the industry has established with substantial compliance with this standard—well before the date they were required to meet the dust control provision. It is important to note these industries have done this while improving efficiency and remaining competive in the world market.
>
> Secondly, the medical surveillance program has played an important role in identifying those affected by cotton dust and transferring them to lower risk areas, thereby reducing exposure and health effects in this manner.
>
> Another selection process which has no doubt played an important role in producing a healthier workforce has been the widespread use of medical criteria for hiring in this industry.
>
> • • • This together with retirement and sometimes compensation of older and disabled cotton textile workers has produced a highly selected and relatively healthy workforce in these companies.

Although the Imbus and ELB surveys were not formal epidemiological studies and did not employ all techniques traditionally used in such studies (control populations, for instance), they provided the Agency with the most current medical surveillance data on a very large number of workers. They provide a very encouraging picture of the health of textile workers today and the success of the cotton dust standard in improving the health of textile workers.

Significant Risk Analysis

The cotton dust standard was based on data demonstrating significant excess risk of byssinosis and other respiratory symptoms in workers exposed to cotton dust in the early 1970's and earlier. Those data also showed that reductions in exposure substantially reduced the risk. Both the Court of Appeals and Supreme Court upheld OSHA's analysis of the studies and OSHA's conclusion that the standard was needed to substantially reduce a significant risk of disease. Indeed the Supreme Court said of OSHA's analysis, "It is difficult to imagine what else the agency could do to comply with the Court's decision in *Industrial Union Department* v. *American Petroleum Institute*." (The "benzene decision" where the Supreme Court set forth the significant risk requirement.) *ATMI* v. *Donovan*, 452 U.S. 490 (1981). As just discussed the two recent sets of studies essentially confirm the need for and success of the cotton dust standard. The Yale study indicates that high exposures over a period of time lead to chronic lung disease that may be irreversible. The Imbus and ELB surveys indicate that the

reductions in exposure, the institution of medical surveillance programs, and other protective measures required by the standard have substantially improved the health of the workforce.

OSHA requested three leading experts in byssinosis and occupationally-related pulmonary disease to give their own views on the standard and subsequent developments. In their statements cited above they agree that the Merchant data were valid and that they accurately represented the conditions of textile workers subject to uncontrolled exposures preceding the early 1970's. They also agree that the standard's requirements for reducing exposures with dust controls and for medical surveillance have substantially improved the health of the work force today as indicated by the new surveys. There is some disagreement about the relative importance of medical surveillance and dust control, but all agree both are needed.

There was no serious challenge during this proceeding to OSHA's original conclusion and these opinions. There was some disagreement on the applicability of the results of the Yale study to today's workforce, and the National Cotton Council submitted a brief two paragraph criticism of the applicability of the standard to weaving operations but provided no detailed analysis (Ex. 276, p. 20). The American Textile Manufacturers Institute concluded in its post hearing brief:

> In sum, the respiratory health of cotton textile workers today has improved markedly over what was reported in past decades; based on the Imbus and ELB surveys, it compares favorably to the respiratory health of workers who are not exposed to cotton dust. However, there continues to be controversy and uncertainty over the extent to which these favorable respiratory health findings are attributable to the reductions in dust levels mandated by the present standard, as opposed to the implementation of medical surveillance programs and the use of respirators and employee transfers in appropriate cases.
>
> Whatever the reason, the fact is that, in combination, these elements of the Standard appear to be having the desired effect. Moreover, most of the capital expenditures needed to achieve the PELs specified in the present Standard have already been committed, and with the exception of the processing of coarse count ring spun yarns, the vast majority of cotton textile operations have largely been brought into compliance with these PELs. For these reasons, the PELs of 200 $\mu g/m^3$ in yarn manufacturing and 750 $\mu g/m^3$ in slashing and weaving should remain unchanged in the revised standard. (Ex. 280, p. 11)

OSHA's original analysis of the need for the cotton dust standard to substantially reduce significant risk of disease was upheld by the Supreme Court. It is confirmed by subsequent studies discussed above, and the opinion of leading experts and relevant unions and trade associations just quoted. The standard has substantially improved the health of cotton textile workers as intended. Therefore there is no need nor purpose in engaging in additional significant risk analysis for employees in the textile industry.

OSHA concludes that the evidence clearly documents the need for a cotton dust standard in this industry. Furthermore, the new evidence demonstrates the effectiveness of the standard in dramatically reducing the prevalence of byssinosis, bronchitis and loss of lung function in cotton textile workers and the standard has indeed substantially reduced significant risk. OSHA commends the textile industry's actions to reduce cotton dust exposure, to institute medical surveillance and to comply with the other requirements of the cotton dust standard.

III. Occupational Health Implications and Significant Risk Analysis From Exposure to Cotton Dust Exposure in the Nontextile Industries and Scope of Coverage

A. Introduction

OSHA issued a standard in 1978 covering most users of cotton. When the final standard was published in 1978, the permissible exposure limits for lint-free respirable cotton dust divided the covered industries into three segments: yarn manufacturing (200 $\mu g/m^3$ 8-hr TWA); slashing and weaving (750 $\mu g/m^3$ 8-hr TWA); and all others including knitting (500 $\mu g/m^3$ 8-hr TWA). The industries covered by the 500 $\mu g/m^3$ PEL came to be called the nontextile industries. This led to the rather confusing designation of the knitting industry as a nontextile industry, nomenclature which is retained in this document.

The scope of coverage of the 1978 standard in the nontextile industries was determined by the evidence in the record and by policy views. The Agency concluded that evidence of adverse health effects in the nontextile industries could be reinforced by the strong evidence in the textile industry and stated:

> Although these studies of nontextile industries do not provide precise dose-response data, this data clearly establishes that exposure to cotton dust in these industries, regardless of the stage of processing in which the dust is generated, results in byssinosis and other respiratory diseases qualitatively indistinguishable from those arising in the textile industry. (43 FR 27382)

As the regulatory history states, this rationale was accepted by the Court of Appeals for cottonseed processing and classing and warehousing. The decision stated:

> The exact nature of the health hazard posed by cotton dust remains subject to medical debate. The agency had before it conclusive evidence that dust found in textile mills causes debilitating disease; it also had some evidence of related, though less severe, health impairments among workers in nontextile industries. Although petitioners point to differences among the industries, OSHA's mandate requires it to protect workers in all industries. We find that OSHA fulfilled this mandate by reasonably relying on medical evidence from the textile industry and evidence of health impairments among nontextile workers. The differences in the industries that were cited by petitioners do not undermine the agency's determination. (617 F. 2nd 636 (1979) p. 666–7)

The knitting industry did not legally challenge OSHA's findings concerning this industry, and although the waste processing industry did challenge the standard, no judicial decision has been made in this case.

Following publication of the final standard in 1978, new studies were completed by NIOSH and other investigators which examined the health of nontextile workers exposed to cotton dust. Based on the new studies, the unsettled legal status of most of the nontextile segments, and the different composition of the dust in different processes, OSHA concluded that data for each segment should be reviewed. OSHA also concluded for these reasons that this review should give the greatest weight to the studies from each particular segment in determining whether regulation was needed for each segment.

OSHA issued an ANPR on February 9, 1982 requesting new information on the health of exposed workers in the nontextile industries (47 FR 5906). On June 10, 1983, OSHA proposed to amend the 1978 cotton dust standard. The Agency proposed to exclude classing, warehousing, knitting, and cottonseed processing from both 29 CFR 1910.1000 and 29 CFR 1910.1043. OSHA proposed to exclude waste processing from 29 CFR 1910.1043 but did not propose to exclude this industry from 29 CFR 1910.1000. Commenters were invited to present evidence and testimony on this subject.

B. Knitting

The 1978 standard set a permissible exposure limit of 500 $\mu g/m^3$ lint-free respirable cotton as an 8-hour TWA for cotton knitting operations which include the knitwear and hosiery industries. No

direct evidence of adverse health effects was cited for knitting, and these operations were covered by the 1978 final standard based on evidence from other sectors.

The first detailed analysis of the status of the respiratory health of knitting workers exposed to cotton dust was submitted to OSHA in January of 1982. This interim report was entitled "Analysis of Pulmonary Function Data of Knitting Industry Workers" and is often referred to as the Boehlecke/Battigelli report. Drs. Brian Boehlecke and Mario Battigelli of the University of North Carolina prepared the report which was submitted to OSHA by the National Knitwear Manufacturers Association (NKMA) in support of its petition for a stay of enforcement of the standard (Ex. 174). A final report was submitted in July of 1982 (Ex. 183).

This report has been discussed in detail elsewhere (47 FR 35255; 48 FR 5268; 48 FR 26967). Briefly, the report found that the respiratory health of the knitwear and hosiery workers studied, specifically the prevalences of chronic cough, chronic phlegm, mild dyspnea, and byssinotic symptoms, were similar to a group of blue-collar workers not exposed to respiratory hazards. The authors did report that 14.6% of the participants showed an overshift decline in FEV_1 of 5% or greater. They state that a similar percentage of workers in wool and synthetic operations showed such a decline. A deleterious effect of smoking was seen. Average dust levels were well below the 500 $\mu g/m^3$ PEL, ranging from 30–443 $\mu g/m^3$ for knitwear plants and 38–269 $\mu g/m^3$ for hosiery plants. The authors compared the plants represented in their report with the industry as a whole and concluded that the study group was representative of the industry.

Based on the information in the report, OSHA published a notice of proposed stay of enforcement of the cotton dust standard for the knitwear and hosiery industries (47 FR 35255) and requested comments. Twenty individuals or groups responded to the notice with written comments. Eighteen of these comments were in support of the stay but did not provide any detailed comments on the Boehlecke/Battigelli report.

Both NIOSH (Ex. 182–20) and Mr. Andy Oberta, president of Environmental Resources Group, Inc. (ERG, Inc.), (Ex. 182–1) provided specific comments on the report. Mr. Oberta stated that ERG, Inc. provides medical exams and exposure monitoring to the knitting industry. He further states that the results of the medical examinations cited in the report were "consistent with those which we have obtained from our own testing of approximately 400 workers in knitting and hosiery mills." (Ex. 182–1) He called attention to the 14.6% of workers with an overshift decline in FEV_1 and was critical of the lack of dose-response information. NIOSH reviewed the report at the request of OSHA and provided detailed comments (Ex. 182–20). It pointed out, among other things, the limited control that the authors had over the selection of the study population and suggested that there may be some evidence of a dose-response relationship that should be followed up. Both NIOSH and Oberta cautioned against the generalization of the results of this study to the entire industry. Mr. Oberta suggested that OSHA consider data from other sources before making a final decision.

Although some commenters pointed to shortcomings in the report, none of the comments disputed the basic findings of the study, namely that there was no excess of chronic respiratory disease in knitting workers at the exposure levels studied. Based on the analysis of the report and a review of the comments, OSHA reached a conclusion that the Boehlecke-Battigelli report provided sufficient information to extend the stay until the review of the standard was completed and published a notice to that effect in the **Federal Register** on February 3, 1983 (48 FR 5267)

As part of the proposed amendments to the standard, OSHA proposed that the entire knitting industry, including knitwear and hosiery manufacturers, be excluded from coverage from both the 1978 standard and the earlier cotton dust standard and requested comments on this proposal (48 FR 26980). Following the publication of that proposal, a number of commenters including the National Knitwear Manufacturers Association and the National Association of Hosiery Manufacturers wrote in support of exempting the knitwear and hosiery industries from coverage under any standard for cotton dust (Exs. 187–4, 187–7, 187–10, 187–11, 187–18, and 187–21). They based their recommendations on the results of the Boehlecke/Battigelli report and on their contention that OSHA had not made a threshold finding of significant risk for workers exposed to cotton dust in this industry. Other commenters, including NIOSH and the American Public Health Association (APHA), cautioned OSHA against exempting the knitting industry because they contended that those workers who were at risk from exposure to cotton dust would be unprotected (Exs. 187–14, 187–8, 187–23, APHA unnumbered comment).

OSHA requested that Dr. Brian Boehlecke testify as an expert witness on the status of the health of knitting workers at the public hearings held in Washington, D.C. in September 1983. In his testimony, Dr. Boehlecke discussed the report that he coauthored with Dr. Battigelli. He also described the sponsorship, sources of medical surveillance data, the blue collar comparison group and the authors' requests for additional data on work histories. He then restated the conclusions of the report:

> In these data, chronic loss of lung function and increased prevalence of respiratory symptoms were clearly associated with cigarette smoking. After controlling for the effect of smoking, we were unable to demonstrate a significant chronic effect of knitting room dust exposure on pulmonary function.
>
> The small acute decrement in lung function over the workshift in these workers was no greater than that reported in workers exposed to dust from synthetic fibers or wool, and may represent a nonspecific effect of knitting room dust.
>
> The prevalence of nonspecific respiratory symptoms in the knitting workers was not increased over that reported in nonexposed blue collar workers and the prevalence of byssinotic symptoms was similar to that of workers exposed to dust from synthetic fibers or wool.
>
> The consistency of results among several types of analysis supports the conclusion that knitting room work was not associated with important adverse effects on the respiratory system in the workers in this study. Although we have presented some information suggesting that the study group was a reasonably representative sample of workers in the knitting trades, additional information would be useful before forming a final judgment on this question. (Tr. 54–55)

Although Dr. Boehlecke stated that the results support exempting the knitting industry from a PEL and exposure monitoring, he expressed reservations about ending medical surveillance requirements based solely on the results of this report and suggested that additional medical surveillance data be collected. He went on to add:

> • • • I believe that consideration should also be given to requiring medical monitoring of workers each two years for a limited period of time to gather information to confirm the conclusions of our report and to ensure adequate protection of the health of current workers should some exceptions to these conclusions be found.
>
> I cannot say with certainty what period of time might be necessary to provide adequate corroboration of our conclusions, but suggest that at least four years of information, that is two follow-up examinations, would be needed to obtain sufficient data. (Tr. 55–56)

In response to a question, Dr. Boehlecke said:

* * * I think that surveillance should be considered every two years in this particular industry, as I said for a limited period of time. If after that period of time no evidence is forthcoming that suggests an important risk to health, then surveillance would not necessarily be mandatory in my opinion. (Tr. 59)

Mr. Robert Blanchard, president of the National Knitwear Manufacturers Association (NKMA), testified that it was the opinion of his organization that there had been no evidence presented which disputed the findings of the Boehlecke/Battigelli report and that the NKMA supported a total exemption of the knitting industry from the cotton dust standard. In response to questioning, he stated that he was unaware of any operations in the knitting industry with exposures exceeding 500 $\mu g/m^3$. In answer to a question as to whether the industry would commit itself to do the additional medical surveillance recommended by Dr. Boehlecke, Mr. Blanchard stated:

I think I understand Dr. Boehlecke as a medical doctor and as a human being; I think that I would like to have everybody checked every month or two to make sure that everybody was in excellent health. However, I feel there's really no justification for his action in this particular case. As I've said before, I think most industry people understand good health is good for their business and obviously it's good for their employees. I see no justification for it, no. (Tr. 756)

He did agree, however, to discuss this matter of continued medical surveilliance with his members and submit their response in a posthearing comment.

Following the hearing, Mr. Blanchard responded by letter to the question. He replied in part:

After investigation, I was able to determine, as I testified, that almost all of the companies represented in the "Analysis of Pulmonary Function Data of Knitting Industry Workers" are continuing to do some type of testing to meet their individual needs; however, such testing is not necessarily the same as done for Dr. Boehlecke's study.

* * * If OSHA wishes to consider monitoring in two and/or four years, we suggest it fund an epidemiological study by NIOSH. Our members, the past knitwear participants, would not hesitate to consider opening their plants for such work. (Ex. 228)

Mr. Sid Smith, president of the National Association of Hosiery Manufacturers (NAHM), concurred with the testimony of Mr. Blanchard when he stated:

* * * The record now contains substantive and technically acceptable data that shows that there is no prevalence of byssinosis symptoms or other respiratory difficulties evidenced in the knitting and hosiery industries based on the number of years worked in knitting, even though the use of cotton yarns is in evidence.

* * * Based on the aforementioned information and data submitted, we concur with the conclusion reached by both OSHA and NIOSH that the workers in the knitting and hosiery industries appear to have no significant risk of impaired health and that, therefore, the industry should be excluded from coverage from CFR 1910.1043 and CFR 1910.1000. (Tr. 762)

In response to a question concerning dust levels, Mr. Smith said: "My recollection is that the majority of those are in the very low end of that range, in the 100 to 200 [$\mu g/m^3$], maybe 250 [$\mu g/m^3$] range." (Tr. 767) He also agreed to contact his membership to determine whether they would be willing to conduct the additional medical surveillance examinations recommended by Dr. Boehlecke.

In one of their posthearing comments (Ex. 231), the NAHM expressed the opinion that it had provided OSHA with full justification for excluding the hosiery and knitting industries from all provisions of the standard including the medical surveillance provisions. They concluded by saying:

If, following total exemption from the cotton dust standard for the knitting and hosiery industries, OSHA would like to make a specific proposal on various issues, we would certainly be open to discussing the matter. (Ex. 231)

OSHA wrote to Mr. Andy Oberta of ERG, Inc. and requested that he provide "any data or other relevant information concerning the health of either knitting or hosiery workers or both" that he had not previously supplied to the record (Ex. 246). For reasons of client confidentiality, Mr. Oberta was unable to provide specific results of medical examinations but he did supply comments on the Boehlecke/Battigelli report based on his company's experience in the knitting industry (Ex. L–1). He stated that dust levels obtained in surveys conducted by ERG, Inc. were "considerably higher than those reported in the B/B [Boehlecke/Battigelli] report." He also reported that when hosiery and knitwear workers were analyzed separately that more hosiery workers than knitwear workers showed evidence of decreased lung function (Ex. 182–1).

Drs. Boehlecke and Battigelli responded to Mr. Oberta's criticism in their posthearing comment (Ex. 274). They stated that their study group was "reasonably representative of the industry as a whole" and that the relatively small difference in the dust levels between their report and the ERG data (less than 75 $\mu g/m^3$ for knitwear and less than 60 $\mu g/m^3$ for hosiery) did not suggest that the plants studied were unrepresentative of the industry as a whole. They agreed that OSHA should be cautious in generalizing their findings, but they did not feel that Mr. Oberta's comments provided "any further insight into the validity of our findings." (Ex. 274)

OSHA requested that NIOSH review and comment on the information submitted by ERG Consultants, Inc. In its posthearing brief, NIOSH repeated its earlier caution about possible selection bias in the study since the study was performed using information submitted voluntarily by employers. These facilities might be expected to have lower dust levels than the industry as a whole. However, NIOSH cautioned OSHA about making comparisons between dust levels in the Boehlecke/Battigelli report and those submitted by ERG Consultants, Inc. They were unable to determine exactly how the mean dust levels were calculated by Mr. Oberta, and whether they were directly comparable with those in the Boehlecke/Battigelli report. NIOSH also pointed out that there are problems comparing the pulmonary function data from the two reports since Mr. Oberta did not take into consideration the smoking status of the two populations and there are no objective indications of the technical quality of the ERG, Inc. data. They did say that further analysis of the data submitted by ERG, Inc. could prove useful (Ex. 285).

The post hearing statement of the ACTWU provided the most detailed critical analysis of the Boehlecke/Battigelli report that was submitted to the record (Ex. 279). They state that a single negative study cannot form the basis for valid conclusions on the health risk to a human population and that the report does not satisfy established criteria for evaluating a negative study. Specifically they questioned the representativeness of the sample, the exposure data and the reliability of work histories. They also contend that one of the tables in the report (Table 22) provided evidence of a dose-response relationship.

Conclusion and Significant Risk Analysis

The state of the health record for the knitting industry has been reviewed above. Within the context of this health record for the knitting industry, OSHA has three decisions to make. Should the exposure limit and related provisions of the section 6(b) cotton dust standard be revoked for the knitting industry? Should the medical provisions of that

standard be revoked for the knitting industry? Should the exposure limit requirements of the 6(a) standard of § 1910.1000 be revoked for the knitting industry? These issues are addressed serially.

It was definitively established by the Supreme Court in *Industrial Union Department, AFL–CIO* v. *American Petroleum Institute* 448 U.S. 607 (1980). (*IUD* v. *API*), that when OSHA issues a new health standard under section 6(b) of the Act which sets a lower exposure limit, the Agency must demonstrate that a significant risk exists which will be substantially reduced by lowering the exposure limit. OSHA has explained its overall approach to significant risk determinations in the context of two final standards and several proposed standards. In the case of carcinogens, these explanations were included in the final standards for inorganic arsenic (48 FR 1864–1899; Jan. 14, 1983) and ethylene oxide (49 FR 25734, 29763–66; June 22, 1984).

OSHA's overall analytical approach for setting worker health standards is a four-step process consistent with recent court interpretations of the OSH Act and rational, objective policy formulation. In the first step, risk assessments are performed where possible and considered with other relevant factors to determine whether the substance to be regulated poses a significant risk to workers. Then, in the second step, OSHA considers which, if any, of the proposed standards being considered for the substance will substantially reduce the risk. In the third step, OSHA looks at the best available data to set the most protective exposure limit necessary to reduce significant risk that is both technologically and economically feasible. In the fourth and final step, OSHA considers the most cost-effective way to achieve the objective.

It is appropriate to consider a number of different factors in arriving at a determination of significant risk. The Supreme Court gave some general guidance as to the process to be followed. It indicated that the Secretary is to make the initial determination of the existence of a significant risk, but recognized that "while the Agency must support its finding that a certain level of risk exists with substantial evidence we recognize that its determination that a particular level of risk is 'significant' will be based largely on policy considerations." (IUD v. API, 448 U.S. 655, 656, n. 62). In order for such a policy judgment to have a rational foundation, it is appropriate to consider such factors as the quality of the underlying data, the reasonableness of the risk assessment, the statistical significance of the findings, the type of risk presented and the comparative significance of the risk relative to the risk in other occupations.

The first issue to be faced in the context of the above facts, law and OSHA policies is whether there is a significant health risk at the current 6(a) exposure limit in knitting justifying a lower exposure limit and the other provisions of § 1910.1043 (excluding the medical and monitoring provisions). OSHA concludes that there is insufficient evidence to meet this test. There is no study in this industry segment demonstrating risk. The one study available indicates no excess risk of byssinosis and similar pulmonary function compared to suitable blue collar controls. The study is substantial in size and of overall high quality. The fact that this study has, like all studies, some areas which could be strengthened and the general scientific principle that a single study does not prove a negative are not bases for determination of significant risk.

Proven risk in one segment may, in appropriate circumstances, provide a basis for determining risk in another segment because of chemical similarity, confirmatory evidence, or other good reasons. However, these factors are much less relevant in the case of the knitting segment because the composition of the cotton dust varies from segment to segment, the exact etiologic agent is unknown and there is no confirming data of risk in the knitting segment. Therefore, the strong evidence of significant risk in yarn production and slashing and weaving is not a sufficient basis for concluding there is significant risk in the knitting industry. The lack of the factors mentioned for extrapolating risk is the basis for OSHA changing its earlier policy for cotton dust of applying risk data in one industry to another.

As can be seen, there is not sufficient evidence indicating risk to justify a lower exposure limit. Therefore there is no need to inquire into the further stages of analysis which OSHA would go through to make a significant risk determination.

The second issue is whether the medical surveillance requirement in § 1910.1043 should be revoked for the knitting industry. OSHA has determined not to include a medical surveillance requirement for the knitting industry for the reasons discussed but NIOSH will perform a follow up longitudinal study. The general principles for retaining medical surveillance are discussed below in the discussion for the cotton seed processing industry.

First, as discussed above, the one study available on knitting, indicated that employees had no greater incidence of nonspecific pulmonary symptoms, lung function declines or byssinosis that control groups. The study was of reasonable quality and large scale.

Second, the knitting employees studied had low exposures, on average, well under both the old (making reasonable hypothesis between total and respirable dust) and the new exposure limits. However, there is evidence in the record that knitting operations are not dusty and that exposures would not rise if there were no limits. Therefore, OSHA has some evidence to support its belief that exposures will rise above current levels.

Third, Dr. Boehlecke, who was one of the authors of the report on knitting employees discussed above, recommended continuing medical examinations every two years "to confirm the conclusions of our report and to insure adequate protection of the health of current workers should some exceptions to the conclusions be found." ACTWU argued that a single negative study can not be the basis for valid conclusions on health risk and that the Boehlecke/Battigelli study did not meet appropriate criteria for evaluating a negative study. As discussed, representatives of the knitting and hosiery industries believed that total exemption from regulation including medical surveillance was called for in light of the Boehlecke/Battigelli report.

Dr. Boehlecke's recommendation that a confirmatory study would be useful and ACTWU's argument that a confirmatory study is appropriate can be met by a prospective study. Unlike NIOSH's earlier cross sectional studies, this study is a longitudinal study. Such a study, unlike routine medical surveillance, can be specifically designed with criteria appropriate for testing a negative hypothesis and can follow employees longitudinally, including employees who quit. In addition, such a study can act as a "backstop" to determine whether the health of employees has been maintained after the elimination of an exposure limit. Of course, if such a study indicated that employees have not remained healthy, OSHA will consider whether further regulation is appropriate.

Accordingly, beginning in Fiscal Year 1987, funding will be provided to initiate a NIOSH study to determine the potential for risk of workers exposed to cotton dust in certain nontextile

industries (knitting, classing, and warehousing). It is expected that the study will survey and track a representative sample over an 8 year period.

The third issue presented is whether OSHA should exempt the knitting industries from the 1971 cotton dust standard of 1000 $\mu g/m^3$ (1 mg/m^3) total dust contained in § 1910.1000, Table Z–1. That standard was issued pursuant to section 6(a) of the OSH Act which states:

Without regard to chapter 5 of title 5, United States Code, or to the other subsections of the section, the Secretary shall, as soon as practicable during the period beginning with the effective date of the Act and ending two years after such date, by rule promulgate as an occupational safety or health standard any national consensus standard, and any established Federal standard, unless he determines that the promulgation of such a standard would not result in improved safety or health for specifically designated employees. In the event of conflict among any such standards, the Secretary shall promulgate the standard which assures the greatest protection of the safety or health of the affected employees.

The 1000 $\mu g/m^3$ standard was an established Federal standard under the Walsh Healy Act applying to government contractors and was adopted in 1971 pursuant to section 6(a). Prior to its adoption the American Conference of Governmental Industrial Hygienists (ACGIH) had adopted that level as a recommended threshold limit value for cotton dust.

In the June 10, 1983 **Federal Register** notice, OSHA proposed to exempt the knitting industry from coverage under the 6(a) standard. OSHA stated:

As discussed above, the 1978 cotton dust standard has never gone into effect for any of the nontextile industries. It has been OSHA's position, however, and the case law indicates, that the 1971 standard (29 CFR § 1910.1000 Table Z–1) which was adopted pursuant to section 6(a) of the Act, covers the nontextile segments. The 1971 standard would therefore, remain in effect for the nontextile segments unless OSHA revokes the standard for nontextile industries.

Based upon the present record, OSHA proposed to exclude the classing, warehousing, cottonseed processing and knitting industries from coverage by § 1910.1000 Table Z–1. OSHA believes that since there is evidence of safe working conditions in the classing, warehousing and knitting industries, it will better effectuate the purposes of the Act to exclude those industries from coverage. Resources spent protecting employees under the existing standard would be better spent on health and safety in other areas. (48 FR 26968)

Several legal tests have been suggested as the basis for revoking 6(a) standards. Section 6(b)(8) of the Act states:

Whenever a rule promulgated by the Secretary differs substantially from an existing national consensus standard, the Secretary shall, at the same time, publish in the Federal Register a statement of the reasons why the rule as adopted will better effectuate the purposes of this Act than the national consensus standard.

Any action to eliminate coverage for the knitting industry requires promulgation of a rule and this section gives guidance as to the legal test to be met to revoke a standard. However, the cotton dust standard was technically an established federal standard and not a national consensus standard.

In comments, several representatives of the nontextile industries have stated what they believe to be the proper test for revoking 6(a) standards. These were most specifically stated in comments submitted on behalf of the National Cotton Batting Institute and the Textile By Products Association. They stated:

OSHA proposes to maintain the "status quo" by keeping the one milligram standard in place for the garnetting industry. There are two reasons, however, why it cannot do so. First, like other section 6(a) regulations, the one milligram total dust standard was never intended to be a permanent standard, but was always intended to be an interim standard, to be supplanted by a regulation promulgated pursuant to section 6(b). Second, and more fundamentally, since 1978, when OSHA first proposed a permanent standard for occupational exposure to cotton dust, this proceeding has been conducted under section 6(b) of the Act, 29 U.S.C. 655(b). Whenever OSHA undertakes a rulemaking pursuant to section 6(b), it is obligated to adhere to the standards set forth in the benzene case. Thus, in determining whether or not to regulate this industry, OSHA had two choices: (1) Either determine that there is a significant risk at current dust levels and promulgate a standard or (2) determine that there is no significant risk and not promulgate a standard. The Act does not allow OSHA to fall back on an interim standard whenever it determines that it cannot meet the "significant risk" requirement. (Ex. 284, p. 2). (See also the National Association of Bedding Manufacturers comments, Ex. 187–22.)

The AFL–CIO also submitted a posthearing comment on this issue. It stated:

As discussed, the "threshold finding" of a significant risk of harm that must be made before a permanent standard is adopted to reduce exposure levels simply has no purpose to serve under the statutory scheme where all that is at issue is the retention of an existing established Federal standard. For Congress saw no need to subject consensus standards and established Federal standards to the kind of analysis that is embodied in the significant risk test, recognizing as Congress did that these standards represented only a "minimum level of health and safety," and that established Federal standards had "already been subjected to the procedural scrutiny mandated by the law under which they were issued" and "in large part, represented the incorporation of voluntary industrial standards."

To be sure, because consensus standards and established Federal standards generally "represent merely the lowest common denominator of acceptance by interested private groups." Congress recognized that OSHA would ultimately have to improve upon such standards through rulemaking under section 6(b) of the Act: "it is essential that section 6(a) standards be constantly improved and replaced as new knowledge and techniques are developed." But it would be contrary to every documented indication of congressional intent to hold that by allowing section 6(a) standards to be improved through section 6(b) proceedings, Congress meant to provide that as a condition of being retained as standards they would be subject to a "significant risk" requirement. Rather, the test should remain as stated in section 6(a): unless it is shown that an established Federal standard "would not result in improved safety or health for specifically designated employees, the need for the standard is not a matter of dispute." (Ex. 278 pp. 7–8. Quotes are to the legislative history or the Act and footnote citations are omitted)

The AFL–CIO added:

Indeed, even putting aside the language of section 6(a), under general principles of administrative law it is the proponent of a rule or order who has the burden of proof in administrative proceedings. *IUD* v. *API, supra.*, 448 U.S. at 653 (plurality opinion). Section 6(b) of the Act indicates that the same procedural principles apply to an agency proposal to "modify" or "revoke" a standard as would apply to a proposal to "promulgate" a standard; and any possible suggestion that OSHA does not bear the burden of proof when it proposes to weaken an existing standard has been put to rest by the Supreme Court's recent decision in *Motor Vehicle Mfrs. Assn.* v. *State Farm Mut. Auto. Ins. Co.*, 103 S. Ct. 2856, 2856–66 (1983). (Ex. 278, pp. 9–10, Footnote omitted)

OSHA believes that when it proposes to eliminate a class from either a 65(a) or 6(b) standard on health grounds, the evidence must affirmatively indicate that significant risk is unlikely to exist for that class at exposures likely to exis after the standard has been eliminated.

The reasons are that this would lead to consistency in eliminating both 6(a) and 6(b) standards and permit OSHA to apply the significant risk test of *IUD* v. *API* to both. An action to eliminate either a 6(a) or 6(b) standard is also a 6(b) rulemaking with the same procedures and same standard for review. OSHA must be able to support with substantial evidence any change it is propounding. The requirements of section 6(b)(8) are applicable whether

OSHA strengthens or weakens a regulation.

However, lack of evidence of risk is not a basis by itself for eliminating a 6(a) standard. The absence of evidence of risk could merely mean that the 6(a) standard (which has been in effect for 13 years) is working and the work force is healthy as a result of compliance with the 6(a) standard. Consequently there is no worker population to study at higher levels. It does not necessarily mean that with uncontrolled exposures there would not be significant risk. Of course, there might be no significant risk at the current exposure, but significant risk may be present at higher exposures which could not be demonstrated because the 6(a) standard is in force.

OSHA believes the AFL–CIO formulation in one respect is incorrect. OSHA believes that Congress did not intend for the Agency to apply different criteria to eliminate a 6(a) standard than to eliminate a 6(b) standard. Also if a different standard applied, this would mean that the guidance of the Supreme Court in *IUD* v. *API* would apply to eliminating some health standards and not others.

The nontextile sector has argued that OSHA must either determine that there is a significant risk at current exposures and promulgate a standard or determine that there is no significant risk and not promulgate a standard. They further argue that OSHA cannot retain a 6(a) standard unless it can affirmatively show there is significant risk at the 6(a) level. This later argument is incorrect. This would mean that when a 6(a) standard has eliminated significant risk which would exist at higher levels, OSHA would have to eliminate that 6(a) standard. Then OSHA would have to wait until employees developed the risk that the 6(a) standard protected against before OSHA could issue a new standard.

It is necessary to apply the test to the facts. As discussed above, there is no evidence of risk in this segment. There is a good quality report which indicates no risk at the rather low levels studied, and little basis for extrapolating the studies in the textile industry to this sector. There is some, though not overwhelming, evidence that exposures will stay low if the segment is exempted from the 6(a) limit. OSHA believes that these factors provide substantial evidence to indicate that no significant risk will exist at the exposure levels likely to prevail if the 6(a) standard is repealed for this segment.

In addition, as OSHA stated in its proposal, it would better effectuate the purposes of the OSH Act if these segments were removed from coverage of 6(a) because resources spent on carrying out the 6(a) standard would be better spent on health and safety in other areas.

The facts present in the knitting industry, also meet the test for repeal propounded by the AFL–CIO. Retaining the 6(a) standard for knitting employees "would not result in improved safety or health" for knitting employees because exposures are likely to remain low and evidence indicates no risk at the lower levels studied.

C. Cottonseed Processing

The 1978 standard set a PEL of 500 $\mu g/m^3$ for cottonseed processing. This was based on health studies in the textile industry and on studies of the health of cottonseed processing workers in the United States, Egypt, and Australia. The record for the 1978 standard contained several studies on the health of workers in this industry (Exs. 6–68, 6–70, 128k, and 128m) and they are discussed in the June 10, 1983 proposal (48 FR 26966–7).

In response to an ANPR published on February 9, 1982 (47 FR 5906), additional information on the health of these workers was submitted to OSHA by NIOSH (Ex. 175–56) and by Dr. Robert Jones, representing a group of investigators at Tulane University (Ex. 175–12). The Procter & Gamble Company, whose workers participated in the Tulane study, also submitted comments and information, some of which was identical to that in Ex. 175–12 (Ex. 175–48). The Tulane and NIOSH studies have been discussed elsewhere (48 FR 26966–7). Briefly, the four cross-sectional studies conducted by the Tulane group showed that effects on lung function, most commonly a decline over the work shift in the forced expiratory volume, were related to length of employment in a cottonseed mill, to jobs in early processing steps, to general allergy, to allergy to cottonseed linters and to smoking, but not to dust levels. The prevalences of byssinosis and chronic bronchitis were lower than those usually observed in textile workers, but the dust levels were higher than those found in textile mills. No long term effects were demonstrated, but the follow-up period which averaged 23 months was very short (Ex. 192–5).

The NIOSH study, entitled "Respiratory Disorders and Dust Exposure in Sectors of the Cotton Industry of the United States. Part 3: Cottonseed Oil Mills," compared cottonseed processing workers with a nonexposed blue collar comparison group. They demonstrated a significant effect on ventilatory changes and chronic cough in cottonseed oil mill workers who smoke, indicating an additive effect with tobacco smoke. The study did not show an increase in the prevalence of byssinosis of chronic bronchitis in these workers (Ex. 175–56).

The National Cottonseed Products Association did not submit any new health studies but rather argued that conditions in foreign mills were very different than conditions in the United States (Ex. 175–38). They offered a detailed critical analysis of both the foreign studies and some of the earlier Tulane studies and concluded that: "The only available evidence regarding cottonseed oil mills establishes that there is no significant risk of material health impairment among oil mill workers."

Based on the evidence and comments in the record, OSHA reached the preliminary conclusion in the June 10, 1983 proposal (48 FR 26968) that workers in the cottonseed processing industry appeared to have no significant risk of impaired health as a result of their exposure to cotton dust and proposed excluding this industry from coverage under 29 CFR § 1910.1043. In the discusson of 29 CFR 1910.1000, OSHA noted that the cottonseed industry was not in compliance with the PEL (1000 $\mu g/m^3$ total dust 8-hr TWA) and that compliance with the PELs specified by either § 1910.1000 or § 1910.1043 could cause severe economic disruptions in the industry. OSHA proposed to delete this industry from coverage under 29 CFR 1910.1000 but requested:

> . . . comments on alternative approaches to protecting worker health in the cottonseed processing industry which would be economically feasible. [48 FR 26968]

In commenting on the proposal, NIOSH disagreed "with OSHA's conclusion that workers in this industry appear to have no significant risk of impaired health as a result of their exposure to cotton dust." (Ex. 187–23) They reinterated the conclusion of their own study in this industry and described the findings of other investigators. They concluded:

> The findings of excess symptoms and adverse ventilatory effects in cottonseed oil mill workers suggest biological activity of these dusts. These effects warrant a standard applying to cottonseed oil mills, in particular, a requirement to provide medical surveillance to identify signs or symptoms of exposure. (Ex 187–23)

Both the National Cotton Council (Ex. 187–18) and Proctor & Gamble (Ex. 187–20) commented in support of OSHA's proposal. Proctor & Gamble restated positions taken in earlier comments that neither acute nor long term health

effects have been shown from exposure to cottonseed linter dust and that cottonseed linter dust is different from cotton dust.

OSHA requested that Dr. Robert Jones, a coauthor of the Tulane University studies on cottonseed processing workers, testify at the public hearings as an expert witness on the health of cottonseed processing workers. Dr. Jones described the four cross sectional studies conducted between 1975 and 1980 by the Tulane group. He also described and commented on the Australian and Egyptian studies and the NIOSH cross sectional study. Dr. Jones concluded from the results of these studies "that the dust in the cottonseed crushing mills has some biologic activity of a kind similar to that found in cotton textile mills," but that the potency of the dust in cottonseed crushing mills is considerably less than the dust in textile mills. (Tr. 205)

Dr. Jones recommended continued medical surveillance for these workers, although he did not recommend setting a PEL. He stated that he did not feel that scientific data demonstrated a dose-response relationship at the dust levels studied in the Tulane and NIOSH studies (0.5 to 2.0 mg/m³). He did, however, state several reasons why continued medical surveillance for these workers would be appropriate:

> The dust in cottonseed oil mills does have some effect, similar in kind to those seen in textile mills. There is evidence of an interaction of cottonseed linter dust with some factors of host susceptibility; namely, smoking in some studies, and general and specific allergy in our studies.
>
> A medical surveillance program offers two benefits. First, it could allow identification and protection of persons who, for any reason, were unusually susceptible to adverse effects of this dust.
>
> Simple prudence dictates that persons with active airways diseases, such as bronchial asthma, or with advanced and potentially disabling lung diseases of any cause, should not be assigned to particularly dusty jobs.
>
> It is also prudent to reassign away from such jobs if longitudinal surveillance shows the development of respiratory illness in a previously healthy worker. The numbers of employees so affected may be understated by large cross-sectional respiratory surveys.
>
> Second, the presence of industrywide health surveillance allows for continuing reassessment of the true levels of risk associated with work in these mills. While I believe that the scientific literature to date does not support the setting of a low permissible exposure limit, the existence of systematic, ongoing medical surveillance would result in an accumulation of health data that could allow reassessment of the need for exposure regulation on a timely basis. (Tr. 206–7)

In response to a question as to what would be an appropriate medical surveillance program for this high-turnover industry, Dr. Jones said:

> Clearly, the type of surveillance I have in mind involves pre-exposure testing, or preplacement testing. For one thing, I suggest that people who have demonstrable impairments of their lung function not be assigned to high risk areas whether in this or in any other industry.
>
> But, if there is a high turnover, it is . . . translatable ultimately into better worker health, to know why people leave an industry.
>
> Accordingly, I would suggest that in any industry with a lot of labor turnover, where people may possibly be leaving because of perceived symptoms from exposure early in their working career, that a terminal examination—at termination of employment—also be offered, or strongly recommended, in order that we may know why people leave the industry. . . . [I]t's of interest to me as a physician and a scientist to know if people are leaving because they're actually developing troubles. (Tr. 208)

The NIOSH cross-sectional study on the cottonseed processing industry was described by Mr. Richard Lemen testifying for NIOSH. He stated that, although the study did not provide a clear dose-response relationship, the results were consistent with findings of the Tulane group and that:

> Both the NIOSH and the Jones studies show that dust found in cottonseed oil mills is not a mere nuisance. This dust has distinct biological activity, as does textile mill dust, and measures should be taken to protect workers from its effects. (Tr. 401)

Mr. Lemen was accompanied by a panel of physicians and industrial hygienists who had helped to conduct the series of five studies on the nontextile industries. One member of this panel was Dr. Alan Engelberg, a physician and former NIOSH employee who helped to direct and interpret the studies. Dr. Engelberg disagreed with Dr. Jones' conclusion that the available data did not support a PEL for the cottonseed processing industry and stated that some dust control was important because the dust was not simply a nuisance dust (Tr. at 406). He did agree that medical monitoring should be required. Other panel members also reiterated NIOSH's recommendation for a PEL based on health effects and not necessarily on feasibility considerations.

The written statement of the National Cottonseed Products Association (NCPA) discussed the findings of the Tulane study and included a review written by Dr. Robert Jones of a draft report of the NIOSH study. They concluded that the record did not support a threshold finding of a significant risk in the cottonseed industry. (Ex. 213a) Dr. Phillip Wakelyn testified on behalf of the NCPA. He supported OSHA's proposal to exclude the cottonseed processing industry from coverage by the standard and pointed to problems, both economic and technological, that would accompany efforts at dust control in this industry. He stated that data in the record would not "support either the requisite threshold finding of significant risk, or a finding of adverse health effects in cottonseed oil mills." (Tr. 1082)

Mr. T.S. Schuler, president of the NCPA, testified that in his 40 years in the cottonseed industry he had not seen any adverse health effects in workers in his industry (Tr. 1076). In response to a question, Mr. Schuler testified that his company did not have a medical surveillance program and that a requirement for such a program "would present a real problem" to the industry (Tr. 1086). He stated that the rural location of most plants would require transporting workers for long distances to see a physician. This point was reiterated in the NCPA's post hearing brief. (Ex. 281)

OSHA was able to obtain some information relating to this matter of providing medical surveillance to small operations that do not have company physicians. Mr. John Lumsden of ELB Associates, an industrial health and safety consulting group that provides in plant medical surveillance examinations, testified at the Columbia hearings. Mr. Lumsden was asked what his company charged to provide the services required to meet the medical surveillance requirements required by the cotton dust standard to a small employer with 20 employees located about 100 miles from their office. He responded that such an employer was below the minimum so that they would charge "about $400 to do the trip, the testing and the computerized report—annual report." (Tr. 1352)

Dr. James Merchant testifying for the American Thoracic Society joined with the recommendation of NIOSH and the World Health Organization (WHO) for a PEL of one milligram per cubic meter (1000 μg/m³) and medical surveillance for the cottonseed industry (Tr. 333).

The National Cotton Council stated that the Tulane study indicated that cottonseed oil mill workers suffered no long term adverse respiratory health effects from their working environment and that the NIOSH study found no acute or chronic problems and no dose-response relationship. Therefore, they concluded that the evidence indicates that no standard is necessary. They

supported OSHA's June 10, 1983 proposal to exclude the cottonseed industry from the standard (Ex. 276).

Conclusions and Significant Risk Analysis

OSHA has carefully considered all the data and comments. The NIOSH and Tulane studies both show no dose-response relationship at the levels studied but they do show that these workers exhibit reactivity to cotton dust. All the medical authorities agree that the dust is reactive though much less so than that seen in textile mills. Based on the data, NIOSH recommended a PEL, exposure monitoring, and medical surveillance. The NCC and NCPA recommended no standard at all. OSHA believes that the data support a middle course. Altering the dust level, at least within the range studied by NIOSH and the Tulane group, does not appear to affect the risk. However, medical examinations will detect reactivity relatively early when it is reversible.

The legal principles and OSHA policies that were discussed under knitting apply equally to cottonseed processing. This section does not repeat that discussion but applies the facts of the cottonseed industry to that analysis.

The first question presented is whether the evidence indicates that a significant health risk exists at the current exposure level which could be reduced by lowering exposures. The evidence indicates that workers exposed at levels equal to ½ to 2 times the present exposure limit do not have an increased incidence of byssinosis or bronchitis compared to controls. It does indicate that there is an excess incidence of overshift declines in FEV_1s but that the decline in overshift FEV_1s is not proportional to dose. Therefore there is little data that reducing exposure would reduce that decline in lung function. (There can be reasons why a dose response relation exists but is masked which are discussed under waste processing, but there is not sufficient evidence to support that hypothesis here.) Dr. Jones has researched this area extensively, and he does not believe an exposure limit is appropriate. As discussed below OSHA does not believe in these circumstances it is appropriate to extrapolate data from the textile industry to this nontextile segment. For these reasons OSHA concludes there is not sufficient evidence of significant risk which could be substantially reduced by lowering exposure limits to justify applying the exposure limit and nonmedical provisions of § 1910.1043 to the cottonseed industry. Accordingly, OSHA is exempting this sector from those provisions.

In 1978, based on the few foreign studies and extrapolating from the textile industry studies OSHA found sufficient evidence to justify a standard in cottonseed processing. That reasoning was upheld by the D.C. Circuit in *AFL–CIO* v. *Marshall*, 617 F. 2d 636, 666 (1979) as applied to cotton seed processing. (The Court reversed and remanded the standard on economic feasibility grounds.)

It is appropriate in these circumstances to explain specifically why OSHA has changed its view. At the time of the 1978 decision, the record in cottonseed processing basically included just the foreign studies, one of which showed risk of byssinosis among cottonseed employees and only one domestic study. Subsequent to that time OSHA has received a series of studies from NIOSH and researchers at Tulane University. These indicate that excess byssinosis and bronchitis are not present among U.S. cottonseed workers.

Secondly, as explained in more detail in the knitting segment, the composition of cotton dust varies from segment to segment and the exact etiologic agent is unknown. Since the composition varies there is less basis for extrapolating risk from the textile industry to the nontextile industry and OSHA believes as a policy matter it should not do so in this instance.

OSHA believes these circumstances, the new studies and a justified change in policy, as well as its overall analysis of the facts, are sufficient basis to justify a change in regulatory requirements. Similar reasoning applies to other nontextile segments though the rationale will not be repeated. OSHA believes that the retention of medical surveillance will provide health protection for cottonseed workers.

The second question is whether medical examinations should be retained for cottonseed processing employees. OSHA has determined that the medical surveillance provisions should not be revoked and should remain in effect for cotton seed processing employees.

The Supreme Court addressed this issue in *IUD* v. *API* when it stated:

> It should also be noted that, in setting a permissible exposure level in reliance on less-than-perfect methods, OSHA would have the benefit of a backstop in the form of monitoring and medical testing.
>
> Thus, if OSHA properly determined that the permissible exposure limit should be set at 5 ppm, it could still require monitoring and medical testing for employees exposed to lower levels. By doing so, it could keep a constant check on the validity of the assumptions made in developing the permissible exposure limit, giving it a sound evidentiary basis for decreasing the limit if it was initially set too high. Moreover, in this way it could ensure that workers who were unusually susceptible to benzene could be removed from exposure before they had suffered any permanent damage.
>
> . . . This is precisely the type of information-gathering function that Congress had in mind when it enacted section (6)(b)(7), which empowers the Secretary to require medical examinations to be furnished to employees exposed to certain hazards and *potential* hazards in order to most effectively determine whether the health of such employees is adversely affected by such exposure. See Legis. Hist., p. 147. (Emphasis added) (448 U.S.C. 658).

The Court's analysis is directly relevant. OSHA is revoking most of the new standard for cotton seed processing and as discussed below is exempting the industry from the 6(a) exposure limit of § 1910.1000 as well. Hence no exposure limits will apply. These conclusions are based on "less-than-perfect" evidence. Therefore OSHA needs to retain "a back stop in the form of medical testing . . . so it could keep a constant check on the validity of the assumption made in developing the permissible exposure limit" or as in this case eliminating the limit. The Supreme Court's reasoning seems even more compelling when an exposure limit is eliminated.

It should be noted that OSHA is repealing the majority of a § 6(b) standard and a section 6(a) standard in its entirety. This reasoning is specifically designed to address this situation.

The Noweir study (Ex. 128 k, discussed in the proposal at 48 FR 26967) indicates that byssinosis develops at high exposures in at least one foreign cottonseed processing industry. In that study, conducted in Egypt, exposures were very high, and the NCC states that a different process was used than that used in the U.S. However, a backstop is clearly needed with the elimination of the permissible exposure limit to assure that byssinosis and chronic bronchitis do not develop afterwards. This is especially true because cotton seed processing is a dusty process and the possibility exists that exposures will rise above current levels.

In addition, there is a clear medical need for retaining medical surveillance. There is reduction in overshift FEV_1s among current employees. As Dr. Jones pointed out above, medical surveillance would allow identification of persons "unusually susceptible to adverse effects of this dust" and to identify "persons with active airway diseases

. . . (who) should not be assigned to particularly dusty jobs." (Tr. 206–7). These factors indicate that medical surveillance should be permanently retained.

The third issue presented is whether OSHA should exempt this industry from the 6(a) standard. That is a more difficult question than for knitting. Some data indicate that very high exposures may lead to byssinosis. In addition, the process is dusty, some exposures are already above the 6(a) limit and OSHA cannot have as much confidence that exposures will not rise if the 6(a) standard is eliminated. On the other hand, the studies indicate no bronchitis or byssinosis at current levels some of which are over the 6(a) limit.

In the context of this record, several other factors become revelant. The cottonseed processing industry is very much a declining industry. The number of facilities has been decreasing and many are small businesses. (The 1978 standard has not been in effect during this period. The decline results from market forces.) Employee turnover is 100% per year and the work is often seasonal. The exposed workforce is relatively small, about eight hundred. The data in the record indicate that compliance with 1 mg/m³ total dust 6(a) standard would be technically and economically difficult, though if interpreted as a respirable dust standard compliance becomes less difficult. (See the discussion under waste processing.)

In the total context, OSHA has determined that the evidence permits it to conclude that a significant health risk will not develop if the 6(a) limit is repealed for this segment. OSHA only makes this determination with the assurance that retention of medical surveillance will provide a backstop if that judgment is incorrect and this surveillance will protect the health of the employees. OSHA believes as indicated in the proposal that, at this point in time, it would better effectuate the purposes of the Act not to require the fairly large expenditures that compliance with the 6(a) standard would require in the face of evidence that byssinosis and bronchitis do not exist at current exposures and the retained medical surveillance provisions will address the issue of overshift FEV_1 declines.

These medical examinations include an initial exam and periodic exams every two years unless the employee falls under the criteria in (h)(3) (i) and (ii). In that case, examinations are required every six months and in some circumstances the employee is to be referred to a specialist for further evaluation.

D. Waste Processing Including Garnetting

The 1978 standard set a PEL of 500 $\mu g/m^3$ for the waste processing industry. This coverage was based on health studies in the textile industry and on studies of waste processing workers in the United States, Britain, and Australia. The record for the 1978 standard contained several studies on the health of workers in this industry (Exs. 99f; 38f; 6–72; 6–71), and they are discussed in the 1978 cotton dust standard (43 FR 27381). An additional health hazard evaluation (Ex. 188–X) was submitted to the Agency following publication of the final standard, and OSHA issued an administrative stay on September 1, 1978 in order to consider this information (43 FR 39087). Following its evaluation of the new information, OSHA concluded that the findings in the 1978 standard were correct and lifted the administrative stay on January 26, 1979 (44 FR 5438).

An early study (Ex. 6–72) of cotton waste mills in the United Kingdom by Dingwall-Fordyce and O'Sullivan found a 30% prevalence of byssinosis, including a 5% prevalence of disabling byssinosis. Bronchitis prevalence was not reported in this study. The authors did not include controls in their study and workers did have some exposure to raw cotton. Chinn and coworkers (Ex. 99f) studied willowing mills in the United Kingdom and found a 53.3% prevalence of bronchitis. A 5% prevalence of byssinosis was reported. In addition, willowers had greater pre-shift and postshift declines in lung function when compared to controls. Simpson measured pre-shift and postshift FEV_1 in six Australian garnetting operations (Ex. 6–71). No control data was reported. About 31% or the workers had postshift FEV_1 declines of 200 milliliters or more.

NIOSH investigators conducted a health hazard evaluation of a U.S. garnetting and mattress-making company in 1973 (Ex. 38f) and in 1977 (Ex. 188–X). No comparison group was included in the studies. In 1973, the bronchitis prevalence was 59% and the byssinosis prevalence was 11.8%. The percentage of workers with a postshift decline in FEV_1 of 5% or more was 20.6%. In 1977 when the cotton dust levels were much lower, the bronchitis prevalance was 34% and the byssinosis prevalence was 1.9%. There was a slight rise in the prevalence of postshift decline in FEV_1.

The ANPR published on February 9, 1982 (47 FR 5906) solicited any additional information on the health of workers exposed to cotton dust in any of the industries covered by the 1978 standard, and OSHA received a study on the waste utilization industry from NIOSH (Ex. 175–56).

The new study from NIOSH was entitled "Characterization of Byssinosis and other Pulmonary Abnormalities in the Cotton Waste Utilization Industry. Part 5" (Ex. 175–56). In 1978 and 1979, NIOSH examined 260 workers in 13 cotton waste utilization plants in the Southeastern United States. A group of 292 blue collar workers employed in non-dusty occupations served as the control group. NIOSH found no significant increase in the prevalence of byssinosis in the cotton waste workers when they were compared to the control group. They did find a significant increase in the prevalence of bronchitis in exposed workers employed in the waste industry for less than two years. This increase was most striking in nonsmoking workers who had been employed for less than two years. In addition, they found that decreases in pulmonary function in some exposed workers appeared to be related to the particular plant in which the individual was employed. No dose-response relationship was demonstrated by this study. The geometric mean dust concentration for many of the plants was around 0.5 mg/m³.

The National Cotton Council (Ex. 175–47) submitted two critical reviews of the NIOSH study as an attachment to its earlier comments. These reviews noted that no evidence of excess prevalence of byssinosis was seen in the workers. The NCC also said that an association between cotton dust exposure and chronic bronchitis in workers with less than two years of experience could not be made because "chronic bronchitis" is defined as chronic only when persisting for at least two years, so it must have pre-existed the work with cotton-related materials. They also criticized the control group used by NIOSH. These criticisms were repeated in their final posthearing brief (Ex. 276).

At the time that NIOSH analyzed the data for their report, data from only six of the more than 30 comparison plants were available to be used as controls. In order to conform to the "Southeast" location of the waste cotton workers (North and South Carolina, Georgia, Alabama and Florida) and to respond to some comments about the more westerly location of some of the comparison plants, NIOSH reanalyzed the data using only "Southeast" comparison plants. This addendum did not replace the original report but was a further analysis of the data (Ex. 175–56). Using this comparison group, NIOSH

found a significant increase in the prevalence of bronchitis in workers (both smokers and nonsmokers) who had worked in the waste cotton industry for more than two years and in nonsmokers with less than two years in the industry. In addition, workers with less than two years in the waste cotton industry had a significantly greater prevalence of bronchitis than workers with more than two years. There was a significant increase in the prevalence of overshift decrements of FEV_1 greater than 10% in workers with greater than two years service, and there was also a significant increase in the prevalence of overshift decrements of FEV_1 greater than 5% in waste cotton workers compared to controls matched in age and smoking. NIOSH found no significant increase in the prevalence of byssinosis or of workers with an FEV_1 of less then 80% of the predicted value.

OSHA concluded that although the data did not support reducing the permissible exposure limit that there was evidence of risk to workers, and there was no evidence of safety in this industry. Therefore, OSHA proposed to continue coverage of the waste processing industry under § 1910.1000 and to delete the industry from coverage under § 1910.1043.

OSHA invited Dr. Alan Engelberg, formerly of NIOSH and a medical project officer on the NIOSH cross-sectional studies, to testify at the public hearings as an expert witness on the waste processing industry. Dr. Engelberg described the results of the NIOSH study and responded at length to the criticisms of the National Cotton Council concerning the control group. He devoted more than half of his written testimony to responding point-by-point to the criticisms of the study made by the National Cotton Council and others. One criticism of the study made by NCC was that the control group came from a different socio-economic group and the basis for this contention was that the group of control workers received $3.80 to $7.40 per hour while the waste cotton workers received $3.35 per hour, the minimum wage. Although socioeconomic status can be correlated with respiratory health, Dr. Engelberg stated that in none of the studies cited by the NCC was socioeconomic defined by wage differential alone. In the Higgins study, three groups were defined: (1) White collar, (2) farm labor and (3) blue collar, and both the waste cotton workers and the control group in the study belong to the blue collar group. Dr. Engelberg provided similar analyses for the two other papers cited by the NCC on this matter. There was also a criticism of NIOSH's definition of the term chronic bronchitis, and Dr. Engelberg responded that the definition used by NIOSH was consistent with the way chronic bronchitis was defined in the papers cited by the NCC. OSHA believes that Dr. Engelberg has satisfactorily answered the criticisms of the NCC and that the results of the NIOSH study are valid.

Dr. Engelberg also provided OSHA with his recommendations concerning this industry. He agreed that a respirable dust standard, measured by the vertical elutriator would be appropriate. He stated "that OSHA should consider an elutriated dust standard equivalent to the proposed total dust standard, to address the fact that the dust in this industry has similar biological effects as cotton dust in other industries." (1983 Tr. at 65) He further recommended that medical surveillance be continued to detect early stages of respiratory disease (Tr. 65; 141).

Dr. Merchant testified in behalf of the American Thoracic Society on the need to retain regulation of the waste processing industry and the need to retain medical surveillance. That was also his conclusion for ginning and cottonseed processing. He agreed that medical surveillance was sufficient for knitting and classing.) However, he added:

> OSHA is proposing to regulate this industry with a one milligram per cubic meter of total dust PEL only. As has been noted in the textile industry, total dust often does not correlate with health effects; hence, OSHA's proposing to utilize total dust which may or may not contain biologically active inhalable dust. Thus, it risks not providing workers adequate protection on the one hand, and over-regulation of the industry on the other.
>
> A more rational plan, in my view, would be to adopt a PEL for inhalable dust between .5 and one milligram per cubic meter together with medical surveillance. As has been demonstrated in the textile sector, both provisions are important in preventing respiratory disease. (Tr. 331–332)

In their testimony, NIOSH discussed the findings of their cross-sectional studies and made their recommendations concerning the protection of these workers. Mr. Richard Lemen, representing the Institute said:

> In conclusion, NIOSH continues to recommend the provisions of its 1974 Criteria Document as the basis of a Cotton Dust Standard. . . . The Criteria Document recommended reduction of dust concentrations to the lowest level feasible and recommended medical monitoring and employee training. (Tr. 401–2)

The National Cotton Council repeatedly stated in their comments and written testimony that OSHA has not made a threshold finding of significant risk in the waste cotton industry and that meeting a 1000 $\mu g/m^3$ total cotton dust standard is economically and technologically infeasible. Therefore, they concluded that this industry should be totally exempted from any standard. Although they opposed coverage of this industry by any standard, Mr. Frank Mitchner of the National Cotton Council agreed that measuring respirable dust is more appropriate than measuring total dust in this industry. A summary of his statement read into the hearing record stated:

> The vertical elutriator, with all its faults, is vastly more appropriate for measuring dust in nontextile operations, or any operation for that matter, than the personal sampler. (Tr. 977)

Both the Textile Fibers and ByProducts Association (Ex. 210B) and the National Cotton Batting Institute (Ex. 211D) presented their own analysis of the evidence in the record and concluded that the health studies in the record could not be used to support a finding of adverse health effects.

The testimony of the industry representatives on this issue was limited to comments and critical analyses of studies in the record. These studies show that workers exposed to cotton dust in this industry develop adverse health effects. No new studies were introduced to provide evidence of safety. No medical expert testified that the evidence supported the elimination of medical surveillance for waste processing workers. Therefore, the evidence in the record provides no basis for eliminating a permissible exposure limit and medical surveillance for this industry.

Conclusions and Significant Risk Analysis

The legal and policy basis for an analysis of the waste processing segment is discussed under the knitting segment. That general discussion is not repeated. On the facts presented it appears more logical to discuss the issues in reverse order for waste processing.

The first question is then whether there is sufficient evidence to demonstrate that significant health risk is unlikely to exist if the waste processing industry were exempted from coverage of the 6(a) standard. It is clear that the evidence does not demonstrate this. A series of studies indicate substantial excess risk of byssinosis, bronchitis and lung function declines. The NCC pointed out that each study has some weaknesses, but that point does not provide a sufficient evidentiary

basis for eliminating all regulation. Indeed, the fact that a number of studies show substantial excess prevalence of disease tends to overcome the fact that each has weaknesses.

As discussed under knitting the burden of proof in eliminating a 6(a) standard is to show that uncontrolled exposures are unlikely to lead to significant risk, not to demonstrate that significant risk exists. However, if no standard existed and OSHA was undertaking a 6(b) rulemaking to determine whether a standard should be promulgated for this sector, OSHA would find that a significant risk existed at uncontrolled exposures which would be substantially reduced by a standard. Several studies taken together show substantial excesses of byssinosis, bronchitis, and pulmonary function declines at high exposures. This is significant risk of material impairment of health and functional capacity. The most recent NIOSH study shows that lower exposures eliminate byssinosis and reduce pulmonary function declines. Therefore a standard such as the 6(a) standard substantially reduces a significant risk.

Further, waste processing tends to be a dusty operation and some exposures are over the 6(a) cotton dust standard as a total dust level measured by a personal sampler. Both Dr. Merchant and Dr. Engelberg recommended that the 1000 $\mu g/m^3$ PEL be interpreted as a vertical elutriator respirable dust standard rather than a total dust standard. This would to be more consistent with the epidemiological studies and more protective for employees. Representatives of the NCC also agreed that if there were to be a level, it should be a respirable dust level. Accordingly OSHA is changing its interpretation of the 6(a) limit in § 1910.1000 to a respirable dust level as measured by a vertical elutriator which will increase employee protection. A footnote has been added to the cotton dust entry of Table Z–1 of § 1910.1000 to indicate this.

As discussed below in the feasibility section it is substantially easier to achieve a respirable dust level than a total dust level. This change therefore responds to the NCC's feasibility concerns and improves the cost-effectiveness of the standard as well.

OSHA has concluded it is appropriate to narrow the definition of waste processing to the operations of waste recycling (sorting, blending, cleaning and willowing) and garnetting as proposed. However, it is excluding bedding assembly operations. OSHA does not believe that risk was demonstrated in bedding assembly, which is a much less dusty operation. However, if a bedding manufacturer has a garnetting operation, the garnetting part of the bedding manufacturer's operations are covered by the standard.

The next question is whether there is significant risk at the 6(a) level which can be substantially reduced by a lower exposure limit. The recent NIOSH study of the current work force does not demonstrate the existence of byssinosis, and the excess incidence of pulmonary function declines and chronic bronchitis does not indicate a dose-response relationship. The ACTWU and Dr. Beck pointed out that a dose-response relationship could be masked when there is an acute reaction which varies among persons. The more reactive employees might transfer to lower dust areas because they could not function in high dust areas, and the less reactive employees willing to work in higher dust because their reaction would not be as great. This would lead to overall excess risk compared to suitable controls but no indicated dose-response relationship (Ex. 279, pp. 113–114; Tr. 1123–5) However, no empirical research is presented to support this hypothesis.

OSHA concludes in light of the absence of byssinosis and demonstrated dose-response that in this particular circumstance there is not sufficient evidence to demonstrate that a lower exposure limit would substantially reduce significant risk. In addition Dr. Merchant, the scientist whose research was a major factor in the development of the cotton dust standard, indicated that it would be a "rational plan" to adopt a 1000 $\mu g/m^3$ respirable dust standard with medical surveillance. This is in essence what OSHA is doing and OSHA believe it will be protective of employees.

The last question is whether medical surveillance should be retained. OSHA concludes it clearly should be retained for waste processing. First, medical surveillance in conjunction with the exposure limit is needed to prevent the development of substantial rates of byssinosis and bronchitis which uncontrolled exposures lead to. Second, the NIOSH study does indicate excess chronic bronchitis and pulmonary function declines at current exposures. Medical surveillance is needed to identify and protect employees who develop these conditions. Third, Dr. Merchant and Dr. Beck testified on the need for medical surveillance. No medically qualified person testified it was unnecessary. Finally, it is a necessary backstop for the decision not to lower exposures to the 500 $\mu g/m^3$ respirable dust level.

E. Cotton Classing

When the 1978 standard was published, OSHA had no direct evidence in the record on the health of workers employed in classing operations. There was, however, evidence that dust levels in some unventilated operations reached 2400 $\mu g/m^3$ and minor changes in the ventilation could reduce the dust levels (43 FR 27369). The Agency included classing operations in the scope of the standard based on indirect evidence from the textile industry.

Following the legal challenges to the standard and the Supreme Court's decision on the Benzene standard, OSHA administratively stayed enforcement of the standard as it applied to cotton classing offices and cotton warehousing because there was a concern that the preamble to the standard had "not adequately describe[d] the rationale for including warehousing and cotton classing operations." (45 FR 50329, July 29, 1980)

Following the publication of the February 9, 1982 ANPR, the American Cotton Shippers Association (Ex. 175–30) commented in favor of excluding classing operation from the standard. They emphasized that there were no studies in the record on the health of classing workers. Because they submitted their comments before the anticipated NIOSH study on USDA classing offices became available, they requested additional time to comment specifically on it. They pointed out that unlike government classing offices, classing associated with merchandizing is more seasonal and cotton classifiers spend only a portion of their workday in this function.

NIOSH submitted a study on the environmental conditions and the respiratory health of workers in 13 USDA cotton classing offices, entitled "Respiratory Disorders and Dust Exposure in Sectors of the Cotton Industry of the United States Part 4: Cotton Classing Offices." (Ex. 175–56) Briefly, this study found that dust levels had been reduced and at the time of the study ranged from 70 $\mu g/m^3$ to 340 $\mu g/m^3$. They found no evidence to suggest an excess prevalence of lung symptoms or diminished lung function in these workers. NIOSH suggested that a second epidemiological study with proper control group be "funded in the near future." (Ex. 175–56)

Based on the findings of the NIOSH study, OSHA proposed to exclude cotton classing operations from coverage by either cotton dust standard (29 CFR 1910.1043 and 29 CFR 1910.1000)

because there was no evidence that workers in classing offices suffer either acute or chronic adverse health effects as the result of their exposure to cotton dust (48 FR 26968). OSHA received very few comments on this issue following publication of the proposal and there was little discussion of this matter in the public hearings.

In their prehearing comments, NIOSH restated the findings of their study and recommended a continuation of dust control (Ex. 187–23). In their testimony and posthearing comments, NIOSH recommended that OSHA adopt the recommendations outlined in the 1974 criteria document. These recommendations included both medical surveillance and the lowest feasible dust level. In posthearing comments, the ACTWU cited a number of reasons that argue against using a single negative study to exclude an industry from the standard but they did not question the findings of the NIOSH study (Ex. 279). The National Cotton Council supported OSHA's proposal to exclude classing from the standard because the record "will not support a threshold finding that . . . classing office workers are exposed to a significant health risk." (Ex. 276)

Conclusion and Significant Risk Analysis

The factual underpinnings are very similar and the analysis identical for the classing segment as for the knitting industry. Therefore, it is only briefly summarized. There is one study in the record which addresses the health of classing workers. This study, conducted by NIOSH, concludes that neither acute nor chronic adverse health effects were seen in these workers, and this finding has not been seriously questioned. There are no studies demonstrating risk in this segment and extrapolation from the textile segment is inappropriate in these circumstances. Therefore, based on the information in the record, OSHA concludes that under current conditions workers in cotton classing offices do not appear to be at significant risk of adverse health effects due to their occupational exposure to cotton dust which could be substantially reduced by a lower exposure limit. Consequently OSHA is exempting the classing segment from all requirements of § 1910.1043.

The employees surveyed in the NIOSH study were working under conditions where the dust levels were being controlled and their exposure were low. OSHA believes exposures will not rise. However, the medical study by NIOSH, discussed above under knitting, will act as a backstop to indicate if the health of the employees remains unimpaired after regulation ceases. Of course, if the study indicates that employees have not remained in good respiratory health, OSHA will consider appropriate regulatory action.

Based on the facts available for classing operations and the analysis presented in the knitting discussion, OSHA also concludes that the evidence demonstrates that a significant health risk will not develop if this segment is not covered by exposure limits. Accordingly, OSHA is exempting this operations from the 6(a) cotton dust exposure limit. This decision will better effectuate the purposes of the Act.

F. Cotton Warehouses

The record for the 1978 standard included a report by Barman of a survey of 70 workers in a single compress/warehouse operation (Ex. 56). In response to the February 9, 1982 ANPR, NIOSH submitted a study of the environmental conditions and respiratory health of workers in this industry. The study was entitled "Respiratory Disorders and Dust Exposure in Sectors of the Cotton Industry of the United States, Part 2: Cotton Compress Warehouses" (Ex. 175–56). The study showed an excess prevalence of bronchitis and decrements in FEV^1 greater than 10%. However, several factors made interpretation of this data difficult. One factor is that a large portion of the study group had been employed in other cotton industries such as ginning. A second factor is that there were a large number of differences between the study group and the control group, specifically racial, geographic and age differences. A third factor is that there was an inverse dose-response relationship between dust levels and decrement in FEV_1. In other words, workers at lower cotton dust levels were more likely to show a decrement in FEV_1 than workers at higher cotton dust levels. The authors suggested that this impairment seen in workers at lower dust levels may have resulted from exposures to other than cotton dust, such as exhaust emissions from idling transport vehicles. At the hearings, NIOSH recommended a standard for this industry that incorporated the recommendations of their 1974 criteria document.

OSHA's proposal to exclude cotton warehousing operations from the standard received few comments, and those received were very general in nature. Commenters either supported OSHA's proposal to exclude warehousing (Exs. 214, 276) or argued that a single negative study was inadequate to exclude an industry from the standard (Ex. 279).

Conclusions and Significant Risk Analysis

The analysis presented for the knitting and cottonseed segments is relevant here. There is only limited data in the record which addresses the health of warehousing workers. The major study, conducted by NIOSH, concludes that there is some evidence of adverse health effects in these workers. The areas where these effects was in the areas of lowest cotton dust exposure. It is not clear, therefore, whether these adverse health effects are due to exposure to cotton dust or to some other factor. There is no evidence in the record that indicates that reducing the dust level will result in a reduction of respiratory symptoms. Therefore, based on the information in the record, OSHA concludes that under current conditions cotton warehousing workers do not appear to be at significant risk of adverse health effects due to their occupational exposure to cotton dust. Consequently, OSHA concludes that the data support deleting cotton warehouse operations from § 1910.1043.

For the same reasons discussed under knitting and classing, OSHA concludes that the medical surveillance requirements need not be retained. However, the medical study by NIOSH discussed above under knitting, will act as a backstop to indicate if the health of the employees remains unimpaired after regulation ceases. Of course, if the study indicates that employees have not remained in good respiratory health, OSHA will consider appropriate regulatory action.

OSHA also concludes that the evidence demonstrates that a significant health risk is unlikely to develop if the exposure limit of the 6(a) standard is eliminated. Exposures tend to be intermittent and operations are usually in open areas with substantial natural ventilation. Therefore, OSHA does not expect exposures or medical conditions to change with the elimination of the 6(a) standard. Accordingly, OSHA is exempting cotton warehousing operations from the cotton dust permissible exposure limit of § 1910.1000, Table Z–1. OSHA concludes that this decision better effectuates the purposes of the Act.

G. Interpretation of Scope and Medical Startup Dates

The 1978 standard applied "to the control of employee exposure to cotton dust in all workplaces" with certain specified exceptions. The National

Cotton Council recommended that OSHA specify exactly where the standard was to apply (Ex. 276, p. 2). This is the approach OSHA took in its proposal and retained in the final. The operations in which the standard is applicable are the operations where coverage is appropriate and justified by health data. This approach makes it clear that the cotton dust standard does not apply to bedding assembly, furniture assembly, tire manufacture and other segments not specified or discussed in this preamble.

The cotton dust standard applies to the operations specified and is not limited to facilities in SIC codes where that operation is the primary operation. For example, garnetting operations are covered by the medical surveillance limit of § 1910.1043 and the exposure limits of § 1910.1000. Bedding assembly is not covered by either standard. Obviously a garnetter using waste cotton is covered as specified, and a bedding assembly facility with no garnetting operations is totally excluded from the standard. However, in a bedding assembly facility which has a garnetting operation, the standard applies to cotton dust exposures in the garnetting area. Similarly, tire production is not covered by either standard. However, if a tire producer has a yarn production operation with cotton dust present, the area of that yarn production operation is covered by the textile standard.

The medical surveillance provisions of § 1910.1043 have been stayed for nontextiles. The medical provisions are being retained as discussed above for cotton seed processing and waste processing and the stays will be lifted. In order to permit time for industries to arrange for medical surveillance in an orderly and efficient manner, a six month period is being permitted before initial medical examination requirement goes into effect. This start up provision is set forth in § 1910.1043(m)(2).

H. Supplementary Submission by Non-Textile Industry After Record Close

The last date for submitting post-hearing briefs to the cotton dust record was December 16, 1983. The record was certified by the presiding Administrative Law Judge on January 12, 1984.

The National Cottonseed Products Association, Cotton Warehouse Association, Textile Fibers and By-Products Association and the National Cotton Batting Institute sent to OSHA on January 2, 1985 a "Supplemental Submission." The Supplemental Submission discussed two matters. First, it discussed the relevance of a case decided November 7, 1984, Forging Industry Ass'n v. Secretary of Labor, 748 F.2d 210 (4th Cir.) to the cotton dust standard. Second, it discussed evidence in the cotton dust record on the relationship between cotton dust-related respiratory disease and smoking.

Initially a panel of the Fourth Circuit in *Forging Industry Ass'n.* held in two to one decision that the OSHA Hearing Conservation Standard, which required medical testing, was invalid because it did not adequately distinguish between hearing loss resulting from workplace noise and hearing loss resulting from aging and noise from non-work-related activity such as target shooting. The Supplemental Submission argued that the case was relevant to providing medical surveillance to nontextile workers because cigarette smoking can aggravate or create some of the pulmonary conditions also caused by exposure to cotton dust.

On April 4, 1985, the Fourth Circuit granted OSHA's petition for a rehearing *en banc* of *Forging Industry Ass'n.* On September 23, 1985, the Fourth Circuit, *en banc*, unanimously upheld all provisions of the OSHA Hearing Conservation Standard. Among other things, the court held that OSHA could require medical examinations to detect conditions which are commonly caused by exposure to harmful agents at the workplace though those conditions may also be aggravated or caused by nonoccupational conditions. In light of the *en banc* decision, the arguments which the Supplemental Submission made based on the initial panel decision no longer have basis.

The Supplemental Submission also made various statements about the interaction between smoking, cotton dust exposure and pulmonary disease and symptoms. It also quoted from various studies on this matter. That discussion should have been submitted no later than the deadline for submission of post hearing briefs and accordingly is late.

However, since it selectively reviews the literature and could be misinterpreted, a brief response is made. OSHA did analyze the relationship between cotton dust and smoking in the preamble to the 1978 standard. OSHA concluded that "presuasive evidence demonstrates the cigarette smoking variable, rather than overwhelming the cotton dust variable is merely related to it." 43 FR 27354 (June 23, 1978). The Supreme Court, of course, upheld OSHA's cotton dust standard for the textile industry which was based on this preamble discussion.

Most of the recent cotton dust studies, including those for nontextiles, control for smoking. When these studies report an increase in pulmonary symptoms for smokers, they are comparing a group of smokers who are not exposed to cotton dust to a group of smokers who are exposed to cotton dust, and the cotton dust exposed workers had the greater response. Similarly in matched pair analysis, exposed workers are matched with controls who have the same smoking history. So if there is an excess of pulmonary symptoms in the group exposed to cotton dust, smoking has been controlled for and that excess is due to cotton dust exposure.

For example, the NIOSH study of the waste utilization industry (Ex. 175–56) indicated a significant increase in bronchitis for smokers employed more than two years and all nonsmokers. It also showed a significant decline in lung function for all exposed workers. Similarly, the NIOSH study of the cotton seed processing industry showed a significant decrease in lung function of exposed workers who are smokers compared to smokers who are not exposed to cotton dust.

Medical exams for cotton dust exposed employees are directly relevant to protecting employees from the effects of cotton dust in textiles, cotton seed processing and waste processing. If an employee (smoker or nonsmoker) is revealed by the initial medical exam to have low lung function, or to have a substantial decline of lung function after the employee's first day on the job, then it is necessary for the employee's health for a physician to review the employee's condition. The physician needs to make a recommendation on whether continued exposure to cotton dust will impair the employee's lung function. A similar review is needed if these conditions develop after a number of years of employment. A few employees will react to cotton dust at very low levels of exposure. Consequently, physicians have not recommended low level exposure cut-offs for medical examinations.

Based on all the evidence in the record as briefly summarized in this discussion, OSHA continues to conclude that medical examinations directly provide some health protection to employees exposed to cotton dust in textiles, cotton seed processing and waste processing from illnesses and declines in lung function resulting from cotton dust exposure. This protection benefits both nonsmokers and smokers. The cotton dust exposure creates additional health problems for smokers different from or greater in extent than the problems caused by smoking alone.

IV. Amendments to the Standard for the Textile Industry

This section of the preamble provides an explanation of amendments to § 1910.1043 as the standard applies to the textile industry. Each amendment to the standard is explained separately or if no amendment was made, as in paragraph (j) "Signs", then this has also been indicated. This explanation also refers to operations other than textiles, where such references are appropriate. For instance, the frequency requirements for medical surveillance in nontextile operations are discussed under paragraph (h) "Medical Surveillance".

A few minor grammatical changes have been made to the language of the standard. These changes are not intended to alter the requirements or otherwise affect the intent of the standard and they are not discussed in the preamble.

A. Scope and Application

OSHA made no proposal to amend the scope of this standard as it applies to yarn manufacturing and slashing and weaving. Indeed, the record, discussed at length in Section II. Occupational Health Implications of Cotton Dust in the Textile Industry and Significant Risk Analysis, documents that a standard is not only necessary to protect workers in the textile industry but also that it has been very effective in reducing the prevalence of respiratory disease. Therefore, OSHA concludes that the evidence continues to support the Agency's earlier conclusions that the application of the cotton dust standard to yarn manufacturing and slashing and weaving operations is necessary to substantially reduce a significant risk that would be present if the standard was not in effect and that there is no basis to change the standard in this area.

In the proposal, OSHA proposed to maintain the scope of coverage for the textile industry but limited the coverage of this segment to yarn production and to slashing and weaving. Most textile mills also have a waste house where soft and hard cotton wastes are collected and baled. These waste products are collected from all phases of the production process and in many cases are removed from the production areas by the ventilation equipment and other engineering controls installed to maintain the PEL. Most textile mills have made a good faith effort to comply with the 1978 standard in their waste house operation (Ex. 280, pp. 106–109). Due to an oversight, the 1983 proposal did not discuss the textile mill waste house operations and this omission left the status of these operations unclear.

It is clear that cotton dust exposure in textile mill waste houses is not directly comparable to exposure in other waste cotton operations not directly associated with a textile mill. First, there is a potential for the exchange of air between the production areas and the waste house. Second, there is the likelihood that waste house workers will spend some of their time in production areas which will affect their risk. Third, compliance with the standard may be made more difficult for the employer when there are a group of workers who do not receive training and are covered by some but not by all of the provisions of the standard. For these reasons, OSHA will continue to require that all provisions of § 1910.1043 apply to waste house operations. That is, the PEL (500 $\mu g/m^3$) will continue to apply as well as all other provisions of the standard.

OSHA has clarified its definition of "washed cotton" and evidence has been presented that commercially viable washing processes are now available. Although, at present, "washed cotton" is not prepared commercially, such commercial preparation is likely to begin in the near future. Although the Washed Cotton Task Force made many recommendations concerning washing methods, the Task Force made no specific recommendations on the protection of employees engaged in the washing process (Tr. 893–894). Evidence and testimony presented by the Washed Cotton Task Force indicated that initial stages of cotton washing (bale opening and mechanical cleaning) are identical to the initial stages of yarn manufacturing (Tr. 893–894). OSHA concludes that there is a significant risk of adverse health effects for workers engaged in these initial processes in cotton washing. (These risks have been discussed in another section of this preamble, Section II. Occupational Health Implications of Cotton Dust Exposure in the Textile Industry.) Therefore, OSHA concludes that the standard § 1910.1043 applies to all employee exposure to cotton dust generated by cotton washing operations from opening until the cotton is thoroughly wetted when the likelihood of a release of cotton dust is virtually eliminated. The standard applies to all employees exposed to this dust regardless of the job that the employee is performing.

As a matter of format, OSHA is omitting the paragraph designated (a)(3) in the 1978 standard. No change in meaning is intended. That paragraph refers to all the types of variances for which employers may apply. Employers have those rights because of the statute, and they are applicable for all standards. However, OSHA does not cross reference the variance provision in any other standard. Therefore, this paragraph is being omitted to maintain consistency of format among all standards. Employers still may apply for and have the same right to receive temporary and permanent variances as provided for by sections (6)(b)(6)(A), 6(b)(6)(C) and 6(d) of the Act and 29 CFR Part 1905.

B. Definitions

1. "Blow Off/Blow Down"

The 1978 standard did not define the term "blow off" and defined the term "blow down" as "the cleaning of equipment and surfaces with compressed air." Limitations were placed on blow down in paragraph (g), which prohibited compressed air blow down cleaning where alternate means were feasible. That provision also required employees performing the blow down to wear respirators and required employees who were not needed for the blow down to leave the area. Comments in response to the February 1982 ANPR indicated that the industry used both terms ("blow down" and "blow off") and that confusion was created by the single definition. In addition, it was pointed out that "blow off" of individual machines was the generally appropriate method of cleaning, and because of its limited nature, required fewer restrictions.

To eliminate confusion as to work practice requirements for compressed air cleaning, OSHA proposed to define "blow down" as the "general cleaning of all pieces of machinery in a processing area by the use of compressed air" and to define "blow off" as "the use of compressed air for cleaning of short duration and usually for a specific machine or portion of a machine." (48 FR 26980) Paragraph (g) of the proposal banned blow down if alternative means of cleaning were feasible, required that employees not needed for blow down leave the area, and required that respirators be used for employees performing either blow off or blow down. (48 FR 26982)

Relatively little testimony was offered relating to this change. Mr. Carroll Bailey, a certified industrial hygienist with the South Carolina Department of Labor, testified as to the need for a provision that would distinguish between "blow down" and "blow off" to eliminate inconsistencies in enforcement. He stated:

The inclusion of a definition for the terms 'blow off' and 'blow down' is long overdue. The lack of this * * * resulted in inconsistency in enforcement * * *

It has not been appropriate to require that a whole area be evacuated during operations that are now defined as "blow off". The wearing of an approved respirator during both operations is certainly essential to the protection of the employee's health. (Tr. 1140).

In his testimony, North Carolina Labor Commissioner John Brooks also endorsed the proposed change of definition, and recommended that "blow down" be defined to "include cleaning of an entire area, walls, ceiling, ventilation duct work and so forth, as well as the machinery." (Tr. 1278).

In prehearing comments, the American Textile Manufacturers Institute (ATMI) supported a provision which would distinguish between "blow down" and "blow off", but offered substitute language, as follows:

Section 1910.1943 (b) under the rulemaking proposal defines 'blow down' as 'the general cleaning of all pieces of machinery in a processing area by the use of compressed air.' In fact, 'blow down' (as opposed to 'blow off') involves the general cleaning of an *entire room* rather than simply 'pieces of machinery' within the room. In order to more accurately reflect this distinction, the definition of 'blow down' should be revised as follows:

Blow down means the general cleaning of an entire room by the use of compressed air." (Ex. 187–17)

ATMI further recommended as a general "rule of thumb" that nonessential employees should be cleared from the room when compressed air is being used to clean an entire room. They further note that often it will not, in their view, be necessary to evacuate the entire room, and that instead an industrial hygienist or "other qualified professional" should determine "which portion of the room needs to be cleared of nonessential employees * * *" (Ex. 187–17).

ATMI's views on "blow off" cleaning are that since a much more limited area is involved, "the area that should be cleared of employees who are not performing the 'blow off' can be defined in terms of a one machine buffer zone in each direction surrounding the machine that is being cleaned. In some cases, however, the 'blow off' operation is so limited in scope * * * that no significant elevation in dust levels occurs in the area surrounding the machine. In such instances, there is no need to clear the area of production employees." (Ex. 187–17).

Not all testimony, however, supported the proposed distinction between "blow down" and "blow off". Objections centered on workers' perception that current requirements were not being implemented by employers. Paul Restivo, a representative of the ACTWU, stated:

OSHA's proposed change related to "blow off" and "blow down" with compressed air is one of the most callous changes which OSHA has proposed. Not only will workers be exposed to excessively high levels of cotton dust during these periods and have to stay in the high dust concentration areas, but the levels will not even accurately be reported.

Under the proposed change, an employer could require employees to stay on the job no matter how high the dust level during periods when one machine is being blown off. A distinction is made between "blow down", blowing several machines, or the general area, and "blow off", blowing one machine.

(Our members) * * * felt their employer would simply have compressed air cleaning conducted in a manner in which only one machine is being cleaned at a time, so that workers wouldn't be able to get out of the dusty area."

Under the present work practices provision, many workers have indicated * * * that their employers give employees who get out of the dusty area during compressed air cleaning a hard time. In fact, some supervisors have gone so far as telling workers that they did not have the right to leave the area during compressed air cleaning." (Tr. 1485–6).

Mary Fowler, a textile worker and a member of ACTWU, voiced her concerns on this matter:

Now, to make things worse, I am told I'll no longer be able to vacate the area where blow offs do occur if this proposed change goes into effect.

At the present time, on each spool you have A-side B-side. If "Blow off" occurs on A-side, the dust comes over the machine, under the machine, and so far we have been able to leave the area and wait until the dust has been removed: then return to work. This has been a plus in my opinion for the workers.

I don't think it's right to tell a worker they cannot get out of that cloud of dust * * * " (Tr. 1514).

Subsequent testimony reiterated these points, and provided some further discussion of the difficulty of defining the area which should properly be evacuated in a limited compressed air cleaning operation. (Tr. 1531–49).

In their posthearing submissions, however, both the Amalgamated Clothing and Textile Workers Union (ACTWU), and ATMI agreed on the following points:

1. OSHA's proposal for definition of "blow down" focused "unduly" on the cleaning of *machinery*.

2. "Blow down" means the "general cleaning of an entire room by the use of compressed air."

3. Work practice requirements in the proposal are appropriate, specifically the provisions that require employees performing the "blow down" or "blow off" to wear suitable respirators, and to require employees whose presence is not required to perform the "blow down" to leave the area during the cleaning operation.

4. The work practice provisions should be understood to require also that employees leave the immediate area affected by the "blow off" even if they do not evacuate the entire room.

5. Depending on the scope of the cleaning involved, it may be appropriate to evacuate an entire room, a portion of a room, or only the area affected by the cleaning of a single machine.

6. To implement this understanding, the standard should contain the following:

Employees whose presence is not required to perform "blow down" or "blow off" shall be required to leave the area affected by the "blow down" or "blow off" during the cleaning operation. (EX. 279, p.64; Ex. 280, p.64).

In light of this record, OSHA is retaining the proposed distinction between "blow down" and "blow off". The definition of "blow down" has been changed to put emphasis on the area affected, as was recommended. "Blow off" is often needed to clean a machine but a wide evacuation is not needed. "Blow off" will, therefore, not apply to cleaning major parts of a room, since that would generate a large amount of airborne dust, making the operation equivalent to a "blow down".

2. "Cotton Dust"

In the ANPR (47 FR 5907), OSHA raised the issue of whether the term "cotton dust" could be more narrowly defined. Few comments were received in response to this issue. Some suggested the exclusion of non-cotton materials such as oil mist, mineral dust, and synthetic fiber dust. Additional information was needed to determine whether and how the 1978 definition should be changed. However, none of the comment provided an adequate evidentiary basis for proposing a change in the definition. Thus, in its June 1983 proposal, OSHA requested comment on the "definition of cotton dust as the total particulate collected by the vertical elutriator." (48 FR 26963).

In the 1978 Standard, OSHA defined cotton dust as:

"* * * dust present in the air during the handling or processing of cotton, which may contain a mixture of many substances including ground up plant matter, fiber, bacteria, fungi, soil, pesticides, non-cotton plant matter, and other contaminants which may have accumulated with the cotton during the growing, harvesting, and subsequent

processing or storage periods. Any dust present during the handling and processing of cotton through the weaving or knitting of fabrics and dust present in other manufacturing operations or processes using new or waste cotton fiber or cotton fiber by-products from textile mills are considered cotton dust." (43 FR 27395).

OSHA explicity recognized that cotton dust is a "heterogeneous mixture", and that the proportion of the various components in that mixture could vary depending upon the type of plant, harvesting and storage methods, and cleaning operations at various stages of processing (43 FR 27354).

Because of uncertainty as to the identity of the specific causative agent(s) of byssinosis, OSHA chose the strategy of regulating total respirable, lint-free dust, rather than promulgating specifications for each component, or for various combinations of components. (43 FR 27355). This approach is consistent with the pioneering work of Drs. Shilling and Roach in Britain, and in research conducted by Dr. James Merchant and others, which underlies the 1978 standard, as well as much research conducted since 1978.

Some investigators have attempted to determine whether the concentration of a specific fraction of the dust could be correlated to the prevalence of respiratory disease. In their pioneering work in the Lancashire cotton industry, Roach and Schilling attempted to correlate dust measurement with prevalence of byssinosis. They found a strong linear association ($r=0.93$) between gross dust level and prevalence of byssinosis. In addition, they also fractioned the dust based on aerodynamic diameter ($<7\mu$, 7μ–2mm, >2mm) and on chemical composition (cellulose, protein and ash). Using the fractionated material, they found a strong linear association ($r=0.94$) between the prevalence of byssinosis and the protein fraction of the medium size dust particles (7μ to 2 mm). All fractions, whether based on size or chemical composition, were in some degree associated with the prevalence of byssinosis. In recommending a samplying method, the authors stated:

> For routine measurement of dust it is necessary to have a method in which the sampling equipment is simple and the assessment of the samples is rapid. As total dust concentration is easy to measure and correlates closely with the prevalence of byssinosis ($r=0.93$), our permissible levels of dustiness are expressed in terms of total dust. (Ex. 6–1)

The installation of exhaust ventilation following the study resulted in a dramatic reduction of the coarse dust particles and a less dusty appearance to the card rooms (Ex. 6–4). However, the reduction in gross dust levels did not solve the problem of byssinosis, and investigators began to question whether monitoring total dust was the most appropriate method. Further investigation indicated that fine dust ($<7\mu$) could account for most of the byssinosis seen in the textile industry (Ex. 6–4, 6–51, 6–66).

This early work set the stage for the work of Merchant and his coworkers. They used a Lumsden-Lynch vertical elutriator which collects particles with a mass median aerodynamic diameter less than 15μ. This dust fraction accounts for all of the fine particles and the lower range of the medium particles. The samples were collected in the work area, and all particles less than 15μ present in that area, regardless of origin, were collected by the vertical elutriator and were taken into account in the dose-response calculations. The result was a strong linear association between dust level measured by the V.E. and prevalence of byssinosis in cotton preparation and yarn area workers ($r=0.99$) and in weaving and slashing workers ($r=0.93$). Some difference in the potency of the dust was noted, however, and the slopes of the two curves were different. In addition, a no-effect threshold was seen for slashing and weaving workers. The authors suggested a possible explanation for the two different dose-response curves:

> . . . Preparation and yarn processing areas are justifiably combined since the dust is of the same composition, the dose-response curves for each area are similar, and the areas are frequently contiguous. When the yarn arrives in slashing department, sizing is added to the yarn and has been found consistently to increase the concentration of lint free dust in the slashing and weaving areas. Therefore, the biologically active airborne material in these workrooms is diluted with biologically inert sizing, making it necessary to consider this dust separately when considering these significantly different dose-response relationships. (Ex. 6–51)

OSHA accounted for the contribution of sizing to the overall composition of the dust when it set a separate permissible exposure limit for weaving and slashing operations. The exact contribution of some of the other materials present during Merchant's study such as soil or mineral dust is not known, but it is clear that the dose-response calculations take these materials into account. Any deletion of these materials from the definition of cotton dust would require additional dose-response studies and would result in a lower permissible exposure limit to maintain the same degree of protection (reduction in risk).

The justification provided for choosing this approach was documented in the preamble to the final standard:

> OSHA has concluded that the weight of evidence in the record requires the implementation of a standard based on "cotton dust" as broadly defined . . . The continuing scientific debate over the identity of the specific agent does not detract from the conclusion that "cotton dust" as defined and regulated by this standard has been shown to cause a constellation of respiratory illnesses . . .
>
> . . . the value of dust composition data alone is extremely limited in assigning risk to various concentrations of dust. Where medical research is available, physical and chemical data is less acceptable. (43 FR 27355)

Thus, dose-response relationships were calculated using total lint-free respirable dust as a basis, and the permissible exposure limits were derived from them. Differences in physical composition of the cotton dust at different stages of processing were accommodated through variations in the permissible exposure limit (PEL) at various stages of processing (43 FR 27355).

This strategy is feasible as a basis for regulation, and according to evidence presented in the record, it has been effective in reducing the prevalence of byssinosis in the textile industry. It has withstood legal challenge and has been affirmed by the Supreme Court.

In the comments presented in response to the proposal, three dust components—mineral dusts, synthetic fiber dust, and lubricating oil mist—were suggested for exclusion from the definition of cotton dust by several parties. A fourth component, pure cellulose, was put forward for exclusion only by the National Cotton Council (Ex. 276). Lubricating oil, humidifier mineral solids and synthetic fibers are present in the air during the handling and processing of cotton, and mineral solids and synthetic fibers were in the environment where early cotton dust sampling and research was conducted. Thus, these substances are reflected in the data used to set dose-response curves, and they are incorporated in the PELs. For this reason, actions taken to exclude them at this time must be based not only on their possible role as agents of byssinosis but also on evidence that they were not properly reflected in the PELs because their quantity in the workplace has changed since the research used to set the PELs was completed.

a. *Lubricating oils.* In the early 1970's when Dr. James Merchant and his associates were conducting their research, typical weave rooms in cotton textile plants had Draper looms, shuttle-

type weaving machines that emitted little lubricating oil (Tr. pp. 693 and 1162). In particular, the Burlington Industries weave rooms used in Merchant's study were equipped with Draper Looms (Ex. 187–27; Ex. 233, Item 1). Since that time, however, throughout the industry many of those machines have been replaced with modern equipment, notably the Sulzer shuttleless loom. Sulzer looms are much more productive than the older machines and are expected eventually to replace them in most operations. Some Sulzer machines emit relatively large quantities of lubricating oil in normal operation and the oil mist contaminates air samples taken in weave rooms equipped with these machines. (Ex. 187–27 Appendix A). This issue was raised in the ANPR of February 9, 1982) (47 FR 5908) but few comments were received. Additional information was requested in the June 10, 1983 proposal (48 FR 26969).

Evidence compiled in testimony and through public comment indicated that the quantity of oil mist collected now in sampling is now much greater than would have been present in earlier years. According to ATMI, as much as 86% of a vertical elutriator sample weight may be oil mist (Ex. 187–17, p 34). ATMI also notes with supporting factual analysis, that the Sulzer looms and the accompanying oil mist were not present in the mills where Merchant's research was done. This position is reiterated in ATMI's and ACTWU's posthearing submissions to the record (EXs. 280, p 32–42; 279, p 32–42), and in the submissions by Georgia Textile Manufacturers, et al. (Ex.187–16 p. 6–10) and by J.P. Stevens & Co. Inc., (Ex 187–28A)

ATMI notes that (1) oil mist from Sulzer looms would be present regardless of the type of fiber being woven; (2) oil mists have not been associated with byssinosis; (3) OSHA already has an oil mist standard (29 CFR § 1910.1000) and, (4) any further regulation of oil mist should be achieved through amendment of that rule rather than through the cotton dust standard.

The National Cotton Council also recommends exclusion of oil mist, and provides two methods of calculating the quantity of oil in air samples. (Ex. 216, p 24).

Dr. John Neefus, speaking as Corporate Industrial Hygienist for Burlington Industries addressed the question of sampling for oil mist in testimony on October 4, 1983. (Tr. 1154–1157) Dr. Neefus noted that the method which involves infra-red absorption analysis has been in use at Burlington for more than 5 years. The method is described at length in Exhibit 233, Item 4.

Not all evidence supported exclusion of lubricating oil mists. NIOSH recommended against exclusion on the grounds that the epidemiologic studies from which the assessment of significant risk was determined "included many 'extraneous' materials in the samples from which dust concentrations are calculated and to which workers are exposed." (Ex. 187–23, p. 18)

NIOSH stated that if OSHA wished to exclude oil mist from the definition of cotton dust, a "practical evironmental sampling method" must be developed "other than or in addition to the vertically elutriated particulate." Subsequent to the NIOSH statement evidence was submitted demonstrating that a method was available to separate out oil mist and that oil mist was not present in major part in the dust samples collected by Merchant and his colleagues.

In response to a question regarding acceptable testing for oil mist, NIOSH representatives noted that a proper evaluation of the desirability of excluding oil mist from the definition of cotton dust would involve not only sampling and analytical methods, but also evaluation of health hazards presented by the oil mist itself. (TR. 455)

This reservation was reiterated in the testimony of Dr. Morton Corn, who agreed, however, that the absence of oil mist from the environments sampled in the Merchant studies would have a bearing on conclusions as to whether it could be a causative agent of byssinosis. (Tr. 511.)

OSHA has decided, based on the record, to exclude oil mist from the definition of cotton dust. The evidence is now clear that oil mist was not included in any significant quantities in the samples measured in the Merchant studies, and thus it was not included in the dose-response relationships. The oil mist now present comes from machinery that was not widely used, if at all, in U.S. mills at the time of the Merchant studies. Therefore, excluding oil mist will not increase risk rates and including oil mists may result in feasibility problems in certain areas. There is no independent evidence that oil mist contributes to byssinosis directly or nor was it part of the total sample on which Merchant's findings were based. Further, both ACTWU and ATMI recommend its omission (Ex. 279, p. 42; Ex. 280, p. 42). Oil mist continues to be regulated independently by 29 CFR 1910.1000 Table Z–1.

b. *Mineral Dusts.* The presence of mineral dusts in the air of workplaces affects the weight of vertically elutriated samples. Since the cotton dust standard calls for gravimetric measurement of dust levels, the added weight of mineral dust from humidification water may be included in the air samples taken in some textile mills. Such mineral dust can be simply removed by demineralization of the humidification water before the dust reaches the mill atmosphere. There may also be mineral dust present in the sample which arises as the result of the way the cotton is grown, harvested, ginned and baled.

Little comment was received as to the inclusion of mineral dust in response to the Advance Notice of Proposed Rulemaking. The issue was raised for further public comment in the proposal published June 10, 1983, although no proposal was made to exclude mineral dusts from the definition of cotton dust. Some comments were received in response to the proposal.

The Georgia Textile Manufacturers argue that there "is no evidence from the Merchant studies that oil mist or mineral dust made any measurable contribution to the filter weight". They note that "dissolved solids in a city water system may also make a significant contribution of filter weights; yet there has been no showing that the dissolved solids pose any significant risk to health." (Ex. 187–16, p. 8–9.) The National Cotton Council also made this point in its August 9 submission. (Ex. 187–18, p. 2)

J.P. Stevens & Company also supported exclusion of "dissolved water solids" and stated that they can "contribute up to 90% of the 'dust' on the elutriator filter" in some textile plants. (Ex. 187–28a, p. 3.) J.P. Stevens acknowledged that the original cotton dust studies did not take dissolved solids levels into account as a separate contaminant, but argued that they were easily identifiable and could be subtracted from the weight of filters. J.P. Stevens did not, however, present evidence that the levels of dissolved water solids were for any reason different than they were when the major studies were conducted.

In posthearing comments, the National Cotton Council provided citations of methods to differentiate between mineral particulates and other components of cotton dust, and recbmmended their exclusion on the grounds that they should instead be regulated under OSHA's standard for nuisance dust. (Ex. 216, p. 23, 24.)

The American Textile Manufacturers Institute's posthearing comments (Ex. 280, p. 109) reiterate the National Cotton Council's points, and recommend that employers be permitted to make at least "a partial adjustment in apparent cotton

dust measurements in those cases where inorganic mineral dust represents a very substantial percentage of the vertical elutriator reading." The effect of such subtractions on permissible exposure levels are not addressed.

ATMI acknowledges, however, that "the level of dissolved solids in the humidification water at the plants studied by Dr. Merchant is not known, but it is highly unlikely that Dr. Merchant's measurements reflected as high a mineral dust component as measurements in many textile plants today". (Ex. 280 p. 112.) The basis for this assertion is not identified, and consequently, it is not possible to compare typical current levels of dissolved solids with those in the environments where research was conducted. There is no evidence in the record that mineral dust levels were not in fact typical with regard to mineral content of humidification water, nor that the plants surveyed by Dr. Merchant included workplaces with exceedingly high or low levels of mineral dust.

Objection to any allowance for mineral dusts in the calculation of total cotton dust exposure came from the Amalgamated Clothing and Textile Workers Union, Labor Commissioner John Brooks of North Carolina, and from NIOSH. The ACTWU objection was based on the fact that mineral dust was already accounted for in the standard's permissible exposure limits, which were based on dose-response relationships including such dust (Ex. 279, p. 119). The union noted also that no evidence was presented to show that mineral dusts of the type found in textile mills were independent of the health effects found there. (Ex. 274, p. 120.) Commissioner John Brooks also testified against changing the definition of cotton dust (Tr. 1287), and noted that the total dust sampling method had not hindered compliance with the standard (Tr. 1280).

NIOSH also recommended against changing the definition of cotton dust, noting that more definitive information is needed about the causal agents of byssinosis. They noted a strong correlation between total respirable dust concentrations and byssinosis (Ex. 187–23, p. 2–4). While NIOSH noted that differences in dose-response relationships may possibly be attributed to differences in dust composition in various workplaces, they concluded that the existing OSHA definition of cotton dust is the best practical definition and should be retained for compliance purposes (Ex. 187–23 p. 7). They reached this conclusion because the dose-response calculations and, consequently, the risk assessment were based on dust samples containing all the materials present in the mill atmosphere.

OSHA did not propose to amend the definition of cotton dust to exclude mineral dusts, and it has concluded that the definition should remain unchanged with respect to mineral dust. Unlike oil mist, mineral dust was clearly present in the atmosphere when the epidemiology studies were performed. No empirical evidence was present that more or less mineral dust from humidification is present in workplaces now than was the case when the research supporting the 1978 standard was performed.

The comments did not present evidence to indicate that equivalency could be established between exposures and health effects for samples with and without mineral dusts. Since such mineral dusts were present during Merchant's research, PELs which were based on his data would have to be recalculated at lower levels than are provided in the present standard to achieve a similar level of worker protection.

For example, assuming that such mineral solids constituted 25% of the weight on a sample filter, and the same percentage applied to Merchant's sample, deletion of the dust would require that the permissible exposure limit be reduced accordingly to maintain the same level of employee protection. This would mean a reduction of the PEL to approximately 150 $\mu g/m^3$ in yarn manufacturing operations and 562.5 $\mu g/m^3$ in weaving operations.

OSHA concludes that it is inappropriate to amend the definition of cotton dust to exclude mineral dust which is present in the mill atmosphere. The epidemiology studies which established the clearest relationship between byssinosis levels and dust in the mills measured total respirable dust present including mineral dust. Therefore, OSHA adopted this approach for regulation and it was upheld by both the Court of Appeals and the Supreme Court. It has proven to be feasible to comply with this definition.

Most importantly, this approach to regulation has been successful in substantially reducing levels of byssinosis and other pulmonary disease among cotton workers. This empirical and objective evidence that the standard works far outweighs theoretical arguments that mineral dust by itself may be inert and therefore it should be subtracted from the sample. No studies have been presented demonstrating that mineral dust in conjunction with cotton dust is inert or comparing response rates with mineral dust included and excluded.

Further excluding mineral dust from samples would lead to the standard's permitting a higher level of cotton present at the existing exposure limit. This would result in a higher level of byssinosis and other pulmonary disease at the current exposure limits. It is inappropriate to permit a higher incidence of disease when controls to achieve a lower incidence of disease have proven feasible. Therefore the approach of excluding mineral dust would require OSHA to set lower exposure limits to prevent the level of disease from increasing. Data and studies to permit determination of the appropriate level to set are not available.

c. *Synthetic Fibers.* Synthetic fiber is present in the air of textile mills which produce cotton blend fabrics. It may be present at all stages of processing, from opening through weaving. Although it does not enter the mill with the cotton, synthetic fiber may be mixed in an "intimate blend" at the opening process, or combined with cotton fibers at later stages of processing. Thus, it is covered by the definition of "cotton dust" which, as noted above, includes "* * * any dust present during the handling and processing of cotton * * *" (43 FR 27395). Little evidence on this topic was presented on this matter in response to the ANPR. In its June 10, 1983 proposal, OSHA proposed no specific change in the definition of cotton dust which would exempt synthetic fibers, but requested that additional information be submitted (48 FR 26969).

In prehearing comments, the American Textile Manufacturers Institute proposed that OSHA establish an adjustment factor to reflect the processing of synthetic blends with varying percentages of cotton, or alternatively, a simple baseline exclusion for operations "in which cotton constitutes less than a specified percentage of the fiber processed during a given period". A 20 percent cotton fiber content was suggested as a threshold and was reiterated in ATMI's post hearing comments (Ex. 280, p. 113). They also noted that the "weighted-average proportion of cotton processed at the 5 plants studied by Dr. Merchant was 89 percent", a proportion higher than many blend mills customarily process.

Burlington Industries presented comments on synthetic fiber dust (Ex. 187–27), including further elaboration on the proportion of cotton fiber being used in the areas studied by Dr. Merchant. They stated that, "Dr. Merchant's

original study was performed in two 100% cotton plants * * * and three blend plants with 75%, 71%, and 50% cotton * * * Weighting these by the number of employees, the average proportion of cotton processed was 89% in both preparation/yarn and slashing/weaving areas * * *"

Burlington argued that because "a large portion of textile plants are processing more than 11% synthetic fiber, the standards set under prevailing conditions of 1970 must not apply uniformly to all cotton processed * * * Burlington strongly supports exclusion of polyester dust fraction from measured respirable dust before applying both the action level and the permissible exposure limit".

Burlington's exhibit also included appendices prepared by Dr. Moon Suh which addressed the issue of synthetic blends from an analytic and statistical viewpoint. Dr. Suh suggests alternative methods of calculating exposures and lower PELs for pure cotton dusts, and suggests variable PELs based on various blend ratios (Ex. 187–27, Appendix B, p. 10). However, he acknowledged the problem with the method that he used. The method is based on the "assumption that dust levels measured under 100% cotton and 100% polyester operations were entirely due to cotton and polyester only. The assumption is not valid if the samples also include minerals, sizing compounds, and/or oil mists which as discussed elsewhere they do. It is difficult, however, to estimate the proportions, of these substances in the Merchant dose response study. (Ex. 187–27, App. B, p. 12).

Burlington also supplied a further analysis using data from 24 cotton and cotton/polyester blend plants (1974–1977) which provided more estimates of the changes in dust levels associated with various percentages of cotton content. This study, however, noted that:

> The estimated R values are too large for the present operational environment where dust levels seldom exceed 500 micrograms in preparation/yarn areas.
>
> An additional analysis can be made using the same statistical model but by applying more recent data. Such as analysis requires considerable amount of time for data acquisition and hence could not be incorporated in this reported at this time. (Ex. 187–27, App. B)"

Thus, the research contributed by Burlington to the record may be useful as a starting point in determining the relation of particular blend percentages to dust levels. The data provided, however, are not sufficient for widespread application, and thus they cannot serve as a basis for exclusion of synthetics from the definition of cotton dust.

Burlington also notes that in slashing and weaving areas, adjustment for mineral dust and other compounds must be made before deriving a variable PEL at different blending ratios. Burlington notes, however that "while chemical assay and other laboratory procedures may provide a guideline for dust apportionment into component fractions, the economic burden for performing such an analysis, even when it becomes feasible, makes it impractical to require it as part of the dust standard. This means that statistical/mathematical techniques must be given a serious consideration in resolving the issue * * *" (Ex. 187–27, App. B, p. 17)

The Amalgamated Clothing and Textile Workers Union testimony objected to this mathematical approach, and took the position that no changes should be made in calculations to allow for synthetics without epidemiological data to support them. (Exhibit 280, p. 119) No new epidemiological studies that address this matter have been submitted to the record. ACTWU notes that because existing PELs were based on data which included synthetics, the existing standard already includes an appropriate allowance for blended fiber operations.

NIOSH strongly recommended the existing definition of "cotton dust" which includes dust from synthetics present be retained because it "is the best practical definition" (Ex. 187–23, p. 4). The basis for NIOSH's recommendation was the strong linear correlation between byssinosis rates and the amount of respirable dust including synthetic dust present in cotton operations. NIOSH pointed out that Merchant's data demonstrating the relationship between byssinosis and total respirable dust included values obtained from mills with up to 50% synthetics present. NIOSH also referred to the impracticality of separating out synthetics.

The Commissioner of Labor for the state of North Carolina also recommended that the definition of cotton dust remain unchanged. (Tr. 1287). Much of the textile industry is located in that state.

OSHA concludes that the evidence in the record does not support excluding synthetics from the definition of cotton dust for reasons similar to those for mineral dusts. The Merchant studies demonstrating byssinosis included a mill with 50% synthetics and there was clear dose-response with samples which contained synthetics. OSHA did not exclude synthetics from the definition of cotton dust for this reason and this decision was upheld by the Supreme Court. The standard has proved feasible.

Most importantly this approach has substantially improved the health of texitle workers in blend mills as well as 100% cotton operations. This empirical and objective evidence far outweighs theoretical arguments not supported by epidemiological studies that some percentage of synthetics should be excluded. No studies have been presented demonstrating that synthetic dust in conjuction with cotton dust is inert or comparing response rates with varying amounts of synthetic dust in the cotton dust.

Further, the whole percentage of synthetics present could not be excluded since synthetics were included in the Merchant studies and are incorporated in his dose-response curves. Consequently excluding the total amount of synthetics present would clearly raise the health risk of the exposed workers at the current exposure limits. Therefore, the approach of excluding synthetics would require OSHA to set lower exposure limits to prevent the level of disease from increasing.

Data are not available to determine what percentage could be excluded without raising the dose-response rate, since the percentage in the dust does not correlate with the percentage of synthetics in the blend. Specifically, there appears to be no reliable way to make a proportional allowance for the amount of synthetics in a particular blend. Burlington has presented limited data which indicates, under certain circumstances, the proportion of polyester dust at various blend levels. However, even at the 10% cotton level, approximately 30 percent of the dust in yarn preparation phases of processing comes from cotton (Ex. 187–27, p 16). There are no epidemiology studies available which have tested such an approach.

d. *Cellulose.* In posthearing comments, the National Cotton Council provided a summary of several studies which indicate that pure cellulose powder cause little or no respiratory response in humans or mammals. (Ex. 276, p. 25) It argued that cellulose should be excluded from the definition of cotton dust. No other party to this proceeding made that argument. OSHA neither proposed to exclude pure cellulose from the definition of cotton dust nor did it raise the issue in the proposal. Other interested parties would not have had adequate notice of this novel concept which was a major departure from other approaches. Indeed, the NCC presented no scientists at the hearing to discuss

this approach, which would have been appropriate because of its novelty.

Cellulose is a major constituent of cotton fiber, comprising approximately 96% of its weight (Ex. 276, p. 25). It was certainly a component of the dust samples in cotton dust research such as the Merchant study which determined the dose-response curve. While the cellulose itself, stripped of other materials found in cotton dust conceivably may present no health risk, it is inherently present in cotton dust. No dose response relationships have been established for cotton dust without cellulose content. No studies have been performed that demonstrate that cellulose does not interact with the other components of the dust and thereby effect the risk.

Removing cellulose would dramatically increase the risk rate at current exposure levels thereby raising risk rates from a lower level which has proven feasible. No mechanism has been suggested by the NCC on how to lower the exposure limit to adjust for this factor.

As also discussed above, cellulose was included in the definition of cotton dust in the standard which was upheld by the Supreme Court, which has proved feasible, and which has substantially improved the health of cotton textile workers. These facts and all the evidence demonstrating a dose-response relationship based on dust samples containing cellulose far outweighs the argument advanced only by the NCC. Its argument that the whose concept of regulation be changed from measuring total respirable lint-free dust to measuring only cotton dust stripped of cellulose (what might be called cotton trash) is a concept unsupported by evidence in the proceeding. It would require a substantial body of scientific studies and expert opinion to justify changing in total concept a regulation which has successfully improved the health of employees, and little evidence has been presented in support of this novel concept. Therefore, OSHA concludes the evidence does not justify excluding cellulose from the definition of cotton dust.

C. Permissible Exposure Limit/Action Level

OSHA proposed to incorporate an "action level" into the cotton dust standard in its June 10, 1983 proposal as discussed at 48 FR 26970. An action level is an exposure level below the permissible exposure limit, above which some provisions of the standard begin to apply and below which fewer provisions of the standard apply.

The 1978 cotton dust standard does not include an action level. Engineering controls and respirators are required only if exposures exceed the permissible exposure limit, but in general, all the other provisions of the standard are required if there is any cotton dust exposure no matter what the level.

The specific proposal OSHA made was to set an action level at 50% of the permissible exposure limit (PEL). Consequently the action level proposed was 100 $\mu g/m^3$ for yarn production and 375 $\mu g/m^3$ for slashing and weaving. The proposal provided that when exposures were under the action level the frequency of medical surveillance could be reached from once a year to once every two years. Periodic monitoring would cease if two consecutive measurements were under the action level until such time as product or process changes indicated that further monitoring was needed. In addition the proposal eliminated the requirement for annual retraining for employees whose exposures were below the action level.

OSHA, after reviewing comments to an advance notice (discussed at 48 FR 26970–1), explained the reasons why it believed an action level was justified. First, it will improve employee health by encouraging employers who can reasonably do so to lower exposure from the PEL to below the action level. These lower exposures are likely to improve employee health. In some cases, the action level both increases the safety factor and results in a lower adverse health response rate for workers whose exposures are reduced below the action level. This health benefit of lower exposure is likely to outweigh any consequences resulting from the reduction of industrial hygiene provisions. OSHA reasoned that retention of the medical surveillance provision for employees exposed under the action level would detect those employees who showed symptoms of byssinosis in time to reverse the symptoms.

Second, OSHA believes the action level substantially increases the cost-effectiveness of the standard. Employers who are in positions to devise ways to reduce exposures of their employees will be able to realize substantial cost-savings from the elimination of some industrial hygiene provisions while improving the health of their employees. The action level improves the flexibility and performance-orientation of the standard by giving the employer a greater choice in adjusting compliance responsibilities to the specific factors present in the workplace while still maintaining health protection.

Third, OSHA has had successful experience with an action level provision for a number of other toxic substances, including nonthreshold substances. In each case the provision was included based on full analysis of the record and the provision has proven successful in practice. The choice of an action level at one-half the PEL was based principally on OSHA's successful use of that level in other standards though the proposal also discussed some statistical literature.

A number of participants addressed OSHA's proposal both in prehearing and posthearing comments and testimony. The ATMI supported OSHA's proposal to incorporate an action level into the standard and OSHA's justification. It concluded:

> In sum, the action level concept proposed by OSHA will make the standard more cost-effective without in any way compromising the protection of employee health. As OSHA points out, similar provisions incorporated in other standards (including standards dealing with carcinogens) "have proven successful in practice." There is every reason to believe the action level concept will be successful in the context of the Cotton Dust Standard as well." (Ex. 187–17, pp. 59–60.)

Carroll F. Bailey, a certified industrial hygienist working for the South Carolina Department of Labor, agreed with the efficacy of incorporting an action level. He stated that an action level will improve employee health by encouraging employers, who can reasonably do so, to lower exposure from the permissible exposure limit to below the action level. (Tr. 1135.) He also pointed out that employers who are in a position to devise ways to reduce exposures to their employees will be able to realize substantial cost savings from the elimination of some industrial hygiene provisions while improving the health of their employees (Tr. 1135–6).

Commissioner Edgar McGowan, Commissioner of Labor for the State of South Carolina, supported the concept of the action level so long as medical surveillance was retained because it encouraged the achievement of a dust level below the PEL. However, he proposed that it be called an "incentive level." (Tr. 1185.)

Dr. James Merchant supported the concept of an action level. He agreed that when exposures were below the action level then medical examinations could be given once every two years "without material increased risk of not detecting significant health effects" (Tr. 293. The words at line 15 "by annual level" should read "biennially."). However, he believed that annual training and monitoring should be

retained even for employees exposed under the action level.

The ACTWU initially opposed the action level as specifically proposed by OSHA (Ex. 157–31, pp. 40–42). Testifying for the ACTWU, Dr. Morton Corn reviewed the initial reason for developing the action level and criticized the inclusion of an action level in the cotton dust standard (Tr. 490–491). He stated that the action level concept was originally created for threshold toxins and that he believed it was not appropriate for nonthreshold substances such as cotton dust. Dr. Corn also reviewed the literature on monitoring which indicated that for environments with low exposure variability a 50% action level gives reasonable confidence that exposures on a given day will not exceed the PEL, but that this is not so for substance with high exposure variability. He indicated this was a reason for not eliminating periodic monitoring when exposures were below an action level.

Dr. Neil Schachter was also critical of incorporation of an action level. He argued:

> In summary, current knowledge suggests that achievement of action levels will not eliminate byssinotic symptoms or ensure against chronic lung disease secondary to cotton dust exposure in workers. Given the unpredictability of individual workers and the potential toxicity of even low dust levels, reductions in monitoring, particularly medical surveillance, may adversely affect the health of workers sensitive to cotton dust. (Tr. pp. 529–530.)

After reviewing the record, in their post hearing comments, both the Amalgamated Clothing and Textile Workers Union (Ex. 279) and American Textile Manufacturers Institute (Ex. 280) made identical recommendations to OSHA on the action level. They recommended that an action level be incorporated into the cotton dust standard at one-half the PEL and that the frequency of medical examinations be reduced to biennially for employees exposed below the action level. However, both parties recommended that annual training and exposure monitoring be retained for exposures below the PEL, including areas below the action level.

Both ATMI and ACTWU supported their views in identical language. They stated:

> In sum, when properly designed, an action level creates incentives to provide greater protection for the health of employees; makes the Standard more flexible, performance-oriented, and cost-effective; and enhances the efficiency and effectiveness of the enforcement program. By making the Standard more rational and sensible to those to whom it applies, the action level is likely to elicit a greater degree of voluntary compliance * * * For these reasons, action levels have 'been in use in other standards covering exposure to toxic substances for several years . . . [and have] proven successful in practice.'
>
> Several witnesses at the hearing initially expressed uncertainty as to whether the rationale for an action level logically applied to substances without dose-response threshold * * *
>
> Regardless of whether a health effects threshold exists, a reduction in exposure levels will lower the health risk and increase the level of health protection. As noted by Carrol Bailey, if the reduction in exposures brings them below a threshold level, the safety factor will be increased, while a reduction in exposures that does not cross a health effects threshold will nonetheless result 'in a lower adverse health response rate' among the workers exposed at lower levels. Moreover, relaxing certain administrative provisions of the Standard (thereby permitting a cost saving) when exposures are reduced below the action level creates a logical incentive for employers to reduce dust levels, thereby increasing the level of health protection for employees. Indeed, the prospect of realizing some significant cost saving is likely to be the principal incentive for an employer to reduce exposures below the action level.
>
> Furthermore, there is nothing at all novel about OSHA's use of an action level for a non-threshold toxic agent . . . [A]ction levels have been incorporated into OSHA standards dealing with acrylonitrile, vinyl choride, inorganic arsenic and benzene, which OSHA considers to be carcinogens for which no health effect threshold is deemed to exist." (Ex. 279, pp. 46–48; Ex. 280, pp. 46–48).

Both ACTWU and ATMI agreed that employee health would be protected if medical examinations were every two years for employees exposed below the action level. (See the discussion at Ex. 279, pp. 49–50; Ex. 280, pp. 49–50) They pointed out that with the exception of Dr. Schachter, all the physicians who testified, [Dr. Merchant (Tr. 293), Dr. Boehlecke (Tr. 57–58); Dr. Imbus (Tr. 96–97) and Dr. Dr. Weill. (Tr. 133)] agreed on this point. For example, Dr. Weill stated that:

> [O]ne could safely have a monitoring program of lung function and other indicators of respiratory health that was instituted for individual workers every second year. (Tr. 155)

OSHA has reviewed the comments and concludes that the evidence supports the inclusion of an action level at one-half the PEL in the cotton dust standard and the reasoning stated in the proposal. An action level improves employee health while improving the cost-effectiveness of the standard. Employee health is improved because employers who can do so will be encouraged to lower exposures to one half the PEL. This improves the health of the employee whether the substance has a threshold or not. For threshold substances it increases the safety factor and for non-threshold substances it reduces the incidence rate. This reasoning has been accepted by ACTWU and ATMI as discussed above.

As the ATMI points out, the action level increases the cost-effectiveness of the standard. Employers who devise innovative ways to reduce exposures below the action level will have their medical surveillance costs reduced. This encourages the employer to reduce exposures and is likely to reduce the net costs of the standard.

OSHA concludes that medical examinations conducted once every two years will be protective for employees exposed below the action level. At those low exposure levels, relatively few employees will develop lung function decrements. The biennial examination will be sufficiently frequent to identify such conditions before they become serious and while they are still reversible. If such symptoms do develop, the standard still requires that semi-annual medical examinations be instituted. As discussed, the appropriateness of biennial examinations for employees exposed below the action level was supported by all but one of the physicians who testified.

As mentioned in the proposal, OSHA has successfully utilized the action level a number of times before, including for carcinogens which were believed to be non-threshold substances. These include inorganic arsenic (§ 1910.1018(b)), vinyl chloride (§ 1910.1017(b)), and acrylonitrile (§ 1910.1045(b)). It is not correct, as one or two commenters initially believed, that OSHA had only incorporated action levels for substances with clearly defined thresholds. Section 6(b)(5) of the OSH Act specifically states OSHA shall take into account "experience gained under the (law)".

As stated in the preamble, OSHA proposed the action level at 50% of the PEL principally because of its past success in utilizing that level in the regulation of the substances mentioned above. As discussed in the proposal, there is literature which indicates that when there is no wide daily fluctuation of exposure, a 50% action level gives a reasonable degree of confidence that the PEL will not be exceeded on individual days. Dr. Corn points out that if there is a wide daily variation in exposure, one cannot have that degree of confidence that some daily exposure will not occasionally exceed the PEL. However,

the principal reason OSHA is adopting the 50% action level is its prior experience.

Second, OSHA is adopting the joint ACTWU–ATMI recommendation that annual exposure monitoring be retained when exposures are under the action level. Third, the final standard retains the provision that employers must remonitor areas including those under the action level when product or process changes or other reasons may lead to increased exposure. (§ 1910.1043(d)(3)(iii)). These latter two provisions should meet some of the concerns expressed by Dr. Corn and Dr. Merchant.

As indicated, OSHA initially proposed to eliminate periodic monitoring when exposures were under the action level (§ 1910.1043(d)(3)(i)). As just discussed, ATMI and ACTWU recommended that yearly remonitoring be retained. Retaining such monitoring meets the concerns of Dr. Merchant and at least in part the concerns of Dr. Corn about undetected increases or large fluctuations. In addition, the development of alternative monitoring devices to the vertical elutriator which are easier to use and the improved provisions of the standard which make it more certain and less complicated to certify alternate monitoring devices, make periodic remonitoring much simpler and quicker. For these reasons OSHA accepts the ATMI and ACTWU recommendation to retain annual monitoring in areas below the action level.

Finally, ACTWU and ATMI both recommended that annual training be retained for employees exposed below the action level (Ex. 279, p. 54; Ex. 280, p. 54). Additional training will to some degree increase the employee's ability to assist in keeping his own exposure low and be aware of the hazards. In addition, the identical recommendations of ACTWU and ATMI are entitled to considerable weight. Consequently, OSHA is adopting this recommendation and retaining annual retraining as specified in the 1978 standard for all employees exposed to cotton dust and not adopting the 1983 proposal to eliminate retraining for employees exposed under the action level.

For the reasons discussed, OSHA is making the following amendments to § 1910.1043. A new paragraph (c)(2) is inserted setting an action level of 100 $\mu g/m^3$ for yarn manufacturing, 250 $\mu g/m^3$ for waste houses in textile mills and 375 $\mu g/m^3$ for slashing and weaving operations. Paragraph (h)(3)(i) is amended to indicate that medical surveillance must be repeated every two years for employees exposed below the action level unless certain medical conditions exist. The June 1983 proposals to amend paragraph (d)(3) to end monitoring and paragraph (i)(1)(ii) to end annual training below the action level were not supported by evidence and comments in the record and were not adopted.

OSHA did not specifically propose to retain a permissible exposure limit or to set an action level for waste houses in textile mills or for certain cotton washing operations. As discussed under the scope section, comment indicates that the 500 $\mu g/m^3$ level should be retained for wastehouses. Accordingly it is appropriate to have 50% action level (250 $\mu g/m^3$) for this area for the same reasons a 50% action level has been instituted in other areas.

As discussed in the washed cotton section, OSHA has expanded the processes which come under the various exemptions for washed cotton. This may encourage the use of those processes. The early stages of the washing processes present the same hazards as yarn manufacturing and accordingly similar regulatory provisions including action level provisions are appropriate.

D. Exposure Monitoring

The 1978 standard requires initial exposure monitoring to determine those areas that exceed the PEL. The standard further requires periodic monitoring in order to identify those areas where exposure levels may require prompt action and specifies the monitoring device to be used, the vertical elutriator (VE). OSHA's 1983 proposal addressed a number of issues related to exposure monitoring that became apparent after the standard became effective in 1981. Proposed amendments were made to address these problems and to make the standard more cost-effective. Specific changes were proposed to decrease the frequency of exposure monitoring and to amend the time for and method of employee notification. Although no changes to the VE equivalency protocol were proposed, OSHA indicated that an equivalency protocol was being developed and would be available prior to the public hearings. The changes that were incorporated into the final standard are discussed below by topic.

1. Criteria for Establishing Equivalency to the Vertical Elutriator

The standard sampling instrument for determining employee exposures to cotton dust specified by the 1978 standard is the Lumsden and Lynch vertical elutriator. This device was used in the epidemiological studies which established the dose-response curve and which served as the basis of the 1978 standard. However, the VE is a relatively awkward monitoring device requiring a substantial amount of industrial hygiene resources.

In its June 1983 proposal, OSHA noted that in addition to the VE, new dust measuring devices are available which are simpler to operate and incorporate more sophisticated technologies, and other devices may be developed. The criteria in the 1978 standard for determining an alternative instrument's equivalency to the VE are not as specific as they could be and are too descriptive in nature. For example, the guidelines do not specify sample size. Thus, the sample size can be arbitrarily set making it difficult to make a statistical statement about the population from which the sample is drawn.

Paragraph (d)(1)(iii)(c) of the 1978 standard specified that it shoud be demonstrated that an alternative sampling device is "equivalent within an accuracy and precision range of plus or minus 25% for 95% of the samples . . ." OSHA received ANPR comments on this criterion. Several commenters stated that this language created a possible ambiguity. For example, K.Q. Robert of USDA (Ex. 175–57) commented that an "accuracy and precision range of ±25% is ambiguous. Precision deals with the reproducibility of a measurement independent of the true value of the measured quantity. Accuracy, on the other hand deals with the difference between the average measured value and the true value."

Therefore, OSHA contracted with Dr. Harrison Wadsworth of Georgia Institute of Technology and Dr. Howard Rockette of the University of Pittsburg to design equivalency testing protocols. The purpose of the protocol would be to resolve the possible ambiguity and create a specific and statistically valid method of determining whether other instruments are equivalent to the VE. Their report, entitled "Revised Proctocol for Establishing Equivalency of Sampling Devices", was submitted jointly by Drs. Wadsworth and Rockette in August 1983 (Ex. 186–5).

This protocol requires a total of 100 samples be collected from at least 10 sites in a mill. That means there should be 10 replicated readings at each of the 10 sites. The dust levels at these sites should vary from one-half to two times the permissible exposure limit. The samples are to be collected using two vertical elutriators and one or two alternative sampling devices. These instruments are arranged close to each other in such a way that they are measuring essentially the same dust levels.

The results of these readings of the vertical elutriators and the alternative device are then computed. These are then used in two statistical equations to determine a critical value which provides the basis for determining whether or not the alternative device is equivalent to the vertical elutriator.

The reason for specifying the specific sample size, the conditions under which the samples are to be collected, the number of sampling instruments to be used, and the statistical equations used is that one can then be 95% confident that at least 90% of the measurements of the alternative device are within 25% of the corresponding vertical eluriator reading. This is a reasonably high degree of confidence that the alternate device is equivalent to the vertical elutriator.

Dr. Rockette testified at the Columbia, S.C. hearings and responded to questions about the protocol. Dr. Rockette was asked whether the Rockette-Wadsworth protocol can be interpreted to demonstrate "the general equivalency of an alternative device" and whether it is reasonable that the ten sites he refers to in the protocol be located in different processing areas. Dr. Rockette responded that in fact he was proposing that this protocol be "the method by which the device be shown to be equivalent [to the VE]" (Tr. 1303), and both he and Dr. Wadsworth feel that different processes should be selected so that they cover the range of values of the cotton dust in the mill.

The Rockette-Wadsworth protocol requires that dust level measurements be taken over a range of 0.5 to 2 times the PEL. Since March 27, 1984 was the deadline for achieving compliance with the PELs using engineering and work practice controls, it is expected that textile mills will be in compliance with the standard and will not have areas 2 times the PEL. Dr. Rockette testified that he and Dr. Wadsworth had given some thought to this condition and concluded that the "initial testing itself might have to be conducted in some type of a simulated laboratory condition." Based on this testimony, OSHA believes that testing above the PEL in a laboratory or other experimental setting reasonably modeled after a mill is appropriate. Accordingly, the language of paragraph (d)(1)(iii) has been amended by inserting the words "and laboratory" to indicate that laboratory comparison may be utilized for exposure over the PEL if no field situation can be found at 2 times the PEL.

Dr. Moon Suh of Burlington Industries questioned some aspects of the protocol (Ex. 244). In reviewing Dr. Suh's comments, Dr. Rockette discovered that a term had inadvertently been omitted from one formula in the manuscript (Ex. L-2). The error was that the term $\bar{X}_D$ in equation (2) was left out of the formula for the critical value. The critical value formula should be $T = KS_D + \bar{X}_D$, and the corrected protocol is found in Appendix E.

In their post hearing briefs, ACTWU (Ex. 279) and ATMI (Ex. 280) jointly stated that "We believe that this protocol provides an appropriate basis for establishing equivalency between alternative sampling devices and the vertical elutriator." They recommended that OSHA adopt this protocol and make it clear that this protocol need not be revalidated in each plant. The National Cotton Council (Ex. 276) also recommend the adoption of the Rockette-Wadsworth protocol.

NIOSH, in its prehearing comment (Ex. 187-23) noted that it reviewed the Wadsworth-Rockette protocol and had "no potential problem with the statistical assumptions presented." In their post hearing comments (Ex. 285), NIOSH offered modifications to the protocol which require more statistical knowledge and calculations on the part of the user. Although the suggested modifications may provide some fine tuning, it is outweighed by the advantage of having a statistically sound equivalency protocol that it is simple and straightforward to use. Therefore, OSHA concludes no modification is needed and that the Rockette-Wadsworth protocol meets the objective.

Based on evidence and testimony in the record, OSHA has concluded that it is appropriate to amend the cotton dust standard to clarify what criteria must be met in order for an alternative sampling device to be considered equivalent to the vertical elutriator. Therefore, the standard has been amended and the requirements are stated in paragraph (d)(1)(iii)(C).

As discussed the amended language clarifies the possible ambiguity of the earlier language and replaces it with specific criteria which are clear and well defined. Appendix E is the Rockette-Wadsworth protocol, and by incorporating it, OSHA will make clear that equivalency testing performed in conformity with this protocol will be accepted by OSHA as valid. The ATMI, ACTWU and NCC have agreed that the protocol and approach is valid.

Developers of other measuring devices may use protocols other than the Rockette-Wadsworth protocol to demonstrate equivalency. However, they must then demonstrate that the alternate protocol meets the criteria outlined in paragraph (d)(1)(iii) of the standard and thus is valid for demonstrating VE equivalency. OSHA is permitting the use of alternate protocols to increase the performance-orientation of the standard.

Paragraph (d)(1)(iv) provides that the manufacturer of an alternate monitoring device can provide to OSHA the data that an alternate device is considered equivalent and, if this is the case, receive a letter so stating from OSHA. An alternate monitoring device may be used without a letter from OSHA stating that it is an equivalent instrument. The manufacturer can provide the data to the employer for the employer to demonstrate equivalency. If the data meets the standard's criteria in the manufacturer's tests, the employer need not repeat that testing in the employer's facility. Also, an employer may demonstrate equivalency in the employer's facility with the employer's own tests.

As Dr. Rockette stated, it was his and Dr. Wadsworth's intention that the protocol be used to establish that an instrument is equivalent to the vertical elutriator and that these instruments need not be validated in each plant provided the instrument is of the same quality as the model tested.

Although the vertical elutriator uses a gravimetric detection method to measure cotton dust, OSHA does not require that an "equivalent instrument" use a gravimetric detection method. One advantage of the gravimetric method is that the sample can be further analyzed, where appropriate, to determine the contribution of lubricating oil to the overall weight of the sample. This further analysis of the sample may be important in some weaving operations, such as those employing Sulzer projectile looms, where lubricating oil, which is not considered cotton dust, may make a significant contribution to the weight of the sample. In operations such as yarn manufacturing, where an analysis of the sample is unnecessary, a simple determination of respirable dust is sufficient. However, if it is necessary to determine the amount of oil present in the sample, it appears to be necessary to collect a dust sample and then analyze the sample for oil content. The use of the VE is appropriate in all operations where cotton dust is to be measured. The decision to use an "equivalent instrument" in lieu of the VE in areas where the potential exists for oil contamination of the sample will be left to the employer. If the employer chooses to use an alternate instrument which does not provide a sample so that the percent of oil can be determined, then the employer may not exclude the oil

from the sample in determining exployee emposure.

2. The CAM/PCAM Model C

A potential alternative sampling device, the CAM/PCAM Model C manufactured and sold by ppm, Inc., has been tested with the VE in a number of side-by-side equivalency trials designed to meet the 1978 standard criteria. In 1980, two of these tests were submitted to OSHA for evaluation and acceptance. In January 1981, OSHA stated in a letter to Dr. John Neefus of Burlington Industries that OSHA believes the CAM instrument system (with the gravimetric certification and the equivalency refinement factor procedures as described in the draft paper "Gravimetric Certification and Equivalency Demonstration Protocols for Alternative Samplers to the Vertical Elutriator") is capable of equivalency to the vertical elutriator in reference specifically to Burlington facilities. Subsequently, the CAM instrument was accepted as equivalent to the vertical elutriator in several State Plan States. OSHA does not intend to require that these states change their decision.

In their post hearing briefs, National Cotton Council (Ex. 276), ACTWU (Ex. 279), and ATMI (Ex. 280) recommend that the CAM/PCAM Model C electro-optical sensors be directly identified in § 1910.1043(d)(1) as acceptable alternatives to the vertical elutriator. The manufacturer, ppm, Inc., (Ex. 203–C) stated that the CAM/PCAM Model C has been shown to be equivalent to the vertical elutriator in 20 of 22 equivalency tests and requested the instrument be directly identified in the standard.

While OSHA believes the CAM/PCAM instruments are likely to be equivalent to the vertical elutriator, the documentation which ppm, Inc. submitted to the record (Ex. 235) as evidence of meeting the Rockette-Wadsworth protocol was not sufficient to meet the protocol. The Rockette-Wadsworth protocol requires 100 samples to be taken at 10 sites in one mill with 10 readings at each site; dust levels represent 0.5 to 2 times the PEL and use of two VEs and one or two alternative devices. In the ppm, Inc. submission, a total of 196 samples came from two employers. The first employer had samples taken at only 6 sites, and the dust level did not meet the 2X PEL requirement. The second employer had samples taken at 8 sites of which one site has more than 10 readings but the other 7 sites only have 5 readings each for a total of 49 readings. Thus, it does not meet the requirement of 100 samples taken at 10 sites with 10 samples at each site.

Because the data submitted does not meet the requirements of the protocol, OSHA cannot identify in the standard CAM/PCAM Model C as an acceptable equivalent instrument to the VE in the standard. However, OSHA believes the CAM/PCAM instrument can probably meet the requirement of the Rockette-Wadsworth equivalency protocol. OSHA encourages all manufacturers of alternative sampling devices to submit proper documentation to show their instruments' equivalency to the VE.

3. Frequency of Monitoring

In the June 1983 proposal, OSHA proposed to reduce monitoring frequency from once every six months to once a year for those employees whose exposure is below the PEL. Further, OSHA proposed that monitoring would be eliminated if the initial monitoring or any subsequent monitoring revealed employee exposure to be below the action level, and an additional monitoring in an interval no greater than one year confirmed that the exposure was below the action level.

There were no specific comments in response to the proposal to reduce monitoring from semi-annually to at least annually for those employees whose exposure level is at or above the action level but at or below the PEL. There were a number of comments on this issue in response to the ANPR which were discussed at 48 FR 26972. For example, ATMI pointed out that OSHA in most health standards reduces monitoring frequency for employees exposed below the PEL and that annual monitoring was justified (Ex. 175–41).

Comments were received on OSHA's proposal to eliminate all exposure monitoring for employees exposed below the Action Level. NIOSH noted that discontinuing exposure sampling "can result in high probability of having workers receive excessive exposure without the ability to detect them by sampling" (Ex. 187–23) Dr. James Merchant commented that "OSHA's proposal to eliminate dust sampling if 'two consecutive monitorings are below the action level within a reasonable period,' in my view is unwise." (Tr. 293) He said there are many variables that affect the dust level and not all of them are detectable or measurable. Therefore, at least annual monitoring of dust concentration would be prudent. Dr. Morton Corn concurred with this view (Ex. 198D, Tr. 293–94). Based on Merchant's and Corn's comments, ATMI and ACTWU recommend that "Exposure monitoring should continue to be required semiannually in areas where the PEL is exceeded and should occur annually in all areas below the PEL, including areas that are below the action level." (Ex. 279 and 280)

OSHA is following its proposal and amending paragraph (d)(3) to provide that periodic monitoring need be repeated annually and not semi-annually for employees exposed below the PEL. This will provide protection for employees by identifying unnoticed changes in the work environment which result in exposures above the PEL. (Paragraph (d)(3)(iii) requires remonitoring if product or process changes may lead to higher exposure.) It will improve cost-effectiveness by reducing monitoring exposes for employees and saves valuable industrial hygiene resources for other duties. In addition, OSHA's experience with other health standards indicates it is adequately protective to reduce monitoring frequencies when exposures are under the PEL. As discussed in the proposal, many comments to the ANPR supported this approach.

There were substantial objections to OSHA's proposal to eliminate routine monitoring for exposures below the action level, and OSHA has retained annual monitoring for employees exposed below the action level. This decision is explained in the action level section, is supported by both ATMI and ACTWU and meets the objections to the proposal stated above.

The 1978 standard requires monitoring on each shift because of variations that can occur between shifts in the same area. The ANPR asked whether in certain circumstances the reading on one shift could be used as representative of all shifts in an area. The North Carolina Department of Labor commented that monitoring should continue to take place on each shift. In its experience there was substantial variation from shift to shift in the same area depending on such variables as production quantity, scheduling and employee work habits.

The ATMI commented that in some circumstances monitoring on a single shift can be sufficiently predictive of all shifts to permit single shift monitoring. In support of this point, the ATMI referred to a study by Dr. Moon Suh of Burlington Industries entitled "Statistical Analysis of Shift-To-Shift Dust Variations Measured in Cotton Textile Operations" as part of ATMI's comments to the ANPR. In this study, Dr. Suh details how a single shift monitoring of cotton dust exposure can apply and if a critical value is met, then a "true day average" can be predicted.

Regarding the study, OSHA's proposal stated:

"The method proposed however, would not identify all shifts where exposure in fact exceeded the PEL. Conceivably, an overall "true-day average" estimated to be below the PEL could mask a single shift average which is actually above it. The study leaves unanswered significant questions concerning the procedures used and the assumptions relied upon. The most important involves the representative characteristics of the fifty firms which supplied data. Potential differences in variability between plants is not addressed. In addition, there are serious questions concerning the pooling of variances across dust levels and work areas in cases where there are wide differences in coefficient of variation values. The report must be considered as inconclusive until further explanations are available." (48 FR 36972)

OSHA concluded that it would not propose to amend the standard to permit single shift monitoring because of the uncertainties on shift-to-shift variability. It opened this issue, however, and requested further comment (48 FR 26972).

At ATMI's request OSHA staff held a meeting with Dr. Suh to explain OSHA's questions. Minutes of the meeting and a memo further explaining the comments are in the record. (Exs. 249 and 204B).

Dr. Suh submitted an additional report as part of the ATMI prehearing comments (Ex. 187–17) and testified on his study at the Washington hearings. (Tr. 687) He stated that there could be increased assurance that the PEL is not exceeded on the unmeasured shifts provided that one of two criteria is met. The criteria are that the measurement is made on the shift:

(a) For which the highest readings were recorded on the two preceding measurement dates, or

(b) For which the person responsible for industrial hygiene at the plant identifies as being likely to have the highest dust levels for the particular work area.

ACTWU (Ex. 279) argued that the proposed method of selecting shifts for single-shift monitoring is unreasonable and unworkable. ACTWU argued if one shift is monitored, no readings will be recorded for the other two shifts and in the future, it will be impossible to determine the "shift for which the highest readings were recorded in the two preceding measurement dates."

Data submitted to OSHA indicate that the highest exposure shift is not easily identified for the single-shift monitoring method. ACTWU submitted data for four successive measurement dates of one company indicating the highest level shifts vary among the three shifts (Ex. 279, Ex. 237F). In a summary of some of their compliance activities, the North Carolina Department of Labor noted substantial differences in exposure readings on various work shifts at the same physical location (Ex. 175–80).

Given the data submitted by ACTWU (Ex. 279) and the South Carolina DOL (Ex. 216) which indicated that the shift with the highest exposure level varies among different shifts and the NCDOL's (Ex. 175–80) comment noting substantial differences on various work shifts at the same location in their compliance activities. OSHA is not deleting the multi-shift requirement. However, those employers who can identify highest exposure shifts and believe the single-shift monitoring method is appropriate for their operation may wish to apply for a variance.

4. Employee Notification

In the proposal, OSHA proposed to amend paragraph (d)(4) to extend the period of notification of monitoring results from 5 to 20 working days and require that each employee be notified "individually" in writing. The extension of time was proposed because of known difficulties in providing notification within the 5-day period required by the 1978 standard. Testimony at the hearing confirmed the necessity of an extension of time.

Edgar McGowan, Commissioner of Labor of the State of South Carolina noted that extension of time will allow employers to translate monitoring results into a language more easily understood by employees (Tr. 1187). Carroll Bailey, Health Supervisor for South Carolina Department of Labor OSHA stated that "even in this computer age, it is often difficult to prepare meaningful data that can be fully understood by the employee "(Tr. 1139). ACTWU and ATMI agreed with the proposed extension of time (Ex. 279 and 280).

Most commenters disagreed with OSHA's proposal to require that employers notify employees "individually". The North Carolina Department of Labor (Ex. 175–80) commented that "posting of sampling results is an acceptable means of employee notification." Commissioner McGowan of South Carolina also stated that "in many plants such posted notices are very effective." (Tr. 1187) In their post hearing briefs, both ATMI (Ex. 280) and ACTWU (Ex. 279) recommended that the word "individually" be stricken from the standard.

On the basis of the testimony on this issue, it appears that a 20 day notification period for posting monitoring results is an effective means of notifying employees. OSHA is not adding the word "individually" to paragraph (d)(4)(i) of this action based on the comments and testimony in the record.

E. Methods of Compliance

OSHA also proposed to amend paragraph (e)(3)(vi) which requires employers to update their written program of engineering controls every 6 months. The proposed amendment eliminated the 6 month requirements and requires updates only when necessary to reflect the current status of the program and current exposures. The proposal has been incorporated into the final amendments with a slight language clarification. There is no need to update the written compliance program if all exposures are under the PEL. (Note the explanation of the change in the proposal, 48 FR 26875, had a typographical error mistakenly referring to paragraph (e)(3)(ii) rather than paragraph (e)(3)(vi).)

Paragraph (e)(3)(i) of the 1978 cotton dust standard requires employer to establish a written program to reduce exposure below the PEL. It was OSHA's intention, of course, that this apply only to employers with exposures over the PEL. However, some misinterpreted the language to apply to employers who had no exposures over the PEL. OSHA proposed to clarify the language to indicate that only employers with exposures over the PEL need to have a written compliance program to reduce exposure below the PEL with engineering controls. That proposal has been incorporated in the final amendments. (Note that the provisions of paragraph (g) that requires all employers with cotton dust present to have a written program of work practices and those provisions remain unchanged.)

The 1978 cotton dust standard in paragraph (e)(4) requires that the effectiveness of all mechanical ventilation equipment be checked every six months and within five days after a production change. OSHA proposed to amend the language of the standard to require that the checks be made at "reasonable intervals." The basis for this proposal was OSHA's judgment that it was more appropriate to leave the exact frequency of such checks to the professional judgment of the plant engineer or other such individual designated by the employer to maintain the equipment (48 FR 26974). The proposed amendment drew very few comments. The ATMI endorsed OSHA's proposal to require such measurements be made at "reasonable intervals." It pointed out that the frequency of such measurements would depend on such

factors as the type and age of the equipment, the characteristics of the particular workplace, and no "hard and fast" rule could be established for the variety of circumstances found in the industry. The ATMI also pointed out that such a provision is consistent with the protection of worker health when periodic exposure monitoring continues to be required regardless of the cotton dust level (Ex. 208, p. 104–105). The ACTWU had "no objection to the proposed amendment of paragraph (e)(4) which would allow the measurements of the ventilation system to be conducted at 'reasonable intervals.' " (Ex. 279, p. 121)

Based on the evidence available, OSHA concludes that its proposal to amend paragraph (e)(4) to require that measurements of the effectiveness of the mechanical ventilation equipment be made at reasonable intervals is consistent with the Agency's desire to make the standard more performance oriented without sacrificing the protection of workers' health. Therefore, paragraph (e)(4) is amended to require that such measurements be made at reasonable intervals.

F. Use of Respirators

The standard requires respirators to be used under the following circumstances: (1) During the time period required to install or implement feasible engineering controls and work practices controls; (2) during maintenance and repair activities in which engineering and work practice controls are not feasible; (3) in work situations where feasible engineering and work practice controls are not yet sufficient to reduce exposure to or below the permissible exposure limit; (4) during work practices of "blow down" and "blow off"; and (5) whenever an employee requests a respirator. The standard further requires that the employer institute a respiratory protection program in accordance with applicable parts of 29 CFR 1910.134 and that the employer select respirators from among those approved by NIOSH under 30 CFR Part 11. The standard also includes a selection table which lists required types of respirators.

1. Changes to the Respirator Table

OSHA proposed no major changes to the respirator use and selection provisions. However, OSHA noted in its June 1983 proposal (48 FR 26972) that since the publication of the 1978 cotton dust standard, NIOSH has retested some "single-use" respirators and approved them as respirators with "replaceable" filters. Based on this action by NIOSH, OSHA proposed a technical change to update the standard and replaced the word "single-use" with the word "disposable" and noted that a "disposable respirator" means the filter element is an inseparable part of the respirator. Because there have been no significant changes in the construction and performance of these respirators according to the 30 CFR Part 11 MSHA/NIOSH respirator testing and certification requirements, OSHA did not propose to change the assigned protection factor of 5 times the PEL.

OSHA also noted in the proposal that because of their weight and bulk, self-contained breathing apparatus (SCBA) and combination supplied air respirator with escape SCBA are impractical and inappropriate for protection against cotton dust where only an air purifying respirator is needed. Their much greater protection factors are not needed because if the cotton dust exposure exceeds the PEL by more than 5 times, the condition is not immediately dangerous to life. However it is permissible to use a respirator providing a greater protection factor. Therefore, the employer could technically supply a heavier and more awkward to wear respirator when only a simpler, lighter one was needed. This is unlikely as a matter of practice because of the greater expense of the heavier respirator. Therefore, it was proposed that these respirators be deleted from Table 1 as required respirators.

NIOSH agreed that the proposed changes to the respirator section were appropriate and stated "at the present time, NIOSH views the changes OSHA has proposed in the respirator provisions of the proposed standard as useful. Users should find the requirements to be clearer." (Ex. 187–13) Carrol Bailey, a certified industrial hygienist and OSHA health supervisor for the South Carolina Department of Labor testified at the hearings that the proposed changes in the standard on the use of respirators "are largely technical in nature and do serve to update the regulations." (Tr. 1139)

Accordingly for the reasons stated the proposed changes are incorporated into the final amendments to the respirator table. To further clarify OSHA's intent, SCABs and supplied air respirators are moved from the body of the respirator table to a note. This does not change the legal situation. They still may be used, but this change is to indicate that OSHA does not believe they will be used very frequently and the OSHA is not, in the case of cotton dust, encouraging their use. (Their greater protectiveness will outweigh their heaviness and awkwardness in situations where there is high exposure to a carcinogen or in situations immediately dangerous to life and health.) However, there may be some situations where a supplied air respirator may be appropriate in the case of cotton dust where the employee does not need to move about. Therefore, the possibility of their use is eliminated.

The Minnesota Mining and Manufacturing Company (3M), a manufacturer of the "disposable" class of respirators, submitted written comments (Ex. 187–12) and testified at the Washington, DC hearings. 3M's representatives contended during the hearings that:

(1) NIOSH recognizes and judges disposable respirators equivalent to respirators with replaceable filters and OSHA should not limit the protection factor of these respirators to five.

(2) OSHA allows use of "disposable" respirators as protection against lead at a level 10 times the PEL. Thus, there is no justification to limit to 5 times the PEL for cotton dust.

(3) Fit tests are available and accepted by OSHA as viable means of assessing the facefit of this type of respirator. OSHA should not use outdated facefit criteria to limit the use of disposable respirators.

(4) The American National Standards Institute (ANSI) has recognized the equivalency of disposable and nondisposable respirators and have incorporated this equivalency in their respirator selection logic in published standards.

(5) Limiting the use of disposable respirators to a protection factor of five would force the cotton industry to purchase more expensive, less comfortable respirators and deprive employees from using the device that is the most accepted by the workers in the industry.

OSHA has carefully reviewed the evidence in the record on the respirator provisions and concludes that there is no justification for changing the protection factor for disposable respirators from 5 to 10 times the PEL. Although it is true that NIOSH recognizes and judges "disposable" respirators equivalent to respirators with replaceable filters, NIOSH's certification test does not test whether a facepiece fits the user and NIOSH does not assign a protection factor in the certification test but tests only filter efficiency and breathing resistance. Consequently, the NIOSH certification does not indicate whether the disposable respirator provides as much protection as a half mask when fit as well as filter efficiency are taken into account.

Lead and cotton dust are different air contaminants and the application and use of respirators for lead and cotton dust are also different. Under the current lead standard, biological

monitoring is required. The biological monitoring required by the lead standard, determining blood lead levels, will give a reasonably direct indication whether the respirator is working from the blood lead levels because it will give a reasonable indication of whether lead is getting into the breathing zone. Pulmonary function testing is not a direct measurement of the efficiency of the respirator because it does not indicate how much cotton dust penetrates the respirator and enters the breathing zone. Furthermore, the lead standard requires the use of respirators with high efficiency filters while the cotton dust standard does not have such a requirement at levels less than 10 times the PEL. The use of dust and mist filters instead of high efficiency filters is only permitted under a current temporary administrative stay of the lead standard.

The ANSI standard "Practices for Respiratory Protection, Z88.2, 1980" did not address the questions on protection factors (PF) provided by disposable respirators. All PF data on air-purifying respirators were developed on quantitative fit testing from respirators equipped with high efficiency filters only. Since there were no "surrogate" disposal respirators available which would not alter the fit characteristics of a disposable respirator, the ANSI respirator protection factor table was developed without any fit testing results from disposable respirators.

To assure proper protection, the facepiece fit must be checked by the wearer each time the respirator is worn. A simple positive or negative pressure test gives a rough indication whether a rigid respirator is working. The employee places his or her hand over the inhalation and exhalation valves and blows or inhales to determine whether air is escaping from the face seal. The disposable dust and mist respirators which are permitted in this standard have neither an inhalation of exhalation valve. Therefore, it is difficult for the user to perform a negative or positive pressure test on this class of respirators in a simple and effective manner to determine whether there is a gross leak.

An alternative to the positive or negative pressure test is to perform a qualitative or a quantitative fit test. Due to the design limitations of these respirators, quantative fit testing is not possible, and OSHA believes it is not appropriate to require the employers to conduct the saccharin QLFT each time the respirator is worn since it is time consuming and because of the nature of the hazard.

For those reasons, OSHA believes that it would be inappropriate to assign a protection factor of 10 to a disposable respirator for cotton dust protection. A protection factor of 5 for the class of disposable dust and mist respirators is the appropriate protection factor to provide an adequate margin of safety to overcome the fitting problem. OSHA further believes that at the present time virtually no employee in the textile industry is exposed to cotton dust at levels greater than 5 times the PEL for an eight hour period. The disposable respirators available in the market today are likely to be the respirator of choice, and the cotton textile industry would not be forced to purchase more expensive and less comfortable respirators.

2. Wage Rate Retention

The 1978 standard [29 CFR 1910.1043(f)(2)(v)] provides that whenever a physician determines that an employee is unable to wear any type of respirator, the employee shall have the opportunity to transfer to another job, if one is available, which involves exposure to cotton dust levels below the permissible exposure limit. In addition, the regulation, as originally issued, required employers to assure that transferred employees would not suffer a loss of earnings, other employment rights or benefits. This latter part of the paragraph is referred to as the "wage rate retention provision".

Both the ATMI and the ACTWU, in their posthearing comments, agreed that the evidence supported the inclusion of a wage rate retention provision in the amended standard. In identical statements, they said:

> As a response to these health-based concerns, it would be appropriate to include in the standard a rate retention provision applicable to employees who are transferred from an area in which dust levels exceed the PEL because of inability to wear a respirator safely and effectively. (Exs. 279, p. 75; 280 p. 75)

In 1981, the Supreme Court, in *ATMI v. Donovan*, 452 U.S. 490 (1981), struck down the wage retention provision of the regulation as promulgated, but left the job transfer provision in effect. The Court held that OSHA failed to provide a sufficient rationale for the wage retention provision because it did not explain how the provision was related to the achievement of a safe and healthful work environment (Id., at 537–538). The Court did not decide the issue of whether OSHA had the underlying authority to promulgate such a provision. The Court noted that there was some evidence on the subject in the record (Id., at 539, footnote 73).

The United States Court of Appeals for the District of Columbia Circuit upheld the validity of OSHA's Medical Removal Protection ("MRP") program for the lead standard in United Steelworkers of America, AFL–CIO v. Marshall, 647 F. 2d 1189 (D.C. Cir. 1980), *cert.* denied, Lead Industries Association Inc. v. Donovan, 101 S. Ct. 3148 (1981). Part of the MRP program for lead involved a wage retention provision for workers who transferred to other jobs or were laid off to avoid continued exposure to unacceptable levels of lead.

In response to the Supreme Court remand in ATMI v. Donovan, the ANPR of February 9, 1982 raised the issue of whether a wage retention provision (47 FR 5406) should be incorporated into the cotton dust standard. Among the comments received, some were in favor of the provision and others were opposed. After consideration of the comments submitted in response to the ANPR on the issue of wage retention, OSHA decided not to include such a provision in the proposed standard because the evidence available at that time was not sufficient to justify it. OSHA stated that the evidence available did not indicate that the provision would have a substantial impact on a significant population of employees and that the evidence then available did not indicate a clearly established link between employee health and the wage retention provision. The Agency also stated that it considered it sound policy not to become involved in determining wages and terms of employment (an area traditionally reserved to employers' personnel practices and the collective bargaining process) unless evidence established occupational health need. As a matter of broad policy, OSHA continues to subscribe to that view.

OSHA has received numerous comments and testimony in response to the proposal. Some evidence presented indicates that exclusion of the wage retention provision could cause workers to withhold information about symptoms of respiratory impairment, thereby posing risks to their health. A number of workers testified that because they have responsibilities which must be met and cannot afford drastic cuts in pay, they would be less likely to report symptoms of disease if they fear losing wages and benefits as a result of a health-related job transfer.

For example, Mr. Reese Boware said:

> I know of workers who have lied on the breathing test and questionnaires just because they feel that if they are transferred because of problems, they will be transferred

to a lower-paying job. Now this is bad for their health because they try to hide their breathing problems. These workers have told me that if their pay was for sure protected, that they would be happy to go to a less hazardous area. Nobody wants brown lung.

However, with prices as high as they are today, no person could afford a drastic pay cut. (TR. 1525–36)

Ms. Derenda Clements testified:

A lot of us are not going to get up there and tell you that they have got a breathing problem, because they do not want to lose that dollar and hour or dollar and a half an hour because they cannot afford it . . . (Tr. 515)

Mr. Samuel Shelton, another worker who testified, said:

If an employee were to be told that he did not have transfer rights with wage retention, they would be more apt not to report all their symptoms to the company, simply because they could not afford to be transferred to another department and take a cut in pay. (Tr. 1166)

Mr. O'Dell Rambo testified to the long lasting effects of wage cuts to older workers who are nearing retirement when he pointed out:

. . . a person's Social Security retirement could be greatly affected because of lower wages during the last five years of work that should have really been the highest earning years of his life. (Tr. 1512)

A number of physicians testified to workers' reluctance to reveal breathing problems. Dr. James Merchant conducted a number of epidemiological studies in the textile industry which involved medical evaluation and interviewing of several hundreds of cotton textile workers and evaluated many textile workers clinically at Duke University Medical Center and at the University of North Carolina. According to Dr. Merchant:

. . . individuals who have impairment who come in for evaluation . . . at least at that time, there was a great deal of apprehension in regard to their continued employment, if their employer was aware that they had obtained this evaluation.

Similarly, we observed on a number of occasions people who were quite symptomatic by observation in terms of respiratory disease, who would give completely negative questionnaires. And I think, in part, that was because of the fear that workers have that if they divulge symptons this in some manner may jeopardize their employment. (Tr. 336)

Dr. E. Neil Schachter stated in his testimony that in an environment where safeguards against job loss or salary loss do not exist, groups of workers in general and individual workers in particular are reluctant to give details of their illnesses. He said:

. . . (B)ased on my experience with clinical examinations of workers with byssinosis and with epidemiologic data available from workers in Columbia, South Carolina, I agree with the assessments made by ACTWU, the Brown Lung Association and Dr. James Merchant, that workers unprotected by rules safeguarding their employment in general and their wages in particular will not be willing to discuss their medical problems openly. These workers will thereby be at risk of having their medical problems worsen without appropriate intervention. (Tr. 530)

Dr. Robert Castellan testified about worker reluctance to participate in the NIOSH-sponsored industry-wide studies because of concern about what impact the results might have on their lives. He stated:

(W)e did have individuals who did show some concern at the beginning of the shift for their pre-shift examination . . . You know, we would discuss with them the situation. They would consent to participate. At the post-shift examination, some of these individuals, we were told by their fellow workers, did leave work without stopping by because they were concerned about what might get placed in their medical record." (Tr. 431)

There were a number of prehearing comments which initially opposed wage rate retention from ATMI and various textile companies. The reasoning was similar to that stated on OSHA's proposal (see Exs. 175–41 p 35, 175–24.)

ATMI and ACTWU have made a series of identical recommendations to OSHA on amendments to the cotton dust standard for textiles. (Exs. 279, pp. 7–76; Ex. 280, pp. 7–76.) These have been discussed throughout this preamble. Among their identical recommendations was that there be a wage retention provision in the cotton dust standard.

In support of its inclusion they stated:

. . . Under the Standard and its supporting rationale, an employee who works in an area where dust levels exceed the PEL is deemed to be facing an unreasonable risk of material impairment of health or functional capacity if he is not effectively utilizing a respirator. To avoid such a result, an employee who is assigned to an area where dust levels exceed the PEL and who is unable to wear a respirator should be transferred to an area in which cotton dust levels are below the PEL.

In order to make this health-based transfer requirement effective, the Standard should assure those employees who are unable to wear respirators effectively that they will not face a substantial economic penalty as a result of disclosing that fact. The Standard requires a physician to make a determination of the employee's ability to wear a respirator and provides for an opportunity to transfer to a position where dust levels are at or below the PEL if the employee is unable to wear any form of respirator. In order to make this determination, the physician must take into account the employee's report of any difficulty in breathing that he experiences when wearing a respirator. Moreover, in some cases, use of a respirator may be counterindicated from a medical standpoint because of other health problems, which may be entirely unrelated to cotton dust exposure. Information of this type must be disclosed to the physician if he is to make a properly informed and soundly based judgment regarding the employee's ability to wear a respirator safely and effectively.

As a response to these health-based concerns, it would be appropriate to include in the Standard a rate retention provision applicable to employees who are transferred from an area in which dust levels exceed the PEL because of inability to wear a respirator. (Ex. 279, pp. 74–75; Ex. 280, pp. 74–75.)

Both data from industry and the Centaur Report indicate that most areas of the industry are in compliance with engineering controls. Therefore, relatively few employees will be wearing respirators. Data which industry supplied indicated that relatively few employees are unable to wear respirators. Consequently a wage retention provision will not create major costs.

Considerable new evidence was presented at the hearing indicating a health need for limited wage retention provision. First, three knowledgeable physicians, as just discussed, testified of some employee reluctance to reveal information necessary for proper health care if the employee feared it might result in transfer to lower paying jobs. Second, the employee testimony brought to OSHA's attention a situation about which it had not been aware. Older employees are concerned that transfer to a lower paid area will not only reduce current pay but will also result in their social security pensions being substantially reduced if their last few years' salary is reduced. It is likely that older workers will comprise a large portion of those employees who would have to be transferred, and it is, of course, important that the health of older employees be maintained through appropriate medical surveillance.

In addition, OSHA believes it is good policy to encourage representatives of employees and employers to develop joint recommendations to OSHA to protect employee health. (OSHA is carrying out policies similar to this in the cooperative assessment agreements for arsenic and lead.) The ATMI and ACTWU have successfully developed identical recommendations of considerable merit supported by the record. The wage rate retention recommendation is an important part of these recommendations. OSHA encourages such joint recommendations for employee health protection and gives significant weight to such

recommendations, especially in areas where employee and employer representatives have considerable experience.

Therefore, because of the new health evidence and the recommendations of the ACTWU and the ATMI, OSHA is incorporating a limited wage retention provision which is sufficient to meet health needs. Paragraph (f)(2)(iv) provides that:

> Whenever a physician determines that an employee who works in an area in which the dust level exceeds the PEL is unable to wear any form of respirator, including a power air purifying respirator, the employee shall be given the opportunity to transfer to another position which is available or which later becomes available having a dust level at or below the PEL. The employer shall assure that an employee who is transferred from an area in which the dust level exceeds the PEL due to an inability to wear a respirator suffers no reduction in current wage rate or other employment rights or benefits as a result of the transfer.

G. Work Practices

The terms "blow down" and "blow off" are discussed in detail in this section under B. Definitions. The addition of the term "blow off" to this standard has necessitated changing paragraph (g)(4) of this section to read, in part:

> Where compressed air is used for cleaning, the employees performing the blow down or blow off shall wear suitable respirators. Employees whose presence is not required to perform the blow off or blow down shall be required to leave the area affected by the blow down or blow off during the cleaning operation.

This makes clear that the degree of evacuation depends on the extent of the cleaning operation. OSHA believes that this change, as supported by ACTWU and ATMI, meets and satisfies the concerns expressed by the witnesses because it makes clear that employees in areas where dust levels are raised by compressed air cleaning are required to evacuate the area. The requirement for appropriate respiratory protection for workers engaged in compressed air cleaning has been retained.

The 1978 standard requires that the work practice provisions of paragraph (g)(1–3) be met regardless of the level of employee exposure. These practices continue to be required because the operations of blow off and blow down, the use of compressed air for cleaning, and floor sweeping all increase the workers' exposure levels. Therefore, overexposure may result even though exposure monitoring may indicate that the PEL is not exceeded. OSHA did not propose to eliminate these provisions, and no comments were submitted recommending elimination.

Paragraph (g)(4) of the 1978 standard required that cotton and cotton waste be handled by mechanical means except where the employers can show that this is infeasible. Shortly after the standard was published, OSHA interpreted this provision by letter to mean that this requirement applied only when exposures were in excess of the PEL (Ex. 239, 240).

As the result of an oversight, OSHA proposed to amend paragraph (g)(4) to require mechanical handling when exposures exceeded the Action Level. The effect was to impose additional requirements on the employer in this area which was not OSHA's intention. Therefore, OSHA is amending paragraph (g)(4) by adding the words, "in areas where employees are exposed to concentrations of cotton dust greater than the permissible exposure limit" to indicate clearly where this provision is required. The net effect is that there is no change in the intent of paragraph (g)(4) from the 1978 standard.

OSHA also proposed to delete paragraph (g)(5) which requires that the employer "inspect, clean, maintain and repair" all engineering controls. Since the standard requires the employer to reduce cotton dust exposure to the level specified by the PEL and to check the effectiveness of the engineering controls at reasonable intervals, OSHA proposed to delete paragraph (g)(5) as a duplicative and an unnecessary specification requirement.

This proposal to delete paragraph (g)(5) was supported by the ATMI (Ex. 280, p. 105–107). They agreed with OSHA's reasoning in this matter and said that, "Where it is necessary to maintain ventilation equipment to achieve this objective, employers will do so" (Ex. 280 p. 105) and that such an incentive is particularly effective when periodic exposure monitoring is continued in all areas.

The ACTWU argued that OSHA should not delete Section (g)(5). They cited the testimony given by Dr. Morton Corn who said that "maintenance for non-productive aspects of the process ae last on the list." (Tr. 495) They also argued that dust levels are subject to variation and that annual or semiannual monitoring might not promptly detect a failure in the ventilation system.

OSHA has considered the comments by the ATMI and the ACTWU in this matter. Although it may be true as Dr. Corn suggests that maintaining non-production equipment generally is not a high priority item, some companies have individuals whose specific job responsibility it is to check and maintain the ventilation equipment (Tr. 522). Furthermore, the goal of the standard is to protect the health of workers by, among other things, reducing the exposure levels to the applicable PELs. Section 6(b)(5) of the Act specifies that "Whenever practicable, the standard promulgated shall be expressed in terms of objective criteria and of the performance desired." OSHA concludes that the requirement to meet the PEL provides adequate incentive to the employer to maintain the engineering controls in the proper working order. In addition, the requirement that the effectiveness of the mechanical ventilation be checked periodically will serve to ensure that once the PEL is achieved that it will be maintained and that the health of exposed workers will continue to be protected. Therefore, section (g)(5) is deleted from the final standard.

H. Medical Surveillance

The 1978 standard required that employees be provided with an opportunity for medical surveillance prior to initial exposure and annually thereafter. Employees who experience an FEV_1 decrement of 5 percent or 200 ml. on a first working day, who have an FEV_1 less than 80 percent of the predicted value, or who in the opinion of a physician have a significant change in their respiratory condition [paragraph (h)(3)(ii)] are to be provided with examinations every six months.

In 1983 OSHA proposed that an "Action Level," an exposure level equal to one half the PEL, be included in the standard. Most employees exposed to cotton dust at levels below the Action Level would be provided with an opportunity for medical surveillance once every two years. Regardless of the dust level, employers would still be required to provide an opportunity for medical surveillance every six months for those employees who meet the criteria outlined in paragraph (h)(3)(ii) of the standard.

Most of the physicians testifying at the hearing agreed that for employees exposed to dust levels below the Action Level, medical examinations every two years would be adequate (1983 Tr. at 57–58, 96–97). In response to a question on this matter, Dr. Hans Weill stated "my personal view is that at levels that low one could safely have a monitoring program of lung function and other indicators of respiratory health that was instituted for individual workers every second year." (Tr. 155) Dr. James Merchant, whose studies provided the dose-response relationship upon which OSHA relied, agreed that most workers

exposed to dust levels less than the Action Level "can probably be followed biennially without material increased risk of not detecting significant health effect." (Tr. 293). He did emphasize, however, that those employees who showed a loss of pulmonary function should continue to receive an examination every six months even if they are exposed below the Action Level (Tr. 293).

Dr. Neil Schachter was the only physician to disagree with the biennial medical examination schedule. He recommended annual exams for all exposed workers. However, he did agree that Dr. Merchant was "one of the most knowledgeable people in [the] field" and was "well qualified to render an opinion on that subject." (Tr. 584)

Both ATMI and ACTWU agreed in their post hearing briefs that this reduction in medical frequency was appropriate (Exs. 279 & 280). See also the discussion of the Action Level above.

Based on evidence and testimony, primarily the expert opinion of physicians who are specialists in pulmonary medicine, OSHA concludes that most employees exposed to cotton dust at levels below the Action Level can be followed by medical examinations every two years without increasing their risk of health impairment. Paragraph (h)(3)(i) is amended accordingly. The reduction in the frequency of medical examinations will help to create an incentive for employers to search for ways to reduce exposures to levels below the Action Level. However, employers will continue to be required to provide an opportunity for medical examinations every six months to employees who show evidence of loss of pulmonary function regardless of the dust level to which those employees are exposed.

Evidence and testimony in the record support the need for preplacement medical examinations. The record documents the fact that individuals, with or without prior cotton dust exposure, may have a severe reaction to exposure to cotton dust.

Dr. Robert Castellan, a member of the NIOSH panel, testified on this subject at the 1983 hearings. Dr. Castellan cited his experience with human test panels during the washed cotton studies. He said:

> In those exposures, we need to screen individuals before we allow them to fully participate in our exposures . . . and, what we do initially is screen them with a questionnaire and baseline spirometry . . . We would not allow them to participate further if they had greater than 30% decrement in FEV_1. We had approximately three who had that great a decrement. One of them was a great—somewhere in the upper 60's, a very severe reaction . . . The two [individuals] that I recall very well, because I happened to be there at the time, had no prior exposure to cotton dust. (Tr. 422–3)

Dr. James Merchant testified to the importance of the use of medical surveillance to detect a decline in lung function over time. Based on his experience and knowledge of the literature, he stated that such declines in lung function may occur within a period of a few weeks. Therefore, he emphasized the need for establishing "a baseline that is a pre-exposure baseline . . . and that provision, I think, needs to be maintained." (Tr. 307)

Dr. Robert Jones outlined the ways that pre-employment medical examinations could provide information to assist the employer in making appropriate placements. He outlined the benefits of such a program as follows:

> First, it could allow identification and protection of persons, who for any reason, were unusually susceptible to adverse effects of this dust. Simple prudence dictates that persons with active airways diseases, such as bronchial asthma, or with advanced and potentially disabling lung diseases of any cause, should not be assigned to particularly dusty jobs.
>
> It is also prudent to reassign away from such jobs if longitudinal surveillance shows the development of respiratory illness in a previously healthy worker. (Tr. 206–7)

Based on the testimony of these medical experts, OSHA concludes that the evidence supports the continuation of the requirement that initial medical examinations be provided prior to the initial assignment.

Paragraph (h)(2)(ii) of the 1978 standard requires that the FVC and FEV_1 be measured as part of the medical surveillance program. The amended standard continues these requirements and require that the FEV_1/FVC ratio must also be calculated as well. The information obtained from calculating this ratio will assist the physician in evaluating the health of the exposed worker by providing information specified in mandatory Appendix D III B. OSHA anticipates that the addition of the FEV_1/FVC ratio will provide no additional testing burden since both measurements are required by the 1978 standard. In addition, OSHA also has evidence in the record that this ratio as already provided routinely by consultants conducting medical surveillance (Ex. 271).

Paragraph (h)(2)(iii) has also been modified to make clear when the employee should be tested and to make it clear that the employee's exposure on the test day should be typical of the employee's day-to-day workplace exposure.

Paragraph (h)(3)(i) has been clarified to make it clear that the results of the standardized questionnaire are to be used to update the employee's Schilling byssinosis grade. This record contains evidence that at least the majority of workers are being regraded following each periodic examination. (Ex. 271, Ex. 175–60).

Paragraph (h)(3)(i) has been amended to indicate that periodic medical examinations be made available every two years to employees in cotton seed processing and waste processing unless they meet the criteria outlined in paragraph (h)(3)(ii) which specify more frequent exams if the employee has substantial change in lung function. Section (h)(3)(ii) provides for referral to a pulmonary specialist if the lung function decline is even greater. This is discussed at length in Section III of this preamble.

Paragraph (h)(5)(i)(A) requires that the employer furnish the employee with the physician's written opinion which contains "the results of the medical examination and tests." The final standard clarifies this requirement by specifying that the test results from the FEV_1, FVC and FEV_1/FVC ratio are part of the physician's written opinion.

I. Employee Education and Training

Paragraph (i)(2)(iii) of the 1978 standard requires employers to distribute to employees materials relating to the Act, the regulations, and the Cotton Dust Standard which are made available by the Assistant Secretary of Labor. It further requires that employees be provided with a training program designed to inform them of the health hazards associated with cotton dust, appropriate protective work practices and use of respirators, the basis and nature of the medical surveillance program, and the contents of the Standard and its appendices. Such a training program will ensure that employees are informed about the information they should know in order to work safely in cotton textile plants.

The Agency proposed to eliminate the requirement to distribute materials made available by the Assistant Secretary, on the grounds that "individual workplace conditions vary and employers can best determine the information most applicable to their specific work site." (48 FR 26974) No other provision of this paragraph was proposed to be amended.

The comments to the proposal and testimony presented at the hearings did not reveal a need in the case of this

standard to continue requiring that employers distribute training materials made available by the Assistant Secretary. Both the ATMI (Ex. 280) and the ACTWU (Ex. 279) agreed with OSHA's rationale for deleting this requirement from the standard and that this provision was not necessary to protect workers' health.

Based on the evidence in the record, OSHA concludes that the requirement to distribute OSHA supplied training materials is not necessary for the protection of workers' health. Therefore, the final standard has been amended to remove this requirement.

J. Signs

OSHA has made no changes to paragraph (j) Signs.

K. Recordkeeping

No changes have been made to the language of the recordkeeing provision in paragraph (k) Recordkeeping. However, other changes in the standard have very substantially reduced the number of records to be kept and the recordkeeping burden.

The medical examination frequency has been reduced by one-half from yearly to once every 2 years for employees exposed below the action level. A substantial number of employees are exposed below the action level and this will reduce the number of records which need to be retained for them by half.

Secondly, the monitoring frequency has been reduced from once every 6 months to yearly for employees exposed below the PEL. As virtually all employees are now exposed below the PEL, this reduces the number of monitoring records by 50%.

The Paper Work Reduction Act report submitted to the Office of Management and Budget calculates the reduction in recordkeeping burden hours and cost savings. Overall estimates of the cost savings of these changes are presented below in Section V.(F) of the preamble.

L. Observation of Monitoring

OSHA has made no changes to paragraph (l) Observation of Monitoring.

M. Effective Date/Extension for Ring Spinning of Coarse Count Yarns

1. Extension

The current OSHA cotton dust standard (29 CFR 1910.1043) requires that by March 27, 1984, all operations to which the standard applies must be in compliance with the permissible exposure limit using engineering and work practice controls. In the preamble to the 1978 OSHA cotton dust standard (43 FR 27350, June 23, 1978), the Agency presented a substantial amount of evidence to demonstrate the technical feasibility of the standard in the textile industry based on the evidence then available.

In keeping with the OSH Act's mandate that OSHA set occupational health standards which most adequately assure employee safety and health "to the extent feasible," beginning in 1981 as evidence of actual implementation of the cotton dust standard became available. OSHA undertook a further review of the feasibility of the standard. As part of this review, OSHA hired a consulting firm, Centaur Associates, to examine a number of issues including the current state of compliance and to review the technological feasibility of completing the compliance programs within the March 27, 1984 deadline specified by the standard.

After visiting 15 plants and interviewing numerous industrial engineers and manufacturers of dust control equipment, Centaur reported that textile experts generally consider the requirement (of the 1978 standard) to come into compliance with the engineering control provisions by March 27, 1984 to be feasible. The Centaur Report (Ex. 185) documented that, in 1982, a large percentage of textile operations were already in compliance with the permissible exposure limit. Moreover, as stated by ATMI (Ex. 280, p. 11), "most of the capital expenditures needed to achieve the PELs specified in the present standard have already been committed, and . . . the vast majority of cotton textile operations have largely been brought into compliance with the PELs."

Nevertheless, Centaur found that a problem existed for specific processes in the manufacturing of certain types of yarn to come into compliance with engineering controls by March 27, 1984. These problem areas were concentrated in ring spinning operations for high-cotton-content, coarse count yarn. These yarns are used in denim, duck, heavy terry cloth, and heavy industrial fabrics. Recent experience with these particular ring spinning processes indicates that ventilation systems may not always be effective and that this production equipment cannot generally be isolated.

Although it appeared that it might not be feasible for employers to lower dust levels to the permissible exposure limit by March 27, 1984 for high-cotton-content, coarse count ring spinning operations, it also appeared that these problems could be overcome in several years. Control technology, including open-end spinning, is rapidly advancing and compliance with the standard should be possible in all operations in the relatively near future.

Based on this information, OSHA proposed in its June 10, 1983 Federal Register notice (48 FR 26962) to extend the deadline for compliance using engineering and work practice controls found in § 1910.1043(m)(2)(ii) from March 27, 1984 to March 27, 1986. The extension applied only to ring spinning, spooling and winding of coarse (yarn count of 14 or lower), high-cotton-content (equal to or greater than 80%) yarn.

This proposal was discussed at length by some of the commenters and additional evidence and testimony were presented on this issue at the hearings. For example, Percy Thackston, Executive Vice President of the Bahnson Company, a supplier of dust control equipment to the textile industry, testified to the inadequacy of control equipment for these operations. Mr. Thackston indicated that for ring spinning through warping and including winding, twisting, spooling and beaming there has not been a major successful, predictable breakthrough in the dust control technology for these operations (Tr. 676). More specifically, he stated that:

> The experience of air handling equipment manufacturers indicates that the state of the art in machinery development and dust suppression systems does not permit assurance that a 200 microgram per cubic meter exposure limit can be achieved and consistently maintained for these areas when the textile product involves coarse count yarns, particularly of high cotton content. (Tr. 676)

Consequently, Mr. Thackston indicated the unwillingness of equipment manufacturers to guarantee the ability of their installed equipment to meet the PEL in these operations (Tr. 676). Therefore, Mr. Thackston supported a two-year extension of the compliance date for these operations so that textile manufacturers and equipment suppliers might have sufficient time to resolve dust control technology in the ring spinning of coarse count yarns (Tr. 678).

James A. King, Vice President of the Textile Manufacturing Division at Cone Mills Corporation, testified that while facilities engaged in the ring spinning of finer yarn counts have minimal problems complying with the 200 $\mu g/m^3$ PEL, those engaged in the ring spinning of coarser count yarns have a "monumental" problem of compliance (Tr. at 681). He identified three factors which contribute to the differences in ability to obtain the same compliance results when comparing finer and coarser count yarn spinning operations

(Tr. 681–682). First the rate of production of coarse yarns per spindle hour is significantly higher in terms of both length and weight delivered. Second, lower grades of cotton, associated with a higher non-lint content, are generally used in the production of coarser count yarns. Third, "the ring spinning frame does not lend itself to the installation of dust capture devices at these several dust release points. This is more critical in the case of coarse yarn spinning due to the fact that a greater quantity of fiber will pass each release point in a given period of time than is the case for finer yarns." (Tr. 682) Mr. King summarized his testimony by indicating that he was unaware of "technological developments of a feasible nature which can result in compliance with the 200 microgram per cubic meter PEL when spinning coarse count cotton and cotton blend yarns" by the effective date of March 27, 1984 (Tr. 684, 707).

Additional testimony on this issue was provided by Labor Commissioner John Brooks of North Carolina who also identified the spinning of coarse count yarns as an area that may encounter technological difficulty in meeting the PEL (Tr. 1274). During questioning, he stated that these operations were the primary component of spinning areas which are not in compliance with the PEL in the State of North Carolina and concurred that a two-year extension would be reasonable (Tr. 1283).

There are several possible solutions to the dust control problem, including the rapid advent of open-end spinning systems. This relatively new technology reduces the dust levels because the fibers are spun within enclosed rotors and ventilation is designed into the machinery. There are, however, some current problems with open-end spun yarn. Mr. James King testified, for instance, that:

> The coarser count yarns produced by open-end spinning, at this time, are not acceptable for all end use products. Open-end spun yarns are still weaker than the equivalent yarn spun on ring spinning. If high strength is an end use requirement, than it becomes necessary to select cotton fibers which are themselves stronger than those used for ring spinning. Unfortunately, these fibers are not readily available in quantities which would be required for a complete change to open-end spinning for a company such as Cone Mills Corporation or for any other major cotton user in the industry. (Tr. 681)

Thus, open end-spun yarn is currently weaker than ring-spun yarns, and broken ends in weaving operations may sometimes result in negative wear and appearance properties in the finished fabric. These factors have led some garment manufacturers to insist that fabric for their apparel be made with ring-spun yarn.

Despite these factors, open-end spinning appears to be the most promising technological means of achieving compliance with the 200 $\mu g/m^{3}$[13] PEL in the spinning of course count yarns. While the primary advantage of open-end spinning has been increased productivity in terms of faster spinning speeds, more recent developments in open end spinning equipment has produced a yarn with greater break strength and fewer imperfections. Mr. King also pointed out that improvements in open-ended spinning have been made which have expanded end use potential for coarse count cotton and cotton blend years (Tr. 684). He also stated that his company was planning to convert from ring spinning to open-ended spinning for a major part of denim yarn production and that such plans would be finalized after the International Textile Manufacturers Association show when the latest technology would be available (Tr. 685). During questioning, Mr. King further acknowledged that open-ended spinning equipment had progressed during the last several years and expected to see further advances in the machinery (Tr. 702).

In addition, an article in *American Textiles* pointed out that rapid advances in open end spinning technology are overcoming these problems. It stated that:

> An an example of how refinements can produce effectively higher speeds, Platt Saco Lowell developed recently a new side feed spinning unit for its Rotospin model 887 and 883 machines. The primary thrust of PSL's research was evidently to produce a yarn with greater breaking strength . . . . They were eminently successful in this (break-strength increased 13 percent), but at the same time the unit produced 70 percent fewer imperfections per 1,000 yards and 17 percent lower coefficient of variation in the yarn parameters. (Ex. 264)

It added:

> * * * improvements in the break strength of open-end yarns have been the main advance that has allowed some denim producers to use [open-end] yarn in the warp and in the filling. Swift Textiles in Columbus, Ga., is doing this along with other companies, and many more are evaluating machines that will spin only warp denim yarns (WestPoint Pepperell's Lindale, Ga., mill). (Ex. 264)

In summary, open-end spinning is more productive than ring spinning operations: new generations of open-end spinning machinery have improved yarn strength and decreased imperfections in finished fabric; and some denim producers currently are using open-end spinning for coarse count cotton yarn with success. Technology is developing rapidly in this area. Consequently, OSHA believes that by 1986 when the extension expires, new equipment will be available to meet the desired wear and appearance properties in the finished fabric and to achieve compliance with this standard.

The posthearing briefs of both the Amalgamated Clothing and Textile Workers Union (Ex. 279) and the American Textile Manufacturers Institute (Ex. 280) recommended, based on the above evidence, that the two year extension proposed by OSHA be granted but with some slight modification to the specifications that OSHA originally proposed for the yarn operations to be covered. For instance, under the proposal, the extension of the compliance date in ring spinning operations would apply where the yarn count is 14 or below and the cotton content is 80 percent or greater. Some commenters felt that these criteria did not encompass the range of ring-spun yarns as to the feasibility problems found to exist and suggested modifications. The testimony of Percy Thackston (Tr. 689) and James King (Tr. 684, 699) pointed out that a somewhat broader range of criteria for the yarn was needed.

Mr. Thackston noted that because the presence of "finishing materials" used on synthetic fibers (or the fibers themselves) may contribute to high dust levels (Tr. 678) and because the analytical method does not distinguish between "cotton dust" and synthetic fibers and/or finishing materials (Tr. 678), the feasibility problems in the processing of coarse count yarns in ring spinning operations are not limited to situations where a high cotton content is involved, but extend to cotton/polyester blends as well. During questioning, Mr. James King similarly stated that Cone Mills had difficulty complying with the PEL in the ring spinning of coarse count yarns in the 50/50 blends in the 13–21 count range (Tr. 699). Therefore, as noted in the ACTWU and ATMI posthearing submissions.

> * * * while the problem is most severe with coarse count yarns having a cotton content of 80 percent or above, the feasibility problems exist in blends having a lower cotton content as well. This is particularly true as the coarseness or the yarn increases. (Ex. 279, 280)

These submissions also pointed out the proposal's exclusion of beaming and warping operations following ring spinning (See discussion Ex. 279, 280, pp. 25–26). OSHA agrees that the feasibility problems associated with controlling dust levels when coarse count yarns are ring spun extends through the beaming

and warping operations and that the exclusion of these operations from the two-year extension of the compliance date was inadvertent.

ACTWU and ATMI concurred that compliance with the 200 $\mu g/m^3$ PEL was generally not feasible by March 1984 in coarse count ring spinning operations. Further, they agreed that the feasibility problems exist in the spinning of cotton/synthetic blends as well as high cotton content yarns. However, at any given yarn count, the feasibility problems become less severe as the cotton content of the yarn decreases. They further suggested that OSHA establish the following sliding scale for the yarn count threshold which would trigger application of the compliance date extension:

- Where the average by weight of the yarn being run is *100 percent cotton*, the extension should apply where the average yarn count by weight is *18 or below*.
- Where the average by weight of the yarn being run is *80 percent or more cotton*, the extension should apply where the average yarn count by weight is *16 or below*.
- Where the average by weight of the yarn being run is *50 percent or more cotton*, the extension should apply where the average yarn count by weight is *14 or below*. (Ex. 279, 280, p. 28)

They also suggested that:

Since it is quite common to run a number of different yarns in the same area, OSHA should provide a method (in an Appendix, if not in the Standard itself) for determining the *average cotton content* and the *average yarn count* of the yarns being run in the relevant operation or monitoring area. The most rational approach to making these determinations—an approach that is consistent with general practice and understanding in the industry—is as follows:

The *average cotton content* should be determined by dividing the total weight of cotton in the yarns being run by the total weight of all the yarns being run in the relevant work area.

The *average yarn count* should be determined by multiplying the yarn count times the pounds of each particular yarn being run to get the "total hank" for each of the yarns being run in the relevant area. The "total hank" values for all of the yarns being run should then be summed and divided by the total pounds of yarn being run, to produce the average yarn count number for all the yarns being run in the relevant work area. (Ex. 279, 280, pp. 28–29)

OSHA believes that these suggestions are well taken for the reasons given. Therefore, it has incorporated these recommendations into the compliance date extension. In addition, for clarification purposes it has incorporated these definitions of average cotton and yarn count in the standard.

In addition to presenting criteria for the basis of the extension of the compliance date in coarse count ring spinning operations, in their posthearing briefs both ACTWU and ATMI suggested that it would be appropriate to require an employer utilizing the extension to comply with additional conditions to provide additional health protection to employees working in those areas covered by the extension. The suggested conditions were as follows:

- An interim PEL 350 $\mu g/m^3$, to be achieved through use of engineering and work practice controls, should apply in areas covered by the extension. Respirators should be worn by employees in such areas where necessary to assure that their time-weighted average exposure to cotton dust does not exceed 200 $\mu g/m^3$.
- Within one month of the effective date of the revised Standard, employers should notify OSHA of the locations of their specific work areas (e.g., ring spinning at a particular plant) that are covered by the compliance date extension.
- Within six months of the effective date of the revised Standard, employers utilizing the compliance date extension should revise their compliance plans, where necessary, to identify the steps they plan to take in order to reduce cotton dust levels to 200 $\mu g/m^3$ through the use of engineering and work practice controls by March 1986.
- Medical surveillance should be provided semiannully to all employees working in areas where the compliance date extension is being applied.
- For areas in which the compliance date extension is being applied, a physician should individually review the test results of employees whose FEV_1 declines more than 10 percent over the work shift or whose FEV_1 is less than 80 percent of the predicted value. (Ex. 279, 280, pp. 30–31)

OSHA has carefully considered these recommendations for the short transitional period before full compliance will be achieved in this sector. As discussed in the wage retention section, OSHA wishes to encourage unions, employers and others to develop cooperative recommendations for OSHA. OSHA gives such recommendations considerable weight and has done so in this document. However, no notice was given to the public of several of these transitional recommendations. In some cases they will divert resources from achieving full compliance, and OSHA believes that they are included already by existing protective provisions of the standard. For these reasons and because such transitional provisions will be in existence for such a brief period, OSHA has not incorporated some of the transitional recommendations into the standard.

The recommendation for a 350 $\mu g/m^3$ interim level had never been proposed nor discussed during any of the hearing process. The recommendation was not made until the last date for post hearing comments limiting the possibility for public comment. In addition, OSHA would have to permit some delay of the effective date of this recommendation as a practical matter, to permit time to install necessary equipment. Consequently, the actual provisions would be effective for a very brief period. Further, as discussed above, new, more efficient and more protective open-end spinning equipment is being developed. OSHA believes employers should be encouraged to install such fully protective equipment as soon as possible and concentrate their engineering and industrial hygiene resources on this goal. It would be counterproductive to encourage efforts and resources to be spent on less protective interim measures. The standard still requires the employees to be protected to the 200 $\mu g/m^3$ level with respirators and engineering controls in the short interim period. Also the interim requirement of the 1978 standard requiring the achievement of 1000 $\mu g/m^3$ with engineering controls is being retained until March 27, 1986. That level is being interpreted as a respirable dust level which is more directly related to employee health. (See the discussion under waste processing.) The specific requirement is now located in § 1910.1043(m)(2)(ii)(E) and not in Table Z–1 of § 1910.1000.

OSHA has adopted the joint recommendation that an updated compliance plan be completed before the March 27, 1986 deadline for installation of controls. First, this will serve to identify the steps that the employer will take to achieve compliance with the 200 $\mu g/m^3$ level by the March 27, 1986 extension date. Second, this will help to ensure that employers meet that date and will encourage employers to utilize their engineering and industrial hygiene resources to come into compliance with the standard. Because of the date which this standard is issued, the date for completing the plan has been set at February 13, 1986 and not the date recommended.

Two of the transitional recommendations suggested changing the medical provisions for employees in the areas covered by the extension. Essentially, these recommendations add one extra medical exam and somewhat decrease the reduction in lung function needed for employees to be referred to a pulmonary specialist. The medical

provisions of the 1978 standard were carefully devised to protect employees: each employee received an annual medical exam; certain decreases in lung function led to semiannual medical exams; and greater decrements in turn, led to referrals to pulmonary specialists. These provisions were devised with the knowledge that many employees would not be protected by engineering controls for up to four years and were designed to protect those employees during that time. The extension essentially extends that period for up to two years for relatively few employees. OSHA believes that the existing medical provisions protect these employees for the reasons stated in the 1978 preamble and that it would create confusion to change the medical surveillance requirements for a few employees for a brief period.

OSHA believes that the recommendation that employers whose operations are covered by the extension notify OSHA of such locations is unnecessary. Most of the facilities affected by the extension are located in North and South Carolina, and both of these states have state plans with cotton dust programs. Furthermore, state officials are already knowledgeable of the kinds of spinning operations located in textile plants in their states. This transitional provision requiring notification would therefore be duplicative paperwork discouraged by the Paperwork Reduction Act.

It should be noted that OSHA granted a temporary extension of the compliance deadlines for the ring spinning of high-cotton-content coarse count yarns from March 27, 1984 to September 27, 1984 to permit the Agency to have time to complete its review of the record and to make appropriate final decisions (49 FR 6717, February 23, 1984). It later extended the stay (49 FR 46737; 50 FR 14698). This discussion represents OSHA's final conclusions.

2. Effective and Start-up Dates

The 1978 cotton dust standard became effective for the textile industry on March 27, 1980 with startup provisions of all paragraphs except engineering controls at various dates in 1980 and 1981. These amendments change none of those startup dates or effective dates, and they are reprinted unchanged to notify employers and the public of the dates that they were required to achieve compliance and of this continuing obligation. Employers were to have achieved compliance with the engineering control provisions by March 27, 1984. That obligation remains unchanged except for ring spinning of high cotton-content, coarse yarns discussed above and is reprinted unchanged to notify employers of this continuing obligation.

The amended provisions of § 1910.1043 take effect on January 13, 1986. On that date, employers are to commence complying with the provisions as amended. Until that date, employers are to comply with the unamended provisions of § 1910.1043 as currently published in the Code of Federal Regulations (1984 and 1985 editions which are identical in this respect) subject to the existing stay for ring spinning of high-cotton content coarse yarns. If the amended provisions are not in effect because of stays or judicial action, then the unamended provisions will remain in effect. It is the intention that there remain no gaps in coverage and that the existing provisions not terminate unless the new provisions are in effect.

There is no separate start-up date with one exception. The one exception is that a startup date six months after the effective date is provided for medical surveillance in cotton seed processing and waste processing. This is discussed above.

N. Washed Cotton

The 1978 standard excluded "washed cotton" as defined from all provisions of the cotton dust standard. Washed cotton was defined as "cotton which has been thoroughly washed in hot water and is known in the trade as purified or dyed." (43 FR 27395) Reasons for this exemption were discussed in the preamble (43 FR 27382). The strongest support for the exemption came from certain studies by Dr. Merchant and colleagues which indicated that cotton which was thoroughly washed, as in preparation for medical uses, was demonstrated to have reduced levels of biologic activity. Specifically, cotton washed in this manner was shown to have little or no effect on the pulmonary function of human test subjects in laboratory trials. It was not determined whether the reduction in respiratory response was due to reduction in the quantity of dust remaining in the cotton, or whether the washing process had eliminated contaminants. Steamed and autoclaved cottons were not exempted because the study indicated that biologic activity remained after cotton was treated with those processes.

The definition of washed cotton provided in the 1978 standard presented two problems. First, it was ambiguous as to the exact washing processes which would produce non-reactive cotton. The only washing process which was clearly covered by it was the severely washed cotton tested by Dr. Merchant, and that yielded fiber which was not suitable for spinning and weaving operations. Second, although "purified or dyed" cotton was exempted, it was not clear what cleansing processes must be included to qualify cotton for exemption.

The promising results of the Merchant studies kindled interest in cotton washing as a potential means of compliance with the 1978 standard. Further research was needed to establish washing parameters which would both protect the health of workers handling washed cotton and yield fiber which could be processed in textile mills.

Consequently, the "Washed Cotton Task Force," formally the "Industry/Government Task Force on Washed Cotton Evaluation," was formed in 1980. It is composed of representatives from the U.S. Department of Agriculture (USDA), the National Institute for Occupational Safety and Health (NIOSH), the Amalgamated Clothing and Textile Workers' Union (ACTWU), the American Textile Manufacturers Institute (ATMI), National Cotton Council (NCC) and Cotton Incorporated. Major funding during the past three years for byssinosis research came from Cotton Incorporated ($5 million), and from USDA ($15 million). Of this total, $6–7 million has been spent on washed cotton (Tr. 828–831). The purpose of the research was to develop processes which would produce cotton which could be worked in textile mills but would not cause the acute symptoms of byssinosis.

The USDA Cotton Quality research facility at Clemson, South Carolina has been the center of the Task Force's human subjects exposure studies. This facility has provided exposure chambers, and monitoring devices for the various trials where human subjects were exposed to cotton washed through various processes to test to see if it created any acute reaction. The cotton was processed there, as it would be in typical mills and also tested for processability.

Cotton procurement and washing has been done through Cotton Incorporated. They have tested various types of cotton on various washing processes. The various washing sites and methods are described fully in the Task Force's statement (Ex. 205B) and oral testimony. (Tr. 833–841)

The method of selecting the human test panels for the washed cotton studies was described as follows:

> Several times since the Clemson cotton dust work was begun, volunteer human subjects have been selected. In general, these selection processes have begun by soliciting

volunteers from the general public and excluding those with respiratory or other medical illnesses which would contraindicate participation. Next, the remaining volunteers have been exposed to cardroom cotton dust (1mg/m³ by vertical elutriator) for six-hour periods. Spirometry has been performed immediately before and after the six-hour exposures, and only subjects who have had an FEV_1 decrement of at least five percent attributable to these cotton dust exposures have been selected to participate in the actual studies . . . In the Clemson experience, approximately 25–30% of exposed volunteers have at least a 5% acute reduction in FEV_1 attributable to six hours of exposure to 1 mg/m ³ vertical elutriated cardroom dust . . .

The study subjects are thus not a random selection of individuals. They have been specifically selected to be relatively sensitive to the acute bronchoconstrictor activity of cotton dust (but not so sensitive as to preclude safe participation—a few with very large acute reductions in FEV_1 have been excluded during the selection process). Only about half had ever worked in cotton mills, and very few gave a history of having had classic byssinosis.

The 1982 ANPR (47 FR 5906) requested comments on how washed cotton should be defined, whether a performance standard keyed to respiratory effects was feasible and appropriate, and whether health or economic effects could be anticipated as a result of changing this definition. There was little public comment on these points.

The Amalgamated Clothing and Textile Workers Union (Ex. 175–36) and the Brown Lung Association (Ex. 175–43) generally opposed change in the definition since research was still in progress.

Those persons commenting in favor of changing the definition indicated, generally, that it should be linked to performance, and that it should be more flexible than the existing provision. American and Efrid Mills suggested a separate definition for "raw washed cotton yarn" (Ex. 175–51). The National Association of Hosiery Manufacturers favored the use of standard, accepted terms, such as "dyed" "scoured", and "bleached" as opposed to a performance definition (Ex. 175–49).

The most substantive comments came from the Washed Cotton Task Force (Ex. 175–44). Those comments described research completed, underway and planned, and provided data on human respiratory response to washed cottons. However, that submission did not include the specific recommendations of the Task Force because research had not been completed. They indicated that the washing research and exposure trails are intended to find ways to eliminate *acute* effects of cotton dust exposure. This effort is somewhat complicated by the fact that the causative agent of byssinosis is still unknown and it is also an object of current research.

Thus, comments received in response to the Advance Notice of Proposed Rulemaking showed a need to pursue a better definition of washed cotton, but provided little new information.

When OSHA issued its June 10, 1983 proposal, it had not received the recommendations of the Washed Cotton Task Force. Consequently OSHA was not in a position to expand the definition of washed cotton, to other processes which would be workable and safe for employees. OSHA stated, however, that if it received evidence of such processes during the public comment period it would consider such processes for inclusion in the final standard definition of washed cotton. The definitions proposed in the 1983 proposal were:

(1) Cotton which has been commercially prepared for medical use (by heating to 270°F with 0.6% caustic solution, washed with soap and tetrasodium pyrophosphate, bleached with 0.1% solution of sodium hypochlorite, and scoured with sulfuric acid at pH of less than 2.0, then washed to a pH of 6.0 to 7.0) or

(2) Cotton yarn or thread which has been scoured in a caustic bath and dyed in a hot, water-based solution.

These washing processes were the ones reported by Dr. Merchant, as not causing acute effects. It was hoped that the Washed Cotton Task Force and other witnesses would provide details on additional acceptable washing methods, and that these could be incorporated in the standard.

The Washed Cotton Task Force submitted its recommendations as comments with extensive supporting documentation on August 26, 1983 (Ex. 190–10). This was before the public hearing and gave adequate notice to any interested member of the public. The members of the Task Force were available to answer questions at the public hearings on OSHA's proposal.

The specific recommendations of the Task Force were the following:

I. Since normal scouring, bleaching, mercerizing and dyeing are more severe than the washing procedure evaluated in the "Tripartite Studies," cottons processed by these processes should be considered "washed cotton" and continue to be exempt from the standard.

II. OSHA should consider as 'washed cotton' cottons that have been (1) classed as *low middling* light spotted or better, unless spotted, tinged or yellow-stained (described in The Classification of Cotton. USDA, AMS, Agriculture Handbook No. 556, . . .); and (2) washed on a rayon rinse system or a continuous batt system as used, evaluated, and described . . . in our studies and at least 28°C with a wetting agent and at a minimum 40:1 water to fiber ratio. Precaution should be taken to limit bacterial growth and endotoxin accumulation in all baths. If these cottons are being processed, the only requirement under the cotton dust standard should be medical surveillance, every year. The Task Force also recommends that environmental monitoring be conducted in mills using cotton.

For cottons classed below *low middling* and all cottons classed as spotted, tinged, or yellow-stained, the dust level should be below 500 micrograms/m³, and they should be at a minimum bleached before being considered "washed cotton" and subject to medical surveillance requirements.

The Washed Cotton Task Force's testimony was submitted in written form and summarized orally at a hearing held in Washington, DC on September 23, 1983. As noted above, two general recommendations were presented.

The basis for these recommendations was the testing results from human subject exposure trails. The Task Force tested various grades of cotton, originating from several growing areas. It examined at least four washing systems, using varying wash parameters (temperatures, water-to-fiber ratio, additives, etc.). After washing, the cotton was taken to the USDA Cotton Quality Research Center, at Clemson, South Carolina where it was processed on typical yarn production equipment. The dusty atmosphere thus generated was then blown into the rooms where test panels were exposed to it. The acute reaction of the exposed persons was then measured with pulmonary function tests, and the results were compared to that of control test panels.

For some types of cotton and some washing processes, the test panels had no acute reaction: their pulmonary function was the same as unexposed control subjects. For other tests, their acute response was less than for unprocessed "raw" cotton, but they showed measurable differences when compared to unexposed controls.

The first recommendation was that an exemption be continued for mercerized, dyed and bleached cotton on the grounds that treatments associated with these processes were more severe than washing procedures evaluated by the group (Ex. 205B). In the course of the oral presentation, the Task Force was asked to provide information specifying the parameters for those three processes. That information was submitted to the Docket on October 28, 1983 (Ex. 256).

The Task Force supplied descriptions for typical processes: continuous warp mercerization, reactive dye (hot), vat dye (reduced), vat dye (pigment), and dye (sulfur). Scouring and bleaching

were also described. These are summarized in the following table:

PROCESSING DESCRIPTIONS

Process	Temperatures	Additives
Mercerization	160 °F to 200°F	Caustic soda.
Scouring	200 °F	Alkali: Soaps.
Bleaching	170 °F to 200°F	"Bleaching Chemicals".
Reactive dye (hot)	120 °F	Dye, soaps.
Vat dye (pigment)	140 °F to 180°F	Dye, soap.
Vat dye (reduced)	140 °F to 180°F	Do.
Dye (sulfur)	160 °F to 180°F	Do.

Note.—All processes are water based. Scouring and bleaching precede all processes.

The bleaching, mercerizing and scouring processes preceding dyeing are extensive, and in terms of the temperature and chemicals applied, they approach the severe washing specifications used in the original washed cotton studies. More important is the fact that they exceed the specifications for successful washing developed through more recent research which resulted in no reactivity. These factors are the basis both for the recommendation of the Task Force that scoured, bleached and dyed cotton and mercerized yarn be exempted from all provisions of the cotton dust standard and for OSHA's conclusion that cotton subject to the processes remain exempted from the standard.

The second recommendation of the Task Force is that certain types of washed cotton be partially exempt from the standard. It is complex, with several variables to be examined. Specifically, cotton grades or classifications, washing systems and bacterial contamination of wash water must be considered in addition to water temperatures, water volumes, and chemical additives.

Cotton Grades and Byssinosis

The USDA establishes a uniform grading system for cotton; it was presented in summary form in the Task Force's testimony (Ex. 187–19, Attachment 2 Table 3). Characteristics of the cotton include average fiber length, micronaire, and color. Bacterial contamination affects cotton color, giving it a yellow cast.

In effect, the panel recommended that a greater degree of exemption for washed higher grade cotton than for washed lower grade cottons. This is based on the acute reaction of test panels exposed to washed cottons of these two types. In both cases, continued medical surveillance is recommended to ensure that no long-term health effect is incurred.

Two studies in the series reported by the Task Force are relevant here. Study number MQ109 tested cottons of varying grades from three growing areas. The lowest grade of cotton, identified as "C43", "T43", and "M43" usually elicited the greatest decrement in $FEV_{1.0}$ among the test panels.

The high variation in pulmonary reaction shown in these tests led the Task Force explicitly to test "worst case cotton"—that is, fiber which was selected for its high levels of bacterial contamination, as indicated by its low grade and growing area, and large decrement in FEV_1. In these tests, large reductions in FEV_1 occurred even where cotton was washed, bleached and scoured on the continuous batt washing system. The minimum reduction in FEV_1 shown (−2.1%) was greater than one type of unwashed California cotton and only slightly less than one type of unwashed Texas cotton. Thus, the study demonstrated that washing even at high temperatures (93°C was used in these trials, with a 40:1 water-to-fiber ratio) does not render certain types of low grade cotton completely harmless. Depending on the specific wash conditions, potency was reduced by at least two-thirds, and by as much as ninety percent. Washing greatly reduces but does not eliminate, this cotton's ability to cause a drop in $FEV_{1.0}$. The residual activity is a matter of some concern, and for this reason, the Task Force recommended that lower grades of cotton be only *partially* exempted from the standard, and that medical surveillance be continued where washed cotton is used.

Washing Systems

The Task Force recommended that exempted cotton be washed on a rayon rinse system, or a continuous batt system. Trials using a wool scouring system were less successful, as were washing tests which employed the batch kier process. (The batch kier system is used in dyeing operations. In the batch kier tests, part or all of the lack of success was attributed to difficulty in sufficiently wetting the cotton. When cotton is dyed in this equipment, it is pre-processed, and there is less difficulty in obtaining uniform wetting).

Tests results reported in Exhibit 187–19 indicate various degrees of effectiveness for the different washing systems under varying conditions. Continuous batt washing consistently was more effective than other methods in eliminating or minimizing reductions in function. However some decreases in FEV_1 in the test panel were still statistically significant for some types of cotton. (They were reported in the series of tests labeled MQ101). The Task Force stated:

> * * * [E]xposure to the hot scoured and bleached cotton * * * again yielded no response. All other washing treatments reduced the bioactivity of card-generated dust and * * * several gave results which were statistically no different than no effect.

Washing on a continuous batt system at high temperatures, with or without scour and bleach, in some cases eliminated all reactivity and in all cases reduced but did not always eliminate the respiratory response. Thus, the continuous batt system provides good results in many tested circumstances, although it has not been documented that it will do so for all types of cotton, nor with every combination of temperature and other variables. In these tests, cotton washed at 60° with a 40:1 water-to-fiber ratio produced responses which were not significantly different from "no response".

The ability of the rayon rinse washing system to mitigate or to eliminate the reactivity of cotton dust was noted in the Task Force's testimony. This portion of the testimony was supported with an extensive study by Dr. Brian Boehlecke, whose research report was included as an appendix to Exhibit 187–19. Dr. Boehlecke tested acute human pulmonary response to cotton washed using the rayon system, and found that, for the test panel as a whole, "exposure to washed cotton dust in concentrations up to 1 mg/m³ appeared to result in pulmonary function response no different statistically from that to no dust exposure." (Ex. 187–19, Appendix B, page 23) Wash temperature used in this test was 68°C, similar to wash temperatures tested in the continuous batt process.

Washing Temperature

The Task Force recommended a washing temperature of "at least 28°C with a wetting agent and a 40:1 water ratio." The basis for this recommendation in research is not clear. Only one trial was reported in which a 28°C wash was used (MQ79–3). In that trial, a 65:1 water-to-fiber ratio was used.

Eight wash-only trials which used the continuous batt or the rayon rinse system are described in Exhibit 187–19. Of these, none were conducted at a water-to-fiber ratio of less than 40:1. Only three trials produced response-free cotton, i.e., MQ111–B, MQ101, and MQ79–C.

These data are too few to make definitive statements about all combinations of effective washing treatments. Combinations of lower water temperature and lesser water volume may be proved effective, but

they are not described in the Task Force submission nor in other evidence presented for OSHA's consideration.

The single washing experiment at 28 °C does not supply enough evidence to indicate that temperature this low sufficiently eliminates reactivity. The supporting study, appended to the testimony, indicates a slightly higher residue of endotoxin than in cotton washed at higher temperatures. Further research on this 28 °C washing may later lead to an expansion of the washed cotton criteria. For the present, however, the evidence is inadequate to support an exemption of cotton washed at 28 °C with a 40:1 water-to-fiber ratio.

In the Task Force testimony, it is clear that the temperature and the water-to-fiber ratios recommended were to be considered minima, and that minimum levels for each variable should not necessarily be paired in practice. In response to a question during the hearing, Dr. Phil Wakelyn, chairman of the Task Force, said that a temperature of "50 °C or above would be a more prudent recommendation." (Tr. 885) in further response to the question, it was pointed out that the influence of the combination of temperature and water-to-fiber ratio was not known although the water-to-fiber ratio appeared not to be "all that critical", and that the proper ratio might vary with the wash system being used; i.e. higher for the rayon system than the continuous batt.

OSHA concludes, based on reviewing all the data and recommendations, that the minimum criteria for meeting washed cotton requirements of the standard are 60 °C and a 40:1 water to fiber ratio. That is the lowest combination which consistently produced no reactivity in the continuous batt system. Higher temperatures and/or higher water ratios which provide more protection are permitted.

The Task Force also recommended that only the better grades of cotton (low middling, light spotted or better not spotted, tinged or yellow stained) be exempted from the PEL, and that an exposure limit of 500 micrograms be established for bleached, washed cotton of lower grades. OSHA concludes this recommendation takes into account the greater reactivity of humans to the lower grade cottons in most of the washing tests.

The Task Force recommended that continued medical surveillance is needed for washed cotton which is not medical grade or dyed because the tests were just for acute reactivity. Consequently, medical examinations are needed as a backstop to make sure that long term chronic effects do not develop when washed cotton is used. OSHA agrees with this recommendation and reasoning. The Task Force recommends that scoured, bleached and dyed cotton, mercerized yarn and medical grade cotton should be exempt from all provisions of the standard including the PEL and from medical surveillance. OSHA agrees with this recommendation, because the conclusions are consistent with both the earlier and the more recent research, the processes are more severe than those processes where OSHA has created partial exemptions and this is consistent with OSHA's 1978 decisions. There is more long term experience with those processes, and the processes are more severe than other permitted types of washing.

Based on its review of the data, comments and the Task Force's recommendations, OSHA has reached several conclusions. The standard provides for full or partial exemption of washed cotton, in the following cases.

1. Cotton that has been washed and otherwise prepared to meet the requirements of medical grade cotton (USP) use is exempt from all provisions of the standard.

2. Cotton that has been scoured, bleached and dyed and mercerized yarn are exempt from all provisions of the standard.

3. Cotton must be washed in a facility which is open to inspection by the Assistant Secretary and which provides sufficient evidence to demonstrate that approved washing methods were used.

4. If an employer uses cotton that is washed in a facility separated from the facility using the washed cotton then documentation of the washing processes and other relevant information must be available at the worksite. In this case, the washing facility must also be open to inspection by the Assistant Secretary.

5. Cotton that is classed as low-middling light-spotted or better is exempt from all provisions of the standard except the requirements for medical surveillance, medical recordkeeping, and appendices B, C, and D as they apply to employees exposed below the action level if the cotton has been washed on a continuous batt washing system or a rayon rinse system with a wash temperature of 60 °C or higher, and with a water-to-fiber ratio of no less than 40:1. Additionally, the growth of bacteria in wash and rinse water must be controlled to limit bacterial contamination of the cotton.

6. Cotton which is of grades lower than low-middling, light spotted, if washed to meet the requirements specified in paragraph 5 and is bleached in addition is exempt from all provisions of the standard except to the requirements named above for washed cotton of higher grades and is subject to a permissible exposure limit of 500 $\mu g/m^3$. Environmental monitoring is also required.

O. Appendices

Appendices A–D are unchanged. Appendix E has been added to provide an acceptable protocol for demonstrating that a cotton dust exposure measuring instrument is equivalent to the vertical elutriator. The basis for adding Appendix E is discussed in Section IV (D)(1) of the preamble.

V. Summary of Regulatory Impact Analysis

A. Introduction

The Draft Regulatory Impact Analysis was discussed in the preamble to the proposed standard and was available for public review and comment during the rulemaking. The Final Regulatory Impact Analysis (RIA) for this standard, available at OSHA's Docket Office, summarizes the factors discussed in this preamble and the preamble to the proposal that led the Agency to reconsider the status of the 1978 cotton dust regulation; and summarizes OSHA's rationale for making the final regulatory determinations which are discussed and made in this preamble. As does this preamble, the final RIA explains how the decision to review the standard was made. This decision was precipitated both by OSHA's need to determine whether the risk of adverse health effects in nontextile industries met the "significant risk" test set forth by the Supreme Court's "Benzene Decision," and by OSHA's growing awareness that various technical revisions were required in the standard's application to the textile industry. As part of this evaluation, the RIA summarizes those issues also discussed in the preamble that relate to the need for regulation, the feasibility, and the cost-effectiveness of the 1978 and the revised standard. The RIA particularly examines those changes which the Agency believes will make the standard more flexible, and performance-oriented, thereby serving to protect workers from dust-related illness in a more effective and less costly manner. The RIA also includes a detailed discussion of economic and technical feasibility which is summarized below.

B. Technical Feasibility/Textiles

Section 6(b)(5) of the OSH Act mandates that OSHA set standards that most adequately assure employee safety

and health "to the extent feasible." Consequently, in the preamble to the 1978 standard, OSHA presented extensive documentation demonstrating that it was technically feasible to reduce dust levels in the cotton textile industry to the PEL's within a 4-year compliance period. The various production processes were described and their applicable dust control techniques were discussed in detail. Examples of successful innovative control technologies, especially those that sharply increased industry productivity while reducing dust levels were thoroughly examined (43 FR 27361–27367). Both the District of Columbia Court of Appeals and the United States Supreme Court subsequently upheld OSHA's determination that the Cotton Dust Standard is feasible for the textile industry.

As part of its review OSHA contracted with Centaur Associates to survey the current state of technical dust control and to review the technological and economic feasibility of alternative regulatory provisions. Centaur completed a comprehensive report (Ex. 185) based upon visits to 15 textile plants, extensive survey data and interviews with numerous industrial engineers and manufacturers of dust control equipment. Centaur concluded that, with the limited exception of certain processes using high cotton content coarse yarns, it was technically feasible for the industry to come into compliance by the March 27, 1984, deadline. This view was corroborated by evidence that many equipment companies guarantee their dust control systems to maintain dust levels below the permissible limits under most circumstances.

The new less "dusty" technologies are typically based on systems characterized by enclosed automatic feeding, transferring and processing of materials. In addition to emitting substantially less dust than the older equipment, such processes eliminate the need to conduct some of the dustiest operations, such as picking, roving and winding operations, while greatly reducing the amount of manual handling required. Commonly used systems include automatic bale openers and feeders, automatic waste collection with pneumatic transport to the waste house, fully enclosed chutefeed cards, open-end spinning systems, and shuttleless looms.

Industry exposure data confirmed that by 1982 the industry had made substantial progress toward achieving compliance. ATMI's survey of companies employing a total of about 72,500 workers reported that roughly 80 percent of cotton textile employees were exposed below the current PEL, with 78 percent of the employees below in twisting, 66 percent below in winding, and 73 percent below in spooling operations (Ex. 175–60). These estimates were substantially confirmed by Lumsden, whose data from 44 textile plants showed about 84 percent of the yarn manufacturing work areas in compliance (Ex. 186–2); and by John Brooks, North Carolina Commissioner of Labor, whose survey of North Carolina textile mills indicated that dust levels were below the PEL in 83 percent of the spinning operations, 77 percent of the winding operations and 81 percent of the twisting operations (Ex. 186–4).

In their post hearing submission (Ex. 280), the ATMI did not challenge either the technical or the economic feasibility of the cotton dust standard with the exception of the need for an extension of the compliance deadline for processing high cotton-content coarse yarns. They noted:

> Morever, most of the capital expenditures needed to achieve the PELs specified in the present standard have already been committed, and, with the exception of the processing of coarse count ring spun yarns, the vast majority of cotton textile operations have largely been brought into compliance with the PELs. For these reasons, the PELs of 200 $\mu g/m^3$ in yarn manufacturing and 750 $\mu g/m^3$ in slashing and weaving should remain unchanged in the revised standard. (This endorsement of the existing PEL's should be read in conjunction with our recommendations for extension of the compliance date in the case of coarse count ring spun yarns and for the exclusion of oil mist from measurements of cotton dust under the standard. If the existing PELs remain unchanged, adoption of our recommendations on the foregoing points . . . is essential.)

In earlier testimony and comments, several commenters pointed out that the available technology was adequate for all but coarse yarn processing. For example, Burlington Industries, Inc. noted that dust in many fiber preparation areas could be controlled by ventilation even without replacing the old machinery, although this was not always cost-effective. For downstream processes, however, they reported that "Despite research efforts, the textile industry, its suppliers, contractors and consulting engineers have not been able to develop "on-frame" capture plenums or systems capable of reducing dust levels to 200 $\mu g/m^3$ for coarse yarn manufacturing beyond drawing (i.e. roving, spinning)" (Ex. 170–14).

John Lumsden, a co-developer of the vertical elutriator used to monitor cotton dust levels, a participant in the byssinosis prevalence studies conducted by Merchant et al., a former director for North Carolina Occupational Health Programs, and a vice president for a health and safety consulting firm for the textile industry, discussed control technology in his 1982 Congressional testimony (Ex. 186–2). Lumsden confirmed that exhaust ventilation and material handling equipment adequately control dust from the opening to the roving process. He stated, however, that "the machines, or frames, that accomplish spinning, twisting, spooling, or winding have not, to this time, been retrofitted with local exhaust ventilation systems." Because dust control in these areas must be achieved through general dilution ventilation where efficiency is variable, Lumsden found that some yarn manufacturing areas will experience dust levels above the OSHA standard.

During these same House Subcommittee hearings, Percy Thackston, Executive Vice President of the Bahnson Company, a major supplier of dust control systems, appearing on behalf of the American Textile Machinery Association reached essentially the same conclusion and summarized the problems in control technology by explaining that:

> Technology is presently available for controlling dust from opening through the card room by use of modern machinery and equipment. . . . From ring spinning through warping, it is a different story. There has not been a major, successful, predictable breakthrough in the dust control technology for these process areas. (Ex. 186–3)

As the evidence and these comments indicate, compliance with engineering controls is clearly feasible with one current exception. This area is ring spinning, winding and spooling of relatively coarse, high-cotton-content yarns that generally are used in denim, duck, heavy terry cloth, and heavy industrial fabrics. Centaur explained that the processing of coarse yard produces more dust because the dust emission rate varies directly with the production rate and more cotton per hour is processed with the low count (coarse) yarns than with the high count (fine) yarns. Based on technical information obtained from air filtration and dust control contractors, Centaur estimated that the dust release rate of certain coarse yarns with a high cotton content is above the cleaning capability of the available air handling systems. Indeed, Centaur reported that the same air filtration and dust control companies that typically guaranteed compliance with the PEL in other production areas refused to assure compliance for the spinning and winding of high-cotton-content coarse yarns because controls

for these processes were not always successful.

The most promising solution to the problem appears to be the rapid advent of open-end spinning systems. This relatively new technology sharply reduces dust levels because the fibers are spun within enclosed rotors and ventilation is designed into the machinery. Indeed, the proper operation of the equipment requires local ventilation and efficient dust control. Moreover, this equipment, which fortuitously is best suited for the production of coarse yarns, significantly boosts spinning productivity and completely eliminates the roving process. Some U.S. denim plants have already converted their spinning operations to open-end systems to take advantage of the production efficiencies and many others are seriously evaluating the machines (*American Textiles*, Ex. 264). With this technology developing rapidly and its production rates already from 4 to 5 times higher than ring spinning (Centaur, Ex. 185, p. 3–48), competitive pressures will make it increasingly more difficult for firms to avoid this conversion.

Nevertheless, the record indicates that open-end systems have not yet overcome several problems. For example, at the present time, yarn produced by open-end spinning is weaker (has lower tensile strength) than yarn that is ring spun. Also, there are some potential problems with broken ends in weaving, and negative wear and appearance properties of finished fabrics.

Because of these difficulties, OSHA has granted a conditional two-year extension of the deadlines for the installation of engineering control requirements for the yarn processing operations including and following the ring spinning of coarse high cotton-content yarns. The evidence indicates that current problems with open end spinning are likely to be solved by the end of this period. This exemption is fully described elsewhere in the preamble. With this exemption, therefore, the evidence clearly indicates that the cotton dust standard is technically feasible and that compliance has largely been achieved.

C. Economic Feasibility/Textiles

OSHA must also demonstrate the economic feasibility of standards proposed under section 6(b)(5) of the OSH Act. OSHA found that the 1978 standard was economically feasible for the textile industry. This finding was specifically upheld by both the District of Columbia Court of Appeals and the United States Supreme Court.

OSHA hired Centaur Associates to study the costs that had been incurred and the costs that still needed to be incurred to achieve compliance with the standard, and to project the economic impacts of the standard. Their data confirm that the standard, as applied to the cotton textile industry as a whole is clearly economically feasible. Moreover, this conclusion is strengthened because it now appears likely that control costs are about one-half of the estimated costs that served as the basis for the court decisions upholding economic feasibility. In addition, the revised standard makes compliance even more cost-effective by further reducing the costs of the standard while retaining the health protection.

In their post hearing comment, ATMI did not question the economic feasibility of the standard. Moreover, their submission did not present specific evidence indicating that the standard would result in serious economic feasibility problems. Similarly, in their earlier response (Ex. 175–60), ATMI did not assert that the textile industry as a whole would be significantly impaired, although they argued that, "... in a number of cases, the economics of the situation make it impossible to justify the expenditures that would be required to achieve the permissible exposure limit. For that reason, several marginal facilities already have been closed, and one can expect that additional closings will occur in the future." The NCC contended that some plants complied with the standard by substituting synthetics for cotton, resulting in lost revenues to cotton farmers, handlers and processors (Ex. 175–47).

The cost of the cotton dust standard was one of the questions included in an ATMI survey, to which about 50 textile companies employing 72,500 workers responded. These firms reported that they had spent approximately $310 million for capital equipment to comply with the standard up to the end of 1981, and they expected to incur approximately $150 million in additional capital expenditures to meet the 1984 requirements. ATMI speculated that the companies responding to this survey may have been the more progressive firms and stated that, "Consequently, for the industry as a whole, it seems fair to assume that considerably more than one-third of the required capital expenditures remain to be made in the future." The responding companies also calculated that they would spend about $20 million in annual energy costs and $6 million in annual maintenance costs to comply with the engineering control requirements (Ex. 175–60).

Centaur Associates, in its study for OSHA (Ex. 185), estimated that the textile industry has already spent $143.3 million in capital costs that are attributable to the regulation, and still needs to spend an additional $102.2 million. Centaur calculated that the 1978 standard required annual energy costs of $27 million, maintenance costs of $2 million, monitoring costs of $2.5 million, and medical surveillance costs of $6.6 million. The proposed action level was estimated to reduce the monitoring and medical surveillance costs by about $3.3 million per year. The ATMI and Centaur estimates are not strictly comparable because Centaur adjusted for productivity gains by assuming that all of the ventilation costs, but only 17.5 percent of the new production equipment costs, are attributable to the OSHA standard. Both surveys, however, support the view that between one-half to two-thirds of the required capital expenditures had already been made by 1982.

Centaur's 1982 projections indicated that total future capital outlays for dust control equipment for an average size plant would be approximately $300,000 per year during 1983 and 1984. Those firms that have expended little on dust control equipment would face higher costs up to approximately $600,000 per year over the 2-year period for the average size plant. Over 60 percent of these expenditures, however, would be offset by associated productivity gains. The 1982 average revenue per plant was estimated by Centaur to be $10.3 million (Ex. 185, P. 7–13). Because cash flow as a percent of sales in the textile industry has averaged 4.65 percent in recent years, an annual average cash flow of $479,000 could be predicted. For many firms, this amount would be adequate to cover the additional capital outlay without new borrowing.

The textile industry, however, was affected by the depressed condition of the national economy in 1982, and its profitability and cash flow in that year were below levels of recent years. Thus, Centaur reported that the capital requirements to comply with engineering controls by 1984 might be more than some plants could generate from internal cash sources.

Centaur concluded, however, that despite the textile industry's weaker financial position in 1982, it was improbable that conditions were such that the required capital expenditures could not be made (Ex. 185, p. 7–14). Centaur noted that even where cash flow was not sufficient to cover capital expenditures, most firms would have adequate access to financial markets

because the greater part of the required capital outlays would be for new equipment to improve plant production rates. In addition, recent tax legislation has substantially reduced the after-tax cost of new capital investment, and interest rates for business loans have subsided since 1982. Centaur, therefore, found it unlikely that the capital expenditures required for OSHA compliance would significantly contribute to plant closings. Of course the rapid economic recovery since early 1983 will make it easier for even those companies that have delayed installing dust control equipment to afford the balance of these expenses. Both ATMI and the Centaur studies indicate that the industry has indeed made commendable and largely successful efforts to achieve compliance with the standard.

Public comments have not provided substantial documentation to refute Centaur's findings of economic feasibility for the textile industry. For example, John Brooks, Commissioner of Labor for North Carolina, a state producing about one-third of the nation's yarn, found that although a few firms may have economic difficulty, compliance is feasible in almost every instance (Ex. 217 p. 5). While a few comments declared that requiring the industry to shift large portions of its investment funds into "nonproductive areas" would have significant adverse effects on its competitive position in either domestic (NCC, Ex. 275) or international markets (ATMI, Ex. 189–5; NCC, Tr. 980), the industry itself notes that its recent modernization, "has made the American textile industry the most productive in the world" (Ex. 189–5, p. 2). Moveover, a recent report on the OSHA standard prepared for the Office of Technology Assessment, U.S. Congress, concluded that:

> It would be hard to claim that OSHA's cotton dust regulation has in any way seriously damaged industry profitability. Some would say that OSHA has actually enhanced and encouraged profitable activities. Many corporate executives and plant managers, while still objecting to various aspects of the cotton dust rule, admit that in many of the plants which they have modernized (and they must modernize to survive), the existence of the OSHA rule cause them to make a more timely decision, and in many cases, a more systematic decision." (Ex. 233, p. ii–iii)

The same notion was expressed in a 1980 issue of the British publication "Economist" which stated that:

> Tougher government regulations on workers' health have unexpectedly, given the industry a leg up. Tighter dust control rules for cotton plants caused firms to throw out tonnes of old inefficient machinery and to replace it with the latest available . . ." (Exh. 200)

Commenting on this article, Mr. James King, a Vice President of Cone Mills, representing ATMI, agreed that both the OSHA standard and the increased demand for wider fabrics of better quality contributed to the rapid pace of modernization (Tr. 705–706). In response to the question, "I take it . . . you have just said that the OSHA standard has encouraged the American companies which were already modernizing and improving their productivity to do so at perhaps even a slightly faster rate than you had been doing so before?", he replied, "I think that generally could be said . . ."

In addition, ACTWU presented data demonstrating the strong economic performance of seven textile firms that had largely complied with the standard (Ex. 198–B, App. 4). The NCC rejected this finding, pointing out that the profits per dollar of net worth for these seven companies were 20 percent above the industry average in the 4 years preceding 1978, but 2 percent below in the four years subsequent to 1978 (Tr. 658; Ex. 276 pp. 34–36). In response, George Perkel, a consultant to ACTWU, prepared a trend analysis indicating that the companies' profit on net worth declined during the 4 years prior to 1978, but rose at a rate of 9 percent a year during the 4 years subsequent to 1978 (Tr. 658–659).

After considering the positions stated above, OSHA believes that there is overwhelming evidence to support the conclusion that the cotton dust standard is economically feasible for the textile industry. Indeed, compliance has, for the most part, already been achieved without any serious significant adverse impact.

D. Technical Feasibility/Nontextiles

The final amendments to the cotton dust standard exempt the nontextile segments from all sections of the new cotton dust standard § 1910.1043 except for the medical surveillance provisions for cottonseed processing and waste processing. In addition, this final rule exempts all segments of the nontextile industry except waste recycling and garnetting operations from the pre-existing permissible exposure limit of 1000 $\mu g/m^3$ of cotton dust (raw) specified in § 1910.1000 (Table Z–1). The bases for these exemptions are the data on health effects which are discussed in section III of this preamble.

OSHA did not propose and the final rule does not exempt waste processing and garnetting operations from the pre-existing standard in § 1910.1000 of 1000 $\mu g/m^3$ of cotton dust. This decision was also based upon the health studies discussed in Section III of this preamble on health implications and scope of coverage in nontextiles. However, following the testimony of all health experts commenting at these proceedings, OSHA is changing its interpretation of the 1000 $\mu g/m^3$ exposure limit so that it applies to respirable dust as measured by a vertical elutriator or equivalent instrument rather than to total dust. Respirable dust correlates better with the adverse health effects of cotton dust and thereby provides an improved measure of employee exposure to the toxic material. This interpretation is also utilized in the § 1910.1043 standard.

Section 6(b)(5) of the OSH Act requires OSHA to determine that a new standard issued under section 6(b) of the Act is techically and economically feasible. When OSHA issued the § 1910.1043 standard specifying a 500 $\mu g/m^3$ respirable dust PEL for nontextiles, OSHA made a determination of technical and economic feasibility based on data in the record. The knitting industry did not challenge that determination. The agency's conclusion as to feasibility for cotton classing and warehousing was upheld by the D.C. Circuit, but the Supreme Court remanded for consideration on other grounds. The D.C. Circuit upheld technical feasibility for cottonseed processing but held that the agency had not demonstrated economic feasibility. No judicial decision was issued for waste processing, which includes both waste recycling and garnetting processes. No purpose would now be served by reviewing those determinations, since the final rule eliminates coverage of these segments by § 1910.1043 with the exception of the medical provisions for cottonseed processing and waste processing discussed below.

The § 1910.1000 standard which will remain in effect for waste recycling and garnetting operations was issued in 1971 pursuant to section 6(a) of the Act that provides that:

> without regard to chapter 5 of title 5, United States Code, or to the other subsections of this section, the Secretary shall, as soon as practicable during the period beginning with the effective date of this Act and ending two years after such date, by rule promulgate as an occupational safety or health standard any national consensus standard, and any established Federal standard, unless he determines that the promulgation of such a standard would not result in improved safety or health for specifically designated employees. In the event of conflict among any such standards, the Secretary shall promulgate the standard

which assures that greatest protection of the safety or health of the affected employees.

The feasibility requirements of section 6(b)(5) did not and do not apply to that 6(a) standard and it was not challenged judicially.

The requirements which continue in effect for waste recycling and garnetting operations in addition to the exposure limit of 1 mg (1000 μg)/m³ for cotton dust, that:

> To achieve compliance . . . administrative or engineering controls must first be determined and implemented whenever feasible. When such controls are not feasible to achieve full compliance, protective equipment or any other protective measures shall be used to keep the exposure of employees to air contaminate within the limits prescribed in this section . . . whenever respirators are used, their use shall comply with 1910.134. (§ 1910.1000(e))

From the statutory provisions it can be seen that the decision to retain a 6(a) standard does not place the burden of proof on OSHA to demonstrate feasibility pursuant to section 6(b)(5). In addition, the fact that an existing area in a waste processing operation is over the 1,000 μg/m³ limit does not demonstrate the lack of feasibility of the 6(a) standard. The specific employer may be out of compliance because the employer failed to install a feasible control which is available. Or pursuant to 1910.1000(e), the employer may have determined that there is no feasible administrative or engineering control and is achieving compliance with respirators as is then permitted if that determination is correct.

Evidence on technical and economic feasibility has been introduced to the record for the waste recycling and garnetting processes. OSHA has reviewed this data, and if the data demonstrated serious feasibility difficulties for the existing standard, OSHA would have reconsidered the 1000 μg/m³ standard for waste recycling and garnetting on feasibility grounds. However, the data demonstrate that the standard is technically feasible and, as discussed in the section below, economically feasible.

As discussed in the scope and application section, OSHA is changing for health reasons its interpretation of the method of monitoring for the 1000 μg/m³ standard. The prior interpretation was that the proper method of monitoring was to measure total dust. OSHA is changing the interpretation to respirable dust as measured by a vertical elutriator or equivalent.

This change is relevant to feasibility determinations. The evidence clearly indicates that respirable dust constitutes only one-third or one-fourth of total cotton dust particulate. Various NIOSH studies demonstrate this fact, and were acknowledged by Dr. Wakelyn and Dr. Ethridge, representing the National Cotton Council. Therefore, it is substantially easier to achieve 1000 μg/m³ of respirable dust than that same level of total dust. This must be kept in mind when reviewing data and comments focusing on 1000 μg/m³ of total dust. In addition it should be kept in mind when considering studies directed at the feasibility of achieving compliance with 500 μg/m³ respirable dust level, that it is, of course, substantially easier to achieve compliance with a 1000 μg/m³ respirable dust level than with a 500 μg/m³ respirable dust level.

In general, compliance with the 1000 μg/m³ respirable dust limit does not appear to be a problem for garnetters. Dr. Wakelyn, testifying on the subject of garnetting operations for the National Cotton Batting Institute (NCBI), indicated that technology does not exist to meet a 1.0 mg/m³ (1,000 μg/m³) *total* dust level but agreed that, "It may, however, be possible for many facilities to meet a 1.0 mg/m³ respirable dust standard. . ." (Ex. 210–C). Similarly, the NCC confirmed that, ". . .it may be possible in most facilities to meet a 1 mg/m³ respirable dust standard" (Ex. 276, p. 13). In two of the three plants for which OSHA has exposure data, all processing areas are already below 1,000 μg/m³ of respirable dust (Ex. L–3; Ex. 118X).

Compliance may not be quite as easy for waste recyclers. In its initial response to OSHA's 1976 proposal to limit dust levels, the NCC reported that Pneumafil, a major dust control vendor, believed that the proposed 200 μg/m³ level could not be achieved in waste recycling, but that dust levels could be reduced sufficiently to permit compliance with a 500 μg/m³ exposure limit (Ex. 99E, p. 17). Since that time, however, experience has indicated that there would be some difficulty achieving 500 μg/m³ in all process areas. NIOSH measured dust levels at all 13 waste recycling plants and reported that respirable dust levels in 8 of the plants had overall geometric mean levels below 500 μg/m³ (Ex. 175–56). In response, the NCC pointed out that about 31 percent of the NIOSH dust samples were taken from non-process areas. NCC also noted that 12 of the 13 recycling plants studied by NIOSH had dust levels above 500 μg/m³, and 11 of the 13 plants had levels above 1,000 μg/m³ in at least some process areas (Ex. 211–C). Norman Paschall, representing the Textile Fibers and By-products Association, testified that the Pneumafil Company had tried and failed to lower dust levels to 500 μg/m³ in his plant (Tr. 1031).

OSHA's final rules, however, require these firms to meet only a 1,000 μg/m³ respirable dust PEL. While Mr. Paschall did not indicate whether his plant had succeeded in reducing dust concentrations to this level, a summary table in the NIOSH submission presents dust level means and standard deviations by individual manufacturing processes. These figures clearly imply that every operation must have achieved dust levels well below 1,000 μg/m³ respirable dust in at least several of the recycling plants (Exh. 175–56, Table 5, p. 47). Thus, OSHA believes that engineering controls capable of reducing dust levels in each type of operation to the PEL do exist and are currently in place in some establishments. As discussed above, if it is determined that feasible administrative and engineering controls are not available to bring a specific area below the PEL, the employer may comply by providing respiratory protection.

OSHA is not eliminating the requirement for medical examinations promulgated in 1978 for the cottonseed processing and waste processing industries. The feasibility of this provision was not seriously questioned during the 1978 rulemaking proceedings. However, a few participants at the 1984 hearing claimed that medical examinations were infeasible for the cottonseed industry. T.S. Schuler, president of the National Cottonseed Products Association (NCPA), pointed out that the cottonseed industry is basically a rural operation and argued that "the medical expertise and doctors are just not available to do it." He said that his employees would have to be transported over a hundred miles to receive the required medical examinations. While acknowledging the existence of medical programs in the Procter and Gamble cottonseed mills, he attributed this capability to their unusual size (Tr. 1087–1089). The NCPA also submitted questionnaire survey responses from about 60 percent (36 out of 62) of the nation's cottonseed mills. Fifty-nine percent of the mills replied that they do not have access to a pulmonary function testing service, but even where the required facilities were available, 76 percent of the time they were more than 50 miles away (Ex. 281).

OSHA, however, believes that the exams could be provided in most instances at reasonable cost. The standard does not require the person administering the test to be a physician as long as that individual has completed

a NIOSH approved training course in spirometry and works under the general supervision of a physician. As the textile industry has found, consultative services often are available to provide the requisite medical services. For example John Lumsden, owner of an industrial hygiene consultation service said that his company would provide medical surveillance for a facility with 20 employees up to 100 miles from their headquarters for $400 (Tr. 1352). See also Exhibit 170–11. In other instances, local physician's offices or regional hospitals could be utilized or a nurse or other employee could be trained at modest cost at the two day NIOSH program. The cost of a spirometer is about $1,000 (Ex. 170–11). Once the demand for such tests is established, a local physician or clinic could easily provide the service. OSHA believes, therefore, that the provision of medical surveillance is technically feasible even in rural areas.

E. Economic Feasibility/Nontextiles

The only segments of the nontextile industry to remain covered by a permissible exposure limit are waste recycling and garnetting. As discussed above in the technical feasibility section, OSHA has determined that the pre-existing 6(a) standard should not be eliminated. Therefore the burden of proof is not on the agency to demonstrate economic feasibility. To the extent that any capital expenditures are required, it is not because of a new action by OSHA, but because of a failure to comply with the existing standard over the past 13 years.

Nevertheless, OSHA has carefully reviewed the evidence of economic feasibility for these segments. This includes the data presented prior to the issuance of the 1978 standard and new data supplied by Centaur, the National Cotton Council (NCC) and others. Based on this evidence, OSHA concludes that the evidence does not demonstrate it is economically infeasible for these segments to come into compliance with the existing standard 1000 $\mu g/m^3$, interpreted as a respirable dust standard. Indeed, OSHA concludes that the evidence clearly demonstrates that it is economically feasible to comply with 1000 $\mu g/m^3$ respirable dust for these segments.

Centaur did not collect independent cost data but updated the pre-1978 engineering cost calculations submitted by the NCC to account for price change, reduction in cotton waste generated by textile mills, and current levels of compliance. They did not attempt to evaluate the accuracy of these cost data or to judge whether the lower estimates presented in Research Triangle Institute's 1976 Inflationary Impact Statement were more appropriate. For example, the major dust control vendor relied upon in NCC's study on waste recyclers estimated that the required controls "would necessitate at least a two-thirds increase in existing cfm . . ." The NCC took this to mean a 167 percent rather than a 67 percent increase in the required cfm and calculated the engineering costs accordingly (Ex. 99E, p. 19). Therefore, the Centaur estimates may be considered an upper bound figure. These estimates indicated that to comply with a PEL of 1,000 $\mu g/m^3$ of total dust, the waste recycling industry would incur capital costs of $11 million and total annual costs of $3.2 million, or roughly 10.4 percent of their total revenues. Similarly, Centaur projected that the garnetting industry would incur capital costs of $13 million and total annual costs of $3.8 million, about 1 percent of their total revenues. These annual compliance costs were estimated to amount to about 3.7 cents per pound of cotton waste processed by recyclers and 1.9 cents per pound of cotton waste processed by garnetters. It should be noted that Centaur believed costs would achieve compliance with 1000 $\mu g/m^3$ of total dust, but that OSHA is changing its compliance interpretation to require 1000 $\mu g/m^3$ of respirable dust. As discussed above, this level is 3 to 4 times easier to achieve than a 1000 $\mu g/m^3$ total dust PEL and consequently the cost to achieve compliance would be substantially less.

Centaur found that the selling price of cotton waste sold by textile firms varied substantially by fiber type but averaged about 10 cents per pound. As compliance costs were estimated at only 2 to 4 cents per pound, Centaur determined that the full financial impact on waste recycling companies would be subtantially moderated through the industry's potential to pass back some proportion of the production cost increases to those firms supplying the unprocessed waste materials. Because sales of cotton waste are not a major source of revenue to any one textile mill and mills would have to pay for solid waste disposal if this outlet disappeared, Centaur concluded that textile mills would have no choice but to accept even sharply reduced revenues from sales of waste cotton to keep the market for waste cotton active (Ex. 185, p. 7–17).

Dean Ethridge, Director of Economic Services for the NCC, objected to Centaur's estimates (Exh. 211–E). He argued that their results are presented as applicable to the proposed 1,000 $\mu g/m^3$ *total* dust standard, whereas their cost data are based upon an earlier NCC study that estimated the cost of meeting a 500 $\mu g/m^3$ *respirable* dust standard. He noted that physical evidence demonstrated that the proposed 1,000 $\mu g/m^3$ *total* dust standard was at least 50 percent more severe than a 500 $\mu g/m^3$ *respirable* dust standard. OSHA, however, does not believe that the Centaur estimates, which are based on industry data, are too low because Centaur adjusted the estimates to reflect current dust conditions.

In addition, Dr. Ethridge claimed that much of the technical and financial data used by Centaur to construct their analysis are outdated. NCC conducted a questionnaire survey and received responses from about 60 percent of the waste processing firms (8 out of 13), and about 38 percent of the garnetting firms (30 out of approximately 80). Applying these data to update the original NCC study "using Centaur's method of updating energy and capital costs," NCC calculated that compliance costs per pound of cotton output were 300 percent higher than Centaur's estimate for the waste recycling industry, and 39 percent higher than Centaur's estimate for the garnetting industry.

A review of NCC's analysis, however, shows several deficiencies. For example, their cost calculations for the waste recycling industry indicate that NCC failed to use an appropriate capital recovery formula (Ex. 211–E, p.7). Applying the formula used by Centaur yields $288,204 as the annualized capital costs per recycling plant in need of new controls rather than $399,936. Moreover, NCC assumed that operating costs amount to 2 percent of capital costs whereas Centaur had provided a plausible rationale for believing that 1.3 percent was more realistic. As NCC did not present any new data to support their assumption, OSHA has applied Centaur's 1.3 percent rate, which lowers the NCC figure for operating costs per plant from $29,499 to $19,174.

On the other hand, NCC substantially underestimated annual energy costs as they apparently did not understand that the Centaur procedure would apply the factors to the new 320,640 cubic feet per minute (cfm) required ventilation system rather than to the 192,000 cfm existing operating system. Consequently, the estimated annual energy cost per firm is approximately twice the NCC estimate, climbing from $36,009 to $60,135. This cost is still substantially below the Centaur estimate of $93,000 because Centaur assumed that typical plants operated at about twice the number of

hours reported in the NCC survey. The sum of these corrections yields a total annualized cost of $367,513 for each out-of-compliance plant to meet a dust limit of 1,000 ug/m³ of total dust.

As noted repeatedly by the NCC, however, the ratio of the weight of total to respirable dust is at least three or four to one (NCC, Ex. 211–E; Tr. 1059). Thus, the above estimates may approximate the cost of dust controls designed to achieve a standard at least three times harder to achieve than the final rule. While the extent of the overestimate is not known precisely, the NCC pointed out that ". . . it is common knowledge that constant increments in severity of dust standards result in more-than-proportionate increases in the cost of meeting the standard." Indeed, an assumed three to one dust ratio was the basis for the NCC presumption that "a conservative estimate of the cost for a 1.0 mg/m³ total dust standard would be 50% above that for meeting a 0.5 mg/m³ vertical elutriated standard." (Ex. 211–E, p.3) Estimating the cost of the final standard by applying the identical logic leads to a downward adjustment of the above compliance cost figures by about two-thirds. On this basis, the adjusted annualized cost per recycling plant needing controls is $367,513 divided by 3 or $122,504, which amounts to about 3.1 percent of the average plant's reported gross revenue (NCC, Ex. 211–E, p.5.). Using these same estimates, the cost of dust control per pound of waste cotton processed comes to 1.1 cents, significantly below the original Centaur estimate of 3.7 cents per pound.

Based on the Centaur assumption that 10 establishments would need dust controls, the above calculations imply that the waste recycling industry would incur capital costs of about $4,916,667 and total annualized costs of about $1,225,000 to come into compliance with the final PEL of 1,000 mg/m³ of respirable dust. At the earlier cost estimate of 3.7 cents per pound to achieve compliance. Centaur concluded that 3 to 5 of the 13 waste recycling firms might decide not to continue their operation. OSHA, however, estimates that compliance with the 1,000 ug/m³ respirable dust PEL would cost only 1.1 cents per pound, part of which would be passed back to the textile mills through a lower purchase price. OSHA, therefore, concludes that it is unlikely that any waste recycling facilities would close their recycling operation because of this standard. Thus, OSHA believes that the 1,000 ug/m³ respirable dust PEL is economically feasible for waste recyclers.

The NCC estimate of the compliance costs to be incurred by the garnetting sector also requires adjustment. Applying Centaur's capital recovery formula and operating cost percentage reduces the NCC estimate of annual operating costs per firm from $29,395 to $21,182 and of annual operating costs per firm from $2,168 to 1,409. Moreover, the NCC survey clearly indicates that Centaur had overestimated energy costs for this industry. Centaur calculated that energy costs were 43.3 per cent of annualized capital costs in the waste recycling industry and, in the absence of better data, applied that ratio to estimate energy costs for garnetters. As discussed above, however, the average energy cost per recycling plant is now estimated at $60,135 (still twice the NCC figure) or about 20.9 percent of annualized capital cost. Replacing the 43.3 percentage by the 20.9 rate lowers the NCC energy cost estimate for garnetters from $12,728 to $4,427. This brings the total annualized costs to $27,018 for the average plant with overexposed workers.

Applying the two-thirds adjustment attributable to the change from total to respirable dust yields total annualized costs per plant of about $9,000. The estimated cost for dust control per pound of cotton waste processed amounts to 0.5 cents, also significantly below Centaur's original estimate of 1.9 cents per pound. As noted above, most garnetting plants may already meet this dust level. Nevertheless, if all garnetting establishments had to install such controls, the resulting capital costs would amount to $2,890,800 and the total annualized costs would sum to $720,480.

Even at the earlier 1.9 cents per pound cost estimate, Centaur predicted that no garnetting operations would close, although a few might decide to process synthetic rather than cotton wastes. At OSHA's revised cost estimate of 0.5 cents per pound for the easier to meet 1,000 ug/m³ respirable dust standard, the $9,000 annual cost per facility should be even more manageable as it is less than 0.7 percent of average gross revenue (NCC, Ex. 211–E, p. 9). Consequently, OSHA concludes that the 1,000 ug/m³ respirable dust level is economically feasible for the industry.

As explained above, the final PEL of 1,000 μg/m³ of respirable dust in the waste recycling and garnetting industries should be significantly less costly to meet than either the 1971 PEL of 1,000 μg/m³ of total dust, or the 1978 PEL of 500 μg/m³ of respirable dust. As a result, the costs imposed will be significantly lower than those estimated by Centaur or NCC, and the company's ability to pass back these costs to the sellers of waste cotton would be even greater than Centaur had anticipated. Consequently, OSHA has determined that the standard is economically feasible for the waste processing and the garnetting sectors.

OSHA of course must demonstrate economic feasibility for the new medical surveillance requirements that are issued under section 6(b) of the OSH Act for cottonseed processing and waste processing. Upon review of the rulemaking record, it is clear that the costs of these provisions are so low in relation to the gross revenues of these sectors that the costs are economically feasible. The 1978 standard required medical examinations annually for all exposed employees, but the revised rule requires that each employee in these industries be tested only once every other year. Centaur estimated that the textile industry's outlay for annual medical surveillance and its associated recordkeeping divided by the number of exposed workers averaged $69 (Ex. 185, p. 4–21). As that industry reports a worker turnover rate of about 40 percent (ATMI, Ex. 175–60), the cost per exam may have been as low as $49. The Environmental Resources Group, Inc., (ERG), Inc., a consultant in Environmental Sciences, offers the test for $300 plus $10 per person tested, which amounts to $13 per test if 100 employees are tested and $70 per test if only 5 employees are tested (Ex. 170–11, p. 3). When asked the price to test 20 workers located 100 miles away, John Lumsden, of ELB Associates, reported that his company's minimum fee of about $400 would apply, making the per employee charge about $20 (Tr. 1352). Responses to the NCPA survey of 36 cottonseed mills showed a median price estimate of $60 per test, although the estimates ranged from $11.50 to $237 (Ex. L–4). Overall, therefore, an estimate of $60 per employee exam appears conservative.

In their comments, however, the NCPA disputed the economic feasibility of the medical surveillance provision for the cottonseed oil industry, maintaining that the reported 100 percent rate of worker turnover (166 employees for 82 jobs) would greatly increase its economic burden (Ex. 281; Ex. L–4). OSHA agrees that unusually high turnover rates will raise compliance costs. Moreover, costs for smaller companies without in-house medical staff will rise more than proportionately because new hires would have to travel to a medical facility both before and after their initial work shift. Nevertheless, as the following

calculations indicate, the costs do not appear to be overly burdensome.

On the assumption that newly hired workers would need an additional 3 hours away from work, that lost production amounts to $5 per hour (these employees reportedly receive the minimum wage), and that travel expenses per exam are $4, the full cost of the initial medical test for each new cottonseed mill employee should average about $79 ($60+$15+$4). Thus, assuming a 100 percent turnover rate for the industry, the annual cost of testing 817 new hires (Centaur, Exh. 191, p. 41) would be $79 x 817 employees which equals $64,543. With turnover rates this high, it is difficult to know how many employees would remain for a biennial examination. Dr. Ethridge of the NCC suggests that on average only 6 percent of the workforce remain employed for a full year (Ex. L–4). Even if 25 percent of the employees remain for 2 years, however, this would add only .25 x $60 x 817 employees = $12,255 of medical costs every other year. The annual cost, therefore, consists of half of this value, which is $6,128 plus the $64,543 estimated above. Thus, OSHA estimates the annual cost of medical surveillance for the cottonseed mill processors at $70,671. With 1981/82 revenues reported at $777.6 million (derived from value per ton and number of tons in Centaur, Ex. 191, pp 49, 51), these compliance costs amount to less than one one-hundredth of one percent of industry sales even in that year of low demand. Clearly this requirement is economically feasible for the cottonseed processing industry.

The worker turnover problem appears less severe for the waste processing companies as the NCC survey (Ex. 232–A) implies rates of 40 percent for recyclers and 21 percent for garnetters, not very different from the approximately 40 percent rate reported for the textile sector (ATMI, Ex. 175–60). Therefore, OSHA assumes that these industries would experience biennial medical surveillance costs similar to the $69 per exposed employee reported for the textile sector (Centaur, Ex. 185). Based on 260 recycling employees (NIOSH, Ex. 175–56) and 880 garnetting employees (NCBI Ex 210–13; NCC Ex. 232A), this approach yields annual medical surveillance costs of $8,970 for the recycling industry (½ x $69 x 260 employees), and $30,360 for the garnetting industry (½ x $79 x 880 employees). These costs come to about $690 for the average recycling plant ($8,970/13 plants), or less than 0.02 percent of the average recycling company's 3.9 million gross revenue (NCC, Ex. 211–E, p. 5); and about $380 for the average garnetting plant ($30,360/80 plants), or about only 0.03 percent of the average garnetting company's $1.3 million gross revenue (NCC, Ex. 211–E, p. 9). Compliance costs of such magnitude would have almost no effect on the industry's profitability and thus are clearly affordable.

F. Cost Savings

Estimates of cost savings were derived for such changes as the revised monitoring frequency, the new action level provision, and the exemption of the nontextile sectors from most requirements of the 1978 standard. Some other changes such as eliminating the requirement to check equipment at specified intervals would lead to further cost savings, but data available did not permit quantification of those savings. Other changes had little or no impact on costs.

For the textile sector, OSHA's new action level and reduced monitoring frequency are estimated to save at least $2.7 million per year. This cost saving reflects the change in both the required frequency of exposure monitoring from semiannually to annually where exposures are below the PEL, and the required frequency of medical surveillance from annually to biennially where exposures are below an action level set at one-half the PEL. Such revisions lower the estimated annual cost for medical surveillance from approximately $6.6 million to $5.1 million, and for exposure monitoring from $2.5 million to $1.2 million. Therefore, the total annual cost savings of these changes, compared with the 1978 standard, are approximately $1.5 million for medical surveillance and $1.2 million for exposure monitoring.

The final action exempts all nontextile industries from all but the medical surveillance requirements for cotton seed processing and waste processing of the 1978 cotton dust standard; and all but waste recycling and garnetting operations from the 1971 cotton dust standard. Consequently, the nontextile industries will accrue substantial savings by not having to comply with the deleted provisions of the 1978 regulation. For example, the engineering control savings that will accrue to the waste recycling sector reflects evidence that meeting the final PEL of 1,000 $\mu g/m^3$ of respirable cotton dust is significantly less costly than meeting the 1978 PEL of 500 $\mu g/m^3$ of respirable cotton dust. The estimated cost savings for this sector total $4.9 million in capital costs and $280,000 in associated annual operating costs. For garnetting operations, the final action is estimated to yield capital cost savings of $2.9 million and associated annual operating cost savings of $200,000. The engineering cost savings for the cottonseed oil industry were based on a study by Centaur, which indicated that compliance with the 1978 PEL would cost $49.5 million in capital investment and $22.5 million in associated annual operating and maintenance costs (Ex. 191, p. 43). Since cotton seed mills are no longer subject to a PEL, these amounts are cost savings for this sector.

In sum, the economic savings that would accrue to the nation's cotton-using industries following the enactment of this revised standard are considerable. OSHA estimates that exempting nontextile industries from the 1978 standard would save $57.3 million in capital costs, $3.3 million in annual medical surveillance and monitoring costs, and $22.9 million in other annual operating costs. Within the textile sectors, OSHA's new action level and monitoring frequency are estimated to save at least $2.7 million per year. In total, therefore, OSHA estimates that the final promulgation of this revised standard will save the cotton industries at least $57.3 million in capital outlays and $28.9 million in annual operating expenses. This lowers the estimated capital costs of the 1978 cotton dust standard by 18.4 percent from $310.6 million to $253.3 million (with all but about $100 million already spent as of 1982), and the annual operating costs of that standard by 45 percent (from $64.8 million to $35.8 million).

G. Summary of Regulatory Flexibility Analysis

OSHA also evaluated the cost of compliance for relatively small firms to determine whether the final action would substantially affect the economic viability of most small companies. Although the revised provisions do not explicitly grant concessions based on firm size, OSHA found that they would give significant relief to the many small firms engaged in the processing of cotton.

The new action level and monitoring frequency will especially benefit the smaller firms in the textile sector. The most difficult dust control problem in the textile industry exists in the yarn preparation processes, where economies of scale typically require fairly large-scale plants for efficient operation. Smaller establishments in this sector, however, tend to perform specialty weaving functions, which create less severe dust control problems than their larger counterparts. Since most small firms already operate at low dust levels, the new action level, which reduces

medical surveillance requirements at low dust levels, should reduce the regulatory obligations of many of these smaller textile establishments.

In situations where dust level limits require engineering controls, potential economies of scale in dust control systems become an important competitive factor. If major economies of scale exist, smaller firms would be at a comparative disadvantage because their unit costs would be higher than those of larger firms. Centaur examined each of the compliance activities required by the standard and reported that dust control costs for most of the textile industry were directly proportional to output levels. Consequently, there was little evidence to suggest that the unit costs of compliance with the cotton dust standard varied with plant size for a given product type. Centaur also found, however, that large textile firms (from over $10 to $25 million is assets) were able to finance capital outlays easier because, on average, they had higher profit margins and a higher cash flow as a percent of sales than did smaller firms. Moreover, the larger firms had better access to borrowed capital. Nevertheless, Centaur concluded that the profit rate differentials were not enough to make a substantial impact on the ability of the smaller firms to comply with the standard or compete with larger firms.

Although the precise number of small firms using cotton in the nontextile sectors is unknown, reports indicate that most of these industries have proportionately large numbers of small establishments. For example, the American Cotton Shippers Association estimated that over 90 percent of the companies merchandizing cotton have fewer than 15 employees (Ex. 175–30), and the 1977 Census of Manufactures indicates that over 50 percent of the nation's cottonseed mills employ fewer than 50 employees. For all nontextile firms, the revised standard reduces regulatory burdens as these companies (except in waste processing) are exempted from either all requirements, or all but the medical surveillance requirements.

Within the waste processing industry, which is covered by the 1971 PEL and therefore must institute engineering controls, all but 1 of the 13 recycling plants is a small business with under 40 employees. As in the textile industry, Centaur found few scale economies for the installation of engineering controls. Yet the larger firms tend to operate more than one work shift which enabled them to spread the capital cost of compliance over a greater output. Dun & Bradstreet financial figures, while not specific to those waste processing firms using cotton (Ex. 211–A), indicate that the larger recycling firms earn after-tax profits of about 1.85 percent of sales compared with 1.5 percent for the smaller firms, but the smaller firms return about 15.6 percent on equity compared with about 9 percent for the larger firms. Centaur projected that from three to five of the smaller companies would have difficulty raising the necessary capital to comply with the proposed PEL of 1000 $\mu g/m^3$ of total dust. The revised standard, however, specifies the PEL in terms of respirable dust rather than total dust, which substantially reduces the capital requirement needed for compliance. As discussed above the change to a respirable dust level eliminates that difficulty and those smaller companies can feasibly comply. In addition, the reduced costs for medical and environmental surveillance would effectively moderate the regulatory burdens imposed upon these small firms.

Ventilation systems in the garnetting of cotton waste industries exhibit significant economies of scale, with unit costs for a three-garnett-line less than one-half that of a single line. On the other hand, the independent garnetters, which generally employ less than 20 workers, tend to operate more work shifts than those garnetters affiliated with larger bedding manufacturers. According to Dunn & Bradstreet data, the profits of independent garnetters (SIC 2293) do not vary by firm size, whereas the profits of the mattress and bedspring industry (SIC 2515) acutally showed higher profits for the smaller firms (Ex. 185). Because garnetters can process synthetic as well as cotton waste, Centaur assumed that no small garnetters would be forced out of the waste fiber business. In addition, the revised standard defines the PEL in terms of respirable rather than total dust, requires less frequent medical surveillance and no monitoring burden, and therefore substantially reduces the regulatory costs imposed upon these small firms.

Pursuant to the Regulatory Flexibility Act of 1980 (Pub. L. 96–354, 94 Stat. 1164, 5 U.S.C. 601 *et seq.*), the Assistant Secretary has assessed the impact of the revised standard and concludes that the enactment of the new action level, the various exemptions, and the other technical revisions will moderate the compliance costs of many small cotton-consuming businesses, and that the regulatory burden of the revised cotton dust standard should not substantially affect the economic viability of small companies.

H. Environmental Assessment—Finding of No Significant Impact

In December 1977, OSHA published a Final Environmental Impact Statement (FEIS) on the 1976 proposed cotton dust standard. The FEIS concluded that the proposed action would not result in any significant impact to the general quality of the human environment external to the workplace, particularly in terms of ambient air quality, water quality, or solid waste disposal. On June 10, 1983, OSHA published a Notice of Proposed Rulemaking (48 FR 26962–26984) for occupational exposure to cotton dust. At that time, information was solicited from the public on a variety of issues including possible environmental impacts of the proposed revised standard. The comment period for the NPRM ended on August 9, 1983, and no new or additional information was received pertaining to environmental issues. The final rule and its major alternatives have been reviewed in accordance with the requirements of the National Environmental Policy Act (NEPA) of 1969 (42 U.S.C. 4321, et seq.), the requirements of the Council on Environmental Quality (40 CFR Part 1500), and OSHA's DOL NEPA regulations (29 CFR Part 11). As a result of this review, the Assistant Secretary has determined that the conclusions drawn in the FEIS remain valid, that no amended impact statement is required, and that the proposed rule will not have a significant impact on the external environment. Impacts on the workplace environment are discussed in other portions of this preamble and in other Agency notices on cotton dust (47 FR 5906–5910, February 9, 1982; 43 FR 27350–27394, June 23, 1978; 41 FR 56498–56527, December 26, 1976).

The preceding paragraphs and the preamble to this Notice serve as the environmental assessment and finding of no significant impact.

VI. Repeal of Standard for Construction Industry and Amendment of § 1910.1000.

A. Repeal of Standard for Construction Industry

The 1978 cotton dust standard was applied to the construction industry by 29 CFR 1910.19(f). In its proposal, OSHA proposed to eliminate coverage of the construction industry by repealing § 1910.19(f). The basis was that OSHA has no knowledge of any exposures in the construction industry. No contrary evidence or comments were received. The construction industry supports the

change. Accordingly OSHA is repealing 29 CFR 1910.19(f) for the reason stated in the proposal.

B. Interpretation of Cotton Dust Entry in Table Z–1 of § 1910.1000

The current entry in Table Z–1 of § 1910.1000 reads "Cotton dust (raw)" and sets an exposure limit of 1 mg/M³ (1000 μg/M³). That limit which has existed since 1971, has applied to all non-textile operations while § 1910.1043 has been stayed as discussed in section I.E. of this preamble above. There is a footnote (with a printer's error in the 1984 ed. of the CFR) stating that "This standard applies in cotton yarn manufacturing until compliance with § 1910.1043 (c) and (e) is achieved."

The table entry remains unchanged. The footnote entry is changed. The current footnote is obsolete and omitted. It indicated that yarn manufacturers were to achieve a 1 mg/M³ PEL with engineering controls until they were required to achieve 200 μg/M³ with engineering controls on March 27, 1984. That date has passed and yarn manufacturers are now required to achieve 200 μg/M³ so there is no purpose in retaining that footnote. (There is an exception for coarse count yarn production discussed in IV.M. above.) The textile industry is now fully covered by §1910.1043 and this entry has no future relevance for the textitle segment.

OSHA is exempting knitting, classing, warehousing and cottonseed processing from 1 mg/M³ limit and retaining coverage of the waste processing industry under this limit based on an analysis of the health data. Accordingly a footnote "e" has been added to the "cotton dust (raw)—1 mg/M³" entry. The second sentence of the footnote indicates that this entry applies generally only to the "cotton waste processing operations of waste recycling (sorting, blending, cleaning, and willowing) and garnetting."

In addition health data indicate that this exposure limit will be more protective of workers if interpreted to be measured as "respirable dust as measured by a vertical elutriator cotton dust sampler or equivalent instrument." The first sentence of the footnote indicate that this is the proper interpretation.

The health reasons for these provisions generally are discussed at length in section III. of this preamble, above. The discussion of the interpretation of measuring technique and the retention of coverage for waste processing operations can be specifically found in section III.D. The feasibility implications of these provisions are discussed in section V.D. and E. above.

It is the intention that there remain no gaps in coverage and that existing provisions not terminate unless the new provisions are in effect.

List of Subjects in 29 CFR Part 1910

Occupational safety and health, Health, Cotton dust.

VII. Authority and Signature

This document was prepared under the direction of Patrick R. Tyson, Acting Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, 200 Constitution Ave, NW., Washington, DC 20210. Accordingly, pursuant to sections 6(b), 8(c) and 8(g) of the Occupational Safety and Health Act of 1970 (29 U.S.C. 655, 657), 29 CFR Part 1911 and Secretary of Labor's Order No. 9–83 (48 FR 35736), 29 CFR Part 1910 is hereby amended as set forth below.

Signed at Washington, DC, this 5th day of December, 1985.

Patrick R. Tyson,

Acting Assistant Secretary for Occupational Safety and Health.

VIII. Amended Standards

PART 1910—[AMENDED]

Part 1910 of Title 29 of the Code of Federal Regulations is hereby amended as follows:

1. The authority citation for Subpart B of Part 1910 is revised to read as set forth below, and the authority citations following all sections in Subpart B of Part 1910, except for source citations (FR citations) and Effective Date Notes, are removed:

Authority: Secs. 4, 6, and 8 of the Occupational Safety and Health Act, 29 U.S.C. 653, 655, 657; Walsh-Healey Act, 41 U.S.C. 35 et seq.; Service Contract Act of 1965, 41 U.S.C. 351 et seq.; Pub. L. 91–54, 40 U.S.C. 333; Pub. L. 85–742, 33 U.S.C. 941; National Foundation on Arts and Humanities Act, 20 U.S.C. 951 et seq.; Secretary of Labor's Orders 12–71 (36 FR 8754), 8–76 (41 FR 2505), or 9–83 (48 FR 35736); and 29 CFR Part 1911.

§ 1910.19 [Amended]

2. Paragraph (f) of § 1910.19 is hereby removed and reserved.

3. The authority citation for Subpart Z of Part 1910 continues to read as follows:

Authority: Secs. 6 and 8, Occupational Safety and Health Act, 29 U.S.C. 655, 657; Secretary of Labor's Orders No. 12–71 (36 FR 8754), 8–76 (41 FR 25059), or 9–83 (48 FR 35736), as applicable; and 29 CFR Part 1911.

Section 1910.1000 Tables Z–1, Z–2, Z–3 also issued under 5 U.S.C. 553.

Section 1910.1000 not issued under 29 CFR Part 1911, except for "Arsenic" and "Cotton Dust" listings in Table Z–1.

Section 1910.1001 also issued under Sec. 107 of Contract Work Hours and Safety Standards Act, 40 U.S.C. 333.

Section 1910.1002 not issued under 29 U.S.C. 655 or 29 CFR Part 1911; also issued under 5 U.S.C. 553.

Sections 1910.1003 through 1910.1018 also issued under 29 U.S.C. 653.

Section 1910.1025 also issued under 29 U.S.C. 653 and 5 U.S.C. 556.

Section 1910.1043 also issued under 5 U.S.C. 551 et seq.

Sections 1910.1045 and 1910.1047 also issued under 29 U.S.C. 653.

Sections 1910.1499 and 1910.1500 also issued under 5 U.S.C. 553.

4. In Table Z–1 of § 1910.1000, the footnote attached to the entry "Cotton Dust (raw)" is removed and a footnote "e" is added to the entry "Cotton Dust (raw)" to read as follows:

§ 1910.1000 Air contaminants.

* * * * *

TABLE Z–1

Substance	p/m³	mg/m³
* * * * *		
Cotton dust (raw)		1[e]
* * * * *		

* * * * *

[e] This 8 hour time weighted average is for respirable dust as measured by a vertical elutriator cotton dust sampler or equivalent instrument. This time weighted average applies to the cotton waste processing operations of waste recycling (sorting, blending, cleaning, and willowing) and garnetting.

5. Section 1910.1043 is revised, except for Appendices A–D which remain unchanged, to read as follows:

§ 1910.1043 Cotton dust.

(a) *Scope and application.* (1) This section, in its entirety, applies to the control of employee exposure to cotton dust in all workplaces where employees engage in yarn manufacturing, engage in slashing and weaving operations, or work in waste houses for textile operations.

(2) This section does not apply to the handling or processing of woven or knitted materials; to maritime operations covered by 29 CFR Parts 1915 and 1918; to harvesting or ginning of cotton; or to the construction industry.

(3) Only paragraphs (h) Medical surveillance, (k)(2)–(4) Recordkeeping—Medical Records, and Appendices B, C and D of this section apply in all work places where employees exposed to cotton dust engage in cottonseed processing or waste processing operations.

(4) This section applies to yarn manufacturing and slashing and weaving operations exclusively using washed cotton (as defined by paragraph (n) of this section) only to the extent

specified by paragraph (n) of this section.

(5) This section, in its entirety, applies to the control of all employees exposure to the cotton dust generated in the preparation of washed cotton from opening until the cotton is thoroughly wetted.

(6) This section does not apply to knitting, classing or warehousing operations except that employers with these operations, if requested by NIOSH, shall grant NIOSH access to their employees and workplaces for exposure monitoring and medical examinations for purposes of a health study to be performed by NIOSH on a sampling basis.

(b) *Definitions.* For the purpose of this section:

"Assistant Secretary" means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee;

"Blow down" means the general cleaning of a room or a part of a room by the use of compressed air.

"Blow off" means the use of compressed air for cleaning of short duration and usually for a specific machine or any portion of a machine.

"Cotton dust" means dust present in the air during the handling or processing of cotton, which may contain a mixture of many substances including ground up plant matter, fiber, bacteria, fungi, soil, pesticides, non-cotton plant matter and other contaminants which may have accumulated with the cotton during the growing, harvesting and subsequent processing or storage periods. Any dust present during the handling and processing of cotton through the weaving or knitting of fabrics, and dust present in other operations or manufacturing processes using raw or waste cotton fibers or cotton fiber byproducts from textile mills are considered cotton dust within this definition. Lubricating oil mist associated with weaving operations is not considered cotton dust.

"Director" means the Director of the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, or designee.

"Equivalent Instrument" means a cotton dust sampling device that meets the vertical elutriator equivalency requirements as described in paragraph (d)(1)(iii) of this section.

"Lint-free respirable cotton dust" means particles of cotton dust of approximately 15 micrometers or less aerodynamic equivalent diameter;

"Vertical elutriator cotton dust sampler" or "vertical elutriator" means a dust sampler which has a particle size cut-off at approximately 15 micrometers aerodynamic equivalent diameter when operating at the flow rate of 7.4 ± 0.2 liters of air per minute;

"Waste processing" means waste recycling (sorting, blending, cleaning and willowing) and garnetting.

"Yarn manufacturing" means all textile mill operations from opening to, but not including, slashing and weaving.

(c) *Permissible exposure limits and action levels*—(1) *Permissible exposure limits.* (i) The employer shall assure that no employee who is exposed to cotton dust in yarn manufacturing and cotton washing operations is exposed to airborne concentrations of lint-free respirable cotton dust greater than 200 $\mu g/m^3$ mean concentration, averaged over an eight-hour period, as measured be a vertical elutriator or an equivalent instrument.

(ii) The employer shall assure that no employee who is exposed to cotton dust in textile mill waste house operations or is exposed in yarn manufacturing to dust from "lower grade washed cotton" as defined in paragraph (n)(5)of this section is exposed to airborne concentrations of lint-free respirable cotton dust greater than 500 $\mu g/m^3$ mean concentration, averaged over an eight-hour period, as measured by a vertical elutriator or an equivalent instrument.

(iii) The employer shall assure that no employee who is exposed to cotton dust in the textile processes known as slashing and weaving is exposed to airborne concentrations of lint-free respirable cotton dust greater than 750 $\mu g/m^3$ mean concentration, averaged over an eight hour period, as measured by a vertical elutriator or an equivalent instrument.

(2) *Action levels.* (i) The action level for yarn manufacturing and cotton washing operations is an airborne concentration of lint-free respirable cotton dust of 100 $\mu g/m^3$ mean concentration, averaged over an eight-hour period, as measured by a vertical elutriator or an equivalent instrument.

(ii) The action level for waste houses for textile operations is an airborne concentration of lint-free respirable cotton dust of 250 $\mu g/m^3$ mean concentration, averaged over an eight-hour period, as measured by a vertical elutriator or an equivalent instrument.

(iii) The action level for the textile processes known as slashing and weaving is an airborne concentration of lint-free respirable cotton dust of 375 $\mu g/m^3$ mean concentration, averaged over an eight-hour period, as measured by a vertical elutriator or an equivalent instrument.

(d) *Exposure monitoring and measurement*—(1) *General.* (i) For the purposes of this section, employee exposure is that exposure which would occur if the employee were not using a respirator.

(ii) The sampling device to be used shall be either the vertical elutriator cotton dust sampler or an equivalent instrument.

(iii) If an alternative to the vertical elutriator cotton dust sampler is used, the employer shall establish equivalency by reference to an OSHA opinion or by documenting, based on data developed by the employer or supplied by the manufacturer, that the alternative sampling devices meets the following criteria:

(A) It collects respirable particulates in the same range as the vertical elutriator (approximately 15 microns);

(B) Replicate exposure data used to establish equivalency are collected in side-by-side field and laboratory comparisons; and

(C) A minimum of 100 samples over the range of 0.5 to 2 times the permissible exposure limit are collected, and 90% of these samples have an accuracy range of plus or minus 25 per cent of the vertical elutriator reading with a 95% confidence level as demonstrated by a statistically valid protocol. (An acceptable protocol for demonstrating equivalency is described in Appendix E of this section.)

(iv) OSHA will issue a written opinion stating that an instrument is equivalent to a vertical elutriator cotton dust sampler if

(A) A manufacturer or employer requests an opinion in writing and supplies the following information:

(*1*) Sufficient test data to demonstrate that the instrument meets the requirements specified in this paragraph and the protocol specified in Appendix E of this section;

(*2*) Any other relevant information about the instrument and its testing requested by OSHA; and

(*3*) A certification by the manufacturer or employer that the information supplied is accurate, and

(B) if OSHA finds, based on information submitted about the instrument, that the instrument meets the requirements for equivalency specified by paragraph (d) of this section.

(2) *Initial monitoring.* Each employer who has a place of employment within the scope of paragraph (a)(1), (a)(4), or (a)(5) of this section shall conduct monitoring by obtaining measurements which are representative of the exposure of all employees to airborne concentrations of lint-free respirable cotton dust over an eight-hour period.

The sampling program shall include at least one determination during each shift for each work area.

(3) *Periodic monitoring.* (i) If the initial monitoring required by paragraph (d)(2) of this section or any subsequent monitoring reveals employee exposure to be at or below the permissible exposure limit, the employer shall repeat the monitoring for those employees at least annually.

(ii) If the initial monitoring required by paragraph (d)(2) of this section or any subsequent monitoring reveals employee exposure to be above the PEL, the employer shall repeat the monitoring for those employees at least every six months.

(iii) Whenever there has been a production, process, or control change which may result in new or additional exposure to cotton dust, or whenever the employer has any other reason to suspect an increase in employee exposure, the employer shall repeat the monitoring and measurements for those employees affected by the change or increase.

(4) *Employee notification.* (i) Within twenty working days after the receipt of monitoring results, the employer shall notify each employee in writing of the exposure measurements which represent that employee's exposure.

(ii) Whenever the results indicate that the employee's exposure exceeds the applicable permissible exposure limit specified in paragraph (c) of this section, the employer shall include in the written notice a statement that the permissible exposure limit was exceeded and a description of the corrective action taken to reduce exposure below the permissible exposure limit.

(e) *Methods of compliance*—(1) *Engineering and work practice controls.* The employer shall institute engineering and work practice controls to reduce and maintain employee exosure to cotton dust at or below the permissible exposure limit specified in paragraph (c) of this section, except to the extent that the employer can establish that such controls are not feasible.

(2) Whenever feasible engineering and work practice controls are not sufficient to reduce employee exposure to or below the permissible exposure limit, the employer shall nonetheless institute these controls to reduce exposure to the lowest feasible level, and shall supplement these controls with the use of respirators which shall comply with the provisions of paragraph (f) of this section.

(3) *Compliance program.* (i) Where the most recent exposure monitoring data indicates that any employee is exposed to cotton dust levels greater than the permissible exposure limit, the employer shall establish and implement a written program sufficient to reduce exposures to or below the permissible exposure limit solely by means of engineering controls and work practices as required by paragraph (e)(1) of this section.

(ii) The written program shall include at least the following:

(A) A description of each operation or process resulting in employee exposure to cotton dust at levels greater than the PEL;

(B) Engineering plans and other studies used to determine the controls for each process;

(C) A report of the technology considered in meeting the permissible exposure limit;

(D) Monitoring data obtained in accordance with paragraph (d) of this section;

(E) A detailed schedule for development and implementation of engineering and work practice controls, including exposure levels projected to be achieved by such controls;

(F) Work practice program; and

(G) Other relevant information.

(iii) The employer's schedule as set forth in the compliance program, shall project completion of the implementation of the compliance program no later than March 27, 1984 or as soon as possible if monitoring after March 27, 1984 reveals exposures over the PEL, except as provided in paragraph (m)(2)(ii)(B) of this section.

(iv) The employer shall complete the steps set forth in his program by the dates in the schedule.

(v) Written programs shall be submitted, upon request, to the Assistant Secretary and the Director, and shall be available at the worksite for examination and copying by the Assistant Secretary, the Director, and any affected employee or their designated representatives.

(vi) The written program required under paragraph (e)(3) of this section shall be revised and updated when necessary to reflect the current status of the program and current exposure levels.

(4) *Mechanical ventilation.* When mechanical ventilation is used to control exposure, measurements which demonstrate the effectiveness of the system to control exposure, such as capture velocity, duct velocity, or static pressure shall be made at reasonable intervals.

(f) *Use of respirators*—(1) *General.* Where the use of respirators is required under this section, the employer shall provide, at no cost to the employee, and assure the use of respirators which comply with the requirements of this paragraph (f). Respirators shall be used in the following circumstances:

(i) During the time periods necessary to install or implement feasible engineering controls and work practice controls;

(ii) During maintenance and repair activities in which engineering and work practice controls are not feasible;

(iii) In work situations where feasible engineering and work practice controls are not yet sufficient to reduce exposure to or below the permissible exposure limits;

(iv) In operations specified under paragraph (g)(1) of this section; and

(v) Whenever an employee requests a respirator.

(2) *Respirator selection.* (i) Where respirators are required under this section, the employer shall select the appropriate respirator from Table I below and shall assure that the employee uses the respirator provided.

TABLE I

Cotton dust concentration	Required respirator
Not greater than:	
(a) 5 x the applicable permissible exposure limit (PEL).	A disposable respirator with a particulate filter.
(b) 10 x the applicable PEL.	A quarter or half-mask respirator, other than a disposable respirator, equipped with particulate filters.
(c) 100 x the applicable PEL.	A full facepiece respirator equipped with high-efficiency particulate filters.
(d) Greater than 100 x the applicable PEL.	A powered air-purifying respirator equipped with high-efficiency particulate filters.

NOTES

1. A disposable respirator means the filter element is an inseparable part of the respirator.
2. Any respirators permitted at higher environmental concentrations can be used at lower concentrations.
3. Self-contained breathing apparatus are not required respirators but are permitted respirators.
4. Supplied air respirators are not required but are permitted under the following conditions: Cotton dust concentration not greater than 10X the PEL—Any supplied air respirator; not greater than 100X the PEL—Any supplied air respirator with full facepiece, helmet or hood; greater than 100X the PEL—A supplied air respirator operated in positive pressure mode.

(ii) The employer shall select respirators from those tested and approved for protection against dust by the National Institute for Occupational Safety and Health (NIOSH) under the provisions of 30 CFR Part 11.

(iii) Whenever respirators are required by this section for concentrations not greater than 100 × the applicable permissible exposure limit, the employer shall, upon the request of the employee, provide a powered air purifying respirator with a high efficiency particulate filter in lieu of the respirator specified in paragraphs (a), (b), or (c) of Table I.

(iv) Whenever a physician determines that an employee who works in an area in which the dust level exceeds the PEL is unable to wear any form of respirator,

including a powered air purifying respirator, the employee shall be given the opportunity to transfer to another position which is available or which later becomes available having a dust level at or below the PEL. The employer shall assure that an employee who is transferred from an area in which the dust level exceeds the PEL due to an inability to wear a respirator suffers no reduction in current wage rate or other benefits as a result of the transfer.

(3) *Respirator program.* The employer shall institute a respirator program in accordance with § 1910.134 of this part.

(4) *Respirator usage.* (i) The employer shall assure that the respirator used by each employee exhibits minimum facepiece leakage and that the respirator is fitted properly.

(ii) The employer shall allow each employee who uses a filter respirator, to change the filter elements whenever an increase in breathing resistance is detected by the employee. The employer shall maintain an adequate supply of filter elements for this purpose.

(iii) The employer shall allow employees who wear respirators to wash their faces and respirator face pieces to prevent skin irritation associated with respirator use.

(g) *Work practices.* Each employer shall, regardless of the level of employee exposure, immediately establish and implement a written program of work practices which shall minimize cotton dust exposure. The following shall be included were applicable:

(1) Compressed air "blow down" cleaning shall be prohibited where alternative means are feasible. Where compressed air is used for cleaning, the employees performing the "blow down" or "blow off" shall wear suitable respirators. Employees whose presence is not required to perform "blow down" or "blow of" shall be required to leave the area affected by the "blow down" or "blow off" during this cleaning operation.

(2) Cleaning of clothing or floors with compressed air shall be prohibited.

(3) Floor sweeping shall be performed with a vacuum or with methods designed to minimize dispersal of dust.

(4) In areas where employees are exposed to concentrations of cotton dust greater than the permissible exposure limit, cotton and cotton waste shall be stacked, sorted, baled, dumped, removed or otherwise handled by mechanical means, except where the employer can show that it is infeasible to do so. Where infeasible, the method used for handling cotton and cotton waste shall be the method which reduces exposure to the lowest level feasible.

(h) *Medical surveillance*—(1) *General.* (i) Each employer covered by the standard shall institute a program of medical surveillance for all employees exposed to cotton dust.

(ii) The employer shall assure that all medical examinations and procedures are performed by or under the supervision of a licensed physician and are provided without cost to the employee.

(iii) Persons other than licensed physicians, who administer the pulmonary function testing required by this section shall have completed a NIOSH-approved training course in spirometry.

(2) *Initial examinations.* The employer shall provide medical surveillance to each employee who is or may be exposed to cotton dust. For new employees, this examination shall be provided prior to initial assignment. The medical surveillance shall include at least the following:

(i) A medical history;

(ii) The standardized questionnaire contained in Appendix B; and

(iii) A pulmonary function measurement, including a determination of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), the FEV_1/FVC ratio, and the percentage that the measured values of FEV_1 and FVC differ from the predicted values, using the standard tables in Appendix C. These determinations shall be made for each employee before the employee enters the workplace on the first day of the work week, preceded by at least 35 hours of no exposure to cotton dust. The tests shall be repeated during the shift, no less than 4 and no more than 10 hours after the beginning of the work shift; and, in any event, no more than one hour after cessation of exposure. Such exposure shall be typical of the employee's usual workplace exposure. The predicted FVE_1 and FVC for blacks shall be multiplied by 0.85 to adjust for ethnic differences.

(iv) Based upon the questionnaire results, each employee shall be graded according to Schilling's byssinosis classification system.

(3) *Periodic examinations.* (i) The employer shall provide at least annual medical surveillance for all employees exposed to cotton dust above the action level in yarn manufacturing, slashing and weaving, cotton washing and waste house operations. The employer shall provide medical surveillance at least every two years for all employees exposed to cotton dust at or below the action level, for all employees exposed to cotton dust from washed cotton (except from washed cotton defined in paragraph (n)(3) of this section), and for all employees exposed to cotton dust in cottonseed processing and waste processing operations. Periodic medical surveillance shall include at least an update of the medical history, standardized questionnaire (App. B–111), Schilling byssinosis grade, and the pulmonary function measurements in paragraph (h)(2)(iii) of this section.

(ii) Medical surveillance as required in paragraph (h)(3)(i) of this section shall be provided every six months for all employees in the following categories:

(A) An FEV_1 of greater than 80 percent of the predicted value, but with an FEV_1 decrement of 5 percent or 200 ml. on a first working day;

(B) An FEV_1 of less than 80 percent of the predicted value; or

(C) Where, in the opinion of the physician, any significant change in questionnaire findings, pulmonary function results, or other diagnostic tests have occurred.

(iii) An employee whose FEV_1 is less than 60 percent of the predicted value shall be referred to a physician for a detailed pulmonary examination.

(iv) A comparison shall be made between the current examination results and those of previous examinations and a determination made by the physician as to whether there has been a significant change.

(4) *Information provided to the physician.* The employer shall provide the following information to the examination physician:

(i) A copy of this regulation and its Appendices:

(ii) A description of the affected employee's duties as they relate to the employee's exposure;

(iii) The employee's exposure level or anticipated exposure level;

(iv) A description of any personal protective equipment used or to be used; and

(v) Information from previous medical examinations of the affected employee which is not readily available to the examining physician.

(5) *Physician's written opinion.* (i) The employer shall obtain and furnish the employee with a copy of a written opinion from the examining physician containing the following:

(A) The results of the medical examination and tests including the FEV_1, FVC, AND FEV_1/FVC ratio;

(B) The physician's opinion as to whether the employee has any detected medical conditions which would place the employee at increased risk of material impairment of the employee's health from exposure to cotton dust;

(C) The physician's recommended limitations upon the employee's

exposure to cotton dust or upon the employee's use of respirators including a determination of whether an employee can wear a negative pressure respirator, and where the employee cannot, a determination of the employee's ability to wear a powered air purifying respirator; and,

(D) A statement that the employee has been informed by the physician of the results of the medical examination and any medical conditions which require further examination or treatment.

(ii) The written opinion obtained by the employer shall not reveal specific findings or diagnoses unrelated to occupational exposure.

(i) *Employee education and training*—(1) *Training program.* (i) The employer shall provide a training program for all employees exposed to cotton dust and shall assure that each employee is informed of the following:

(A) The acute and long term health hazards associated with exposure to cotton dust;

(B) The names and descriptions of jobs and processes which could result in exposure to cotton dust at or above the PEL.

(C) The measures, including work practices required by paragraph (g) of this section, necessary to protect the employee from exposures in excess of the permissible exposure limit;

(D) The purpose, proper use and limitations of respirators required by paragraph (f) of this section;

(E) The purpose for and a description of the medical surveillance program required by paragraph (h) of this section and other information which will aid exposed employees in understanding the hazards of cotton dust exposure; and

(F) The contents of this standard and its appendices.

(ii) The training program shall be provided prior to initial assignment and shall be repeated annually for each employee exposed to cotton dust, when job assignments or work processes change and when employee performance indicates a need for retraining.

(2) *Access to training materials.* (i) Each employer shall post a copy of this section with its appendices in a public location at the workplace, and shall, upon request, make copies available to employees.

(ii) The employer shall provide all materials relating to the employee training and information program to the Assistant Secretary and the Director upon request.

(j) *Signs.* The employer shall post the following warning sign in each work area where the permissible exposure limit for cotton dust is exceeded:

WARNING

COTTON DUST WORK AREA

MAY CAUSE ACUTE OR DELAYED

LUNG INJURY

(BYSSINOSIS)

RESPIRATORS

REQUIRED IN THIS AREA

(k) *Recordkeeping*—(1) *Exposure measurements.* (i) The employer shall establish and maintain an accurate record of all measurements required by paragraph (d) of this section.

(ii) The record shall include:

(A) A log containing the items listed in paragraph IV (a) of Appendix A, and the dates, number, duration, and results of each of the samples taken, including a description of the procedure used to determine representative employee exposure;

(B) The type of protective devices worn, if any, and length of time worn; and

(C) The names, social security numbers, job classifications, and exposure levels of employees whose exposure the measurement is intended to represent.

(iii) The employer shall maintain this record for at least 20 years.

(2) *Medical surveillance.* (i) The employer shall establish and maintain an accurate medical record for each employee subject to medical surveillance required by paragraph (h) of this section.

(ii) The record shall include:

(A) The name and social security number and description of the duties of the employee;

(B) A copy of the medical examination results including the medical history, questionnaire response, results of all tests, and the physician's recommendation;

(C) A copy of the physician's written opinion;

(D) Any employee medical complaints related to exposure to cotton dust;

(E) A copy of this standard and its appendices, except that the employer may keep one copy of the standard and the appendices for all employees, provided that he references the standard and appendices in the medical surveillance record of each employee; and

(F) A copy of the information provided to the physician as required by paragraph (h)(4) of this section.

(iii) The employer shall maintain this record for at least 20 years.

(3) *Availability.* (i) The employer shall make all records required to be maintained by paragraph (k) of this section available to the Assistant Secretary and the Director for examination and copying.

(ii) Employee exposure measurement records and employee medical records required by this paragraph shall be provided upon request to employees, designated representatives, and the Assistant Secretary in accordance with 29 CFR 1910.20(a)–(e) and (g)–(i).

(4) *Transfer of records.* (i) Whenever the employer ceases to do business, the successor employer shall receive and retain all records required to be maintained by paragraph (k) of this section.

(ii) Whenever the employer ceases to do business, and there is no successor employer to receive and retain the records for the prescribed period, these records shall be transmitted to the Director.

(iii) At the expiration of the retention period for the records required to be maintained by this section, the employer shall notify the Director at least 3 months prior to the disposal of such records and shall transmit those records to the Director if the Director requests them within that period.

(iv) The employer shall also comply with any additional requirements involving transfer of records set forth in 29 CFR 1910.20(h).

(l) *Observation of monitoring.* (1) The employer shall provide affected employees or their designated representatives an opportunity to observe any measuring or monitoring of employee exposure to cotton dust conducted pursuant to paragraph (d) of this section.

(2) Whenever observation of the measuring or monitoring of employee exposure to cotton dust requires entry into an area where the use of personal protective equipment is required, the employer shall provide the observer with and assure the use of such equipment and shall require the observer to comply with all other applicable safety and health procedures.

(3) Without interfering with the measurement, observers shall be entitled to:

(i) An explanation of the measurement procedures;

(ii) An opportunity to observe all steps related to the measurement of airborne concentrations of cotton dust performed at the place of exposure; and

(iii) An opportunity to record the results obtained.

(m) *Effective date.*—(1) *General.* This section is effective March 27, 1980, except as otherwise provided below.

(2) *Startup dates.*—(i) *Initial monitoring.* The initial monitoring required by paragraph (d)(2) of this

section shall be completed as soon as possible but no later than March 27, 1980.

(ii) *Methods of compliance: engineering and work practice controls.* (A) The engineering and work practice controls required by paragraph (e) of this section shall be implemented no later than March 27, 1984 except as set forth in paragraph (m)(2)(ii)(B) of this section.

(B) The engineering and work practice controls required by paragraph (e) of this section shall be implemented no later than March 27, 1986, for ring spinning operations (including only ring spinning and winding, twisting, spooling, beaming and warping following ring spinning) where the operations meet the following criteria:

(*1*) The weight of the yarn being run is 100 percent cotton and the average yarn count by weight is 18 or below;

(*2*) The average weight of the yarn run is 80 percent or more cotton and the average yarn count by weight is 16 or below; or

(*3*) The average weight of the yarn being run is 50 percent or more cotton and the average yarn count by weight is 14 or below:

(C) When the provisions of paragraph (m)(2)(ii)(B) of this section are being relied upon, the following definitions shall apply:

(*1*) The average cotton content shall be determined by dividing the total weight of cotton in the yarns being run by the total weight of all the yarns being run in the relevant work area.

(*2*) The average yarn count shall be determined by multiplying the yarn count times the pounds of each particular yarn being run to get the "total hank" for each of the yarns being run in the relevant area. The "total hank" values for all of the yarns being run should then be summed and divided by the total pounds of yarn being run, to produce the average yarn count number for all the yarns being run in the relevant work area.

(D) Where the provisions of paragraph (m)(2)(ii)(B) of this section are being relied upon, the employer shall update the employer's compliance plan no later than February 13, 1986 to indicate the steps being taken to reduce cotton dust levels to 200 $\mu g/m^3$ through the use of engineering and work practice controls by March 27, 1986.

(E) Where the provisions of paragraph (m)(2)(ii)(B) of the section are being relied upon, the employer shall maintain airborne concentrations of cotton dust below 1000 $\mu g/MG53$ mean concentration averaged over an eight-hour period measured by a vertical elutriator or a method of equivalent accuracy and precision with engineering and work practice controls and shall maintain the permissible exposure limit specified by paragraph (c)(1)(i) of this section with any combination of engineering controls, work practice controls and respirators.

(iii) *Compliance program.* The compliance program required by paragraph (e)(3) of this section shall be established no later than March 27, 1981.

(iv) *Respirators.* The respirators required by paragraph (f) of this section shall be provided no later than April 27, 1980.

(v) *Work practices.* The work practices required by paragraph (g) of this section shall be implemented no later then June 27, 1980.

(vi) *Medical surveillance.* The medical surveillance required by paragraph (h) of this section shall be completed no later than March 27, 1981 for the textile industry and no later than June 13, 1986 for the cotton seed processing and waste processing industry.

(vii) *Employee education and training.* The initial education and training required by paragraph (i) of this section shall be completed as soon as possible but no later then June 27, 1980.

(3) *Amendments.* The amendments to this section published on December 13, 1985 become effective on February 11, 1986. If the amendments are not in effect because of stays of enforcement or judicial decisions, the provisions published in 29 CFR Parts 1900 to 1910, received as of July 1, 1985 are effective.

(n) *Washed Cotton*—(1) *Exemptions.* Cotton, after it has been washed by the processes described in this paragraph, is exempt from all or parts of this section as specified if the requirements of this paragraph are met.

(2) *Initial requirements.* (i) In order for an employer to qualify as exempt or partially exempt from this standard for operations using washed cotton, the employer must demonstrate that the cotton was washed in a facility which is open to inspection by the Assistant Secretary and the employer must provide sufficient accurate documentary evidence to demonstrate that the washing methods utilized meet the requirements of this paragraph.

(ii) An employer who handles or processes cotton which has been washed in a facility not under the employer's control and claims an exemption or partial exemption under this paragraph, must obtain from the cotton washer and make available at the worksite, to the Assistant Secretary, to any affected employee, or to their designated representative the following:

(A) A certification by the washer of the cotton of the grade of cotton, the type of washing process, and that the batch meets the requirements of this paragraph;

(B) Sufficient accurate documentation by the washer of the cotton grades and washing process; and

(C) An authorization by the washer that the Assistant Secretary or the Director may inspect the washer's washing facilities and documentation of the process.

(3) *Medical and dyed cotton.* Medical grade (USP) cotton, cotton that has been scoured, bleached and dyed, and mercerized yarn shall be exempt from all provisions of this standard.

(4) *Higher grade washed cotton.* The handling or processing of cotton classes as "low middling light spotted or better" which has been washed:

(i) On a continuous batt system or a rayon rinse system.

(ii) With water,

(iii) At a temperature of no less than 60° C,

(iv) With a water-to-fiber ratio of no less than 40:1, and

(v) With bacterial levels in the wash water controlled to limit bacterial contamination of the cotton.

shall be exempt from all provisions of the standard except the requirements of paragraphs (h) Medical Surveillance, (k)(2)–(4) Recordkeeping-Medical Records, and Appendices B, C, and D of this section.

(5) *Lower grade washed cotton.* The handling and processing of cotton of grades lower than "low middling light spotted," that has been washed as specified in paragraph (n)(4) of this section and has also been bleached, shall be exempt from all provisions of the standard except the requirements of paragraphs (c)(1)(ii) Permissible Exposure Limit, (d) Exposure Monitoring, (h) Medical Surveillance, (k) Recordkeeping, and Appendices B, C and D of this section.

(6) *Mixed grades of washed cotton.* If more than one grade of washed cotton is being handled or processed together, the requirements of the grade with the most stringent exposure limit, medical and monitoring requirements shall be followed.

(o) *Appendices.* (1) Appendices B, C, and D of this section are incorporated as part of this section and the contents of these appendices are mandatory.

(2) Appendix A of this section contains information which is not intended to create any additional obligations not otherwise imposed or to detract from any existing obligations.

(3) Appendix E of this section is a protocol which may be followed in the validation of alternative measuring devices as equivalent to the vertical elutriator cotton dust sampler. Other protocols may be used if it is demonstrated that they are statistically valid, meet the requirements in paragraph (d)(l)(iii) of this section, and are appropriate for demonstrating equivalency.

* * * * *

(Appendices A through D are unchanged and not reprinted.)

Appendix E—Vertical Elutriator Equivalency Protocol

a. *Samples to be taken*—In order to ascertain equivalency, it is necessary to collect a total of 100 samples from at least 10 sites in a mill. That is, there should be 10 replicate readings at each of 10 sites. The sites should represent dust levels which vary over the allowable range of 0.5 to 2 times the permissible exposure limit. Each sample requires the use of two vertical elutriators (VE's) and at least one but not more than two alternative devices (AD's). Thus, the end result is 200 VE readings and either 100 or 200 AD readings. The 2 VE readings and the 1 or 2 AD readings at each time and site must be made simultaneously. That is, the two VE's and one or two AD's must be arranged together in such a way that they are measuring essentially the same dust levels.

b. *Data averaging*—The two VE readings taken at each site are then averaged. These averages are to be used as the 100 VE readings. If two alternate devices were used, their test results are also averaged. Thus, after this step is accomplished, there will be 100 VE readings and 100 AD readings.

c. *Differences*—For each of the 100 sets of measurements (VE and AD) the difference is obtained as the average VE reading minus the AD reading. Call these differences D_i. Thus, we have.

$$D_i = VE_i - AD_i,\ i = 1,2, \ldots ,100 \qquad (1)$$

Next we compute the arithmetic mean and standard deviations of the differences, using equations (2) and (3), respectively.

$$\overline{X_D} = \frac{1}{N}\sum_{i=1}^{N} D_i \qquad (2)$$

$$S_D = \sqrt{\frac{\sum D_i^2 - \frac{(\sum D_i)^2}{N}}{N-1}} \qquad (3)$$

where N equals the number of differences (100 in this case), $\overline{X}_D$ is the arithmetic mean and S_D is the standard deviation.

We next calculate the critical value as $T = KS_D + |\overline{X}_D|$ where K = 1.87, based on 100 samples.

d. *Equivalency test.* The next step is to obtain the average of the 100 VE readings. This is obtained by equation (4)

$$X_{VE} = \frac{1}{N}\left(\sum_{i=1}^{N} VE_i\right) \qquad (4)$$

We next multiply 0.25 by $\overline{X}_{VE}$. If $T < 0.25\ \overline{X}_{VE}$ we can say that the alternate device has passed the equivalency test.

(The information collection requirements contained in the section are under consideration by the Office of Management and Budget. They will not take effect until approved.)

[FR Doc. 85-29293 Filed 12-9-85; 8:45 am]

BILLING CODE 4510-26-M