CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

13-601/S029

Trade Name: Mucomyst

Generic Name: acetylcysteine

Sponsor: Mead Johnson and Company

Approval Date: 9/1/1978

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

13-601/S029

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NDA 13-601/S-029

SEP 0 1 1978

Mead Johnson and Company
Attention: Jay K. Gunther, Ph.D.
Evansville, Indiana 47721

Gentlemen:

Please refer to your supplemental new drug application of June 21, 1978 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mucomyst (acetylcysteine) 10% and 20% Solutions.

The supplemental application provides for addition of a statement to the package insert indicating that sodium bicarbonate is compatible with Mucomyst.

We have completed the review of this supplemental application and it is approved. Our letter of September 14, 1963 detailed the conditions relating to the approval of this application.

Sincerely yours,

PGW 8/31/78

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

APPROVAL

cc: NDA 13-601/S-029
~~HFD-616~~ (CINN-DO HFR-5200)
HFD-160
HFD-160/Doc.Room
R/D IOneson(HFD-160) 7/10/78
R/D Init. RAJerussi 7/25/78
R/D Init. PGWalters 7/25/78
ft pd 7/25/78

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 13-601/S-029

DATE APPROVAL LETTER ISSUED: SEP 01 1978

TO: Press Relations Staff *(PA-40)*

FROM: [X] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [X] SUPPLEMENT TO NDA [ ] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [X] HUMAN [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Mucomyst 10% and 20% Solutions — acetylcysteine

DOSAGE FORM: sterile vials of 10% and 20% solutions for use in nebulizer

HOW DISPENSED: [X] RX [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

N-acetyl-2-cysteine 10% and 20%

NAME OF APPLICANT *(include City and State)*

Mead Johnson and Company
Evansville, Indiana 47721

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Mucolytic agent

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

Labeling change

FORM PREPARED BY

NAME: Irving Oneson — DATE: 7/10/78

FORM APPROVED BY

NAME: R. A. Jerussi — DATE: 7/25/78

Form FD 1642 (4/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

13-601/S029

LABELING

15251

NDA #13-601

Labeling: orig
NDA No: 13-601 Rc'd. 6-23-78
Reviewed by: [illegible]
7-10-78

SEP 0 1 1978

℞ CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

MUCOMYST®
(ACETYLCYSTEINE)

U.S. Patent No. 3,091,569

DESCRIPTION Acetylcysteine is the nonproprietary name for the N-acetyl derivative of the naturally occurring amino acid, L-cysteine. Chemically, it is N-acetyl-L-cysteine.

The compound is a white crystalline powder which melts at 104–110° C and has a very slight odor. It has a molecular weight of 163.2. The agent is supplied in vials containing a 10% or 20% solution of acetylcysteine as the sodium salt.

ACTIONS The viscosity of pulmonary mucous secretions depends on the concentrations of mucoprotein and to a lesser extent deoxyribonucleic acid (DNA). The latter increases with increasing purulence owing to cellular debris. The mucolytic action of acetylcysteine is related to the sulfhydryl group in the molecule. This group probably "opens" disulfide linkages in mucus thereby lowering the viscosity. The mucolytic activity of acetylcysteine is unaltered by the presence of DNA, and increases with increasing pH. Significant mucolysis occurs between pH 7 and 9.

INDICATIONS Mucomyst (acetylcysteine) is indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in such conditions as:

Chronic bronchopulmonary disease (chronic emphysema, emphysema with bronchitis, chronic asthmatic bronchitis, tuberculosis, bronchiectasis and primary amyloidosis of the lung)
Acute bronchopulmonary disease (pneumonia, bronchitis, tracheobronchitis)
Pulmonary complications of cystic fibrosis
Tracheostomy care
Pulmonary complications associated with surgery
Use during anesthesia
Post-traumatic chest conditions
Atelectasis due to mucous obstruction
Diagnostic bronchial studies (bronchograms, bronchospirometry, and bronchial wedge catheterization)

CONTRAINDICATIONS – Mucomyst (acetylcysteine) is contraindicated in those patients who are sensitive to it.

WARNINGS **After proper administration of acetylcysteine, an increased volume of liquefied bronchial secretions may occur. When cough is inadequate, the open airway must be maintained by mechanical suction if necessary. When there is a large mechanical block due to foreign body or local accumulation, the airway should be cleared by endotracheal aspiration, with or without bronchoscopy.**

Asthmatics under treatment with Mucomyst (acetylcysteine) should be watched carefully. If bronchospasm progresses, this medication should be immediately discontinued.

PRECAUTIONS With the administration of acetylcysteine, the patient may initially notice a slight disagreeable odor which soon is not noticeable. With a face mask there may be a stickiness on the face after nebulization which is easily removed by washing with water.

Under certain conditions, a color change may take place in the solution of acetylcysteine in the opened bottle. The light purple color is the result of a chemical reaction which does not significantly impair the safety or mucolytic efficacy of acetylcysteine.

Continued nebulization of an acetylcysteine solution with a dry gas will result in an increased concentration of the drug in the nebulizer because of evaporation of the solvent. Extreme concentration may impede nebulization and efficient delivery of the drug. Dilution of the nebulizing solution with Sterile Water for Injection, U.S.P., as concentration occurs, will obviate this problem.

ADVERSE EFFECTS – Adverse effects have inclu
Sensitivity and sensitization to Mucomyst have
susceptible patients, particularly asthmatics (see
degrees of bronchospasm associated with the admi
Most patients with bronchospasm are quickly rel
given by nebulization.

DOSAGE AND ADMINISTRATION – Mucomyst
stoppered glass vials containing 10 ml. or 30 ml. T
lesser concentration with either sterile normal salin
The 10% solution may be used undiluted.

Nebulization – face mask, mouth piece, tracheosto
When nebulized into a face mask, mouth piece, o
solution or 2–20 ml. of the 10% solution m
recommended dose for most patients is 3–5 ml. o
10% solution 3 to 4 times a day.

Nebulization – tent, Croupette
In special circumstances it may be necessary to n
this method of use must be individualized to take
and the patient's particular needs. This form c
volumes of the solution, occasionally as much
period. If a tent or Croupette must be used, the
solution (using 10% or 20% acetylcysteine) that v
tent or Croupette for the desired period. Adminis
prolonged periods, including overnight, may be des

Direct Instillation
When used by direct instillation, 1–2 ml. of a 10
as every hour.

When used for the routine nursing care of patie
10 to 20% solution may be given every 1
tracheostomy.

Acetylcysteine may be introduced directly
bronchopulmonary tree by inserting (under local
plastic catheter into the trachea. Two to 5 ml. of
by means of a syringe connected to the catheter.

Acetylcysteine may also be given through a pe
to 2 ml. of the 20% or 2–4 ml. of the 10% solution
by a syringe attached to the catheter.

Diagnostic Bronchograms
For diagnostic bronchial studies, 2 or 3 administrat
or 2–4 ml. of the 10% solution should be giv
intratracheally, prior to the procedure.

ADMINISTRATION OF AEROSOL
Materials
Mucomyst may be administered using convention
Certain materials used in nebulization equipment
reactive of these are certain metals (notably i
materials may come into contact with acetylc
following acceptable materials should be used:
aluminum, chromed metal, tantalum, sterling silve
tarnished after exposure, but this is not harmful to

ADVERSE EFFECTS – Adverse effects have included stomatitis, nausea and rhinorrhea. Sensitivity and sensitization to Mucomyst have been reported very rarely. A few susceptible patients, particularly asthmatics (see Warnings), may experience varying degrees of bronchospasm associated with the administration of nebulized acetylcysteine. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization.

DOSAGE AND ADMINISTRATION – Mucomyst (acetylcysteine) is available in plastic stoppered glass vials containing 10 ml. or 30 ml. The 20% solution may be diluted to a lesser concentration with either sterile normal saline or Sterile Water for Injection, U.S.P. The 10% solution may be used undiluted.

Nebulization – face mask, mouth piece, tracheostomy
When nebulized into a face mask, mouth piece, or tracheostomy, 1–10 ml. of the 20% solution or 2–20 ml. of the 10% solution may be given every 2–6 hours; the recommended dose for most patients is 3–5 ml. of the 20% solution or 6–10 ml. of the 10% solution 3 to 4 times a day.

Nebulization – tent, Croupette
In special circumstances it may be necessary to nebulize into a tent or Croupette, and this method of use must be individualized to take into account the available equipment and the patient's particular needs. This form of administration requires very large volumes of the solution, occasionally as much as 300 ml. during a single treatment period. If a tent or Croupette must be used, the recommended dose is the volume of solution (using 10% or 20% acetylcysteine) that will maintain a very heavy mist in the tent or Croupette for the desired period. Administration for intermittent or continuous prolonged periods, including overnight, may be desirable.

Direct Instillation
When used by direct instillation, 1–2 ml. of a 10 to 20% solution may be given as often as every hour.

When used for the routine nursing care of patients with tracheostomy, 1 to 2 ml. of a 10 to 20% solution may be given every 1 to 4 hours by instillation into the tracheostomy.

Acetylcysteine may be introduced directly into a particular segment of the bronchopulmonary tree by inserting (under local anesthesia and direct vision) a small plastic catheter into the trachea. Two to 5 ml. of the 20% solution may then be instilled by means of a syringe connected to the catheter.

Acetylcysteine may also be given through a percutaneous intratracheal catheter. One to 2 ml. of the 20% or 2–4 ml. of the 10% solution every 1 to 4 hours may then be given by a syringe attached to the catheter.

Diagnostic Bronchograms
For diagnostic bronchial studies, 2 or 3 administrations of 1 to 2 ml. of the 20% solution or 2–4 ml. of the 10% solution should be given by nebulization or by instillation intratracheally, prior to the procedure.

ADMINISTRATION OF AEROSOL
Materials
Mucomyst may be administered using conventional nebulizers made of plastic or glass. Certain materials used in nebulization equipment react with acetylcysteine. The most reactive of these are certain metals (notably iron and copper) and rubber. Where materials may come into contact with acetylcysteine solution, parts made of the following acceptable materials should be used: glass, plastic, aluminum, anodized aluminum, chromed metal, tantalum, sterling silver, or stainless steel. Silver may become tarnished after exposure, but this is not harmful to the drug action nor to the patient.

Nebulizing Gases
Compressed tank gas (air) or an air compressor should be used to provide pressure for nebulizing the solution. Oxygen may also be used but should be used with usual caution in patients with severe respiratory disease and CO_2 retention.

APPARATUS Mucomyst (acetylcysteine) is usually administered as fine nebulae for its local effect, and the nebulizer used should be capable of providing optimal quantities of a suitable range of particle sizes.

The selection of apparatus for nebulization depends upon the desired particle size and rate of administration. Commercially available nebulizers will produce nebulae of acetylcysteine satisfactory for retention in the respiratory tract. Most of the nebulizers tested will supply a high proportion of the drug solution as particles of less than 10 microns in diameter. Mitchell[a] has shown that a range of particle size up to 10 microns should be satisfactorily retained in the respiratory tract.

Units that nebulized acetylcysteine with a satisfactory efficiency were the Maxi-Myst Nebulizer (Mead Johnson Pharmaceutical Division, Evansville, Indiana), Mist-O_2-Gette ET-I-T (Mist O_2 Gen Equipment Co., 2711 Adeline St., Oakland, Calif.), De Vilbiss 42 (The De Vilbiss Co., Somerset, Pa.), and Vaponefrin Standard Plastic Nebulizer (Vaponefrin Co., Division U.S. Vitamin & Pharmaceutical Corporation, 800 Second Avenue, New York, New York). Other units tested performed with equivalent or lesser efficiency of nebulization.

Hand bulbs may be used but are not recommended for routine use for nebulizing Mucomyst (acetylcysteine) because their output is generally too small. Some hand-operated nebulizers deliver particles that are larger than optimum for inhalation therapy.

Heated (hot pot) Nebulizer
Mucomyst should not be placed directly into the chamber of a heated (hot pot) nebulizer. A heated nebulizer may be part of the nebulization assembly to provide a warm saturated atmosphere if the Mucomyst aerosol is introduced by means of a separate unheated nebulizer. Usual precautions for administration of warm saturated nebulae should be observed.

The nebulized solution may be breathed directly from the nebulizer. Nebulizers may also be attached to plastic face masks, plastic face tents, plastic mouth pieces, conventional plastic oxygen tents, or head tents. Suitable nebulizers may also be fitted for use with the various intermittent positive pressure breathing (IPPB) machines.

The nebulizing equipment should be cleaned immediately after use; the residues may occlude the fine orifices or corrode metal parts.

Prolonged Nebulization
When three-fourths of the initial volume of acetylcysteine solution has been nebulized, a quantity of Sterile Water for Injection, U.S.P. (approximately equal to the volume of solution remaining) should be added to the nebulizer. This obviates any concentration of the agent in the residual solvent remaining after prolonged nebulization.

Storage of Opened Vials
If only a portion of the solution in the vial is used, to minimize contamination the remainder should be stored in a refrigerator and used within 96 hours.

COMPATIBILITY The physical and chemical compatibility of acetylcysteine solutions with other drugs commonly administered by nebulization, direct instillation, or topical application, has been studied.

Acetylcysteine should not be mixed with all antibiotics. For example, the antibiotics tetracycline hydrochloride, oxytetracycline hydrochloride, and erythromycin lactobionate were found to be incompatible when mixed in the same solution. These agents may be administered from separate solutions if administration of these agents is desirable.

a. Amer. Rev. Resp. Dis. 82:627-639, 1960.

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COMPATIBILITY The physical and chemical compatibility of acetylcysteine solutions with other drugs commonly administered by nebulization, direct instillation, or topical application, has been studied.

Acetylcysteine should not be mixed with all antibiotics. For example, the antibiotics tetracycline hydrochloride, oxytetracycline hydrochloride, and erythromycin lactobionate were found to be incompatible when mixed in the same solution. These agents may be administered from separate solutions if administration of these agents is desirable.

a. Amer. Rev. Resp. Dis. 82:627-639, 1960.

IN VITRO COMPATIBILITY[1] TESTS OF ACETYLCYSTEINE

PRODUCT AND/OR AGENTS	MANUFACTURER (TRADEMARK)	COMPATIBILITY RATING	RATIO TESTED[6]	
			ACETYLCYSTEINE	PRODUCT OR AGENT
BRONCHODILATORS				
Isoproterenol HCl[2]		Compatible	3.0%	0.5%
Isoproterenol HCl[2]		Compatible	10%	0.05%
Isoproterenol HCl[2]		Compatible	20%	0.05%
Isoproterenol HCl	Winthrop (Isuprel 1%)	Compatible	13.3% (2 parts)	.33% (1 part)
Aerolone Compound	Lilly	Compatible	13.3% (2 parts)	(1 part)
Bronkosol	Breon	Compatible	13.3% (2 parts)	(1 part)
Epinephrine HCl	Parke, Davis (Adrenalin HCl 1:100)	Compatible	13.3% (2 parts)	.33% (1 part)
CONTRAST MEDIA				
Iodized Oil U.S.P.	Fougera (Lipiodol)	Incompatible	20%/20 ml	40%/10 ml
DECONGESTANTS				
Phenylephrine HCl[2]		Compatible	3.0%	.25%
Phenylephrine HCl	Winthrop (Neo-Synephrine HCl Nasal Solution, 0.5%)	Compatible	13.3% (2 parts)	.17% (1 part)
ENZYMES				
Pancreatic Dornase (mix and use at once)	Merck (Dornavac)	Compatible	16.7%	8,000 U/ml
Chymotrypsin	Armour	Incompatible	5%	400 γ/ml
Trypsin	Armour	Incompatible	5%	400 γ/ml
SOLVENTS				
Alcohol		Compatible	12%	10-20%
Propylene Glycol		Compatible	3%	10%
STEROIDS				
Dexamethasone 21-Phosphate	Merck (Decadron Phosphate)	Compatible	16%	0.8 mg/ml
Prednisolone 21-Phosphate[5]	Merck (Hydeltrasol)	Compatible	16.7%	3.3 mg/ml
OTHER AGENTS				
Hydrogen Peroxide		Incompatible	(All ratios)	
Sodium Bicarbonate, U.S.P.		Compatible	20% (1 part)	4.2% (1 part)

[1] The rating, **Incompatible**, is based on the formation of a precipitate, a change in clarity, immiscibility, or a rapid loss of potency of acetylcysteine or the active ingredient of the PRODUCT AND/OR AGENT in the admixture.
The rating, **Compatible**, means that there was no significant physical change in the admixture when compared with a control solution of the PRODUCT AND/OR AGENT, and that there was no predicted chemical incompatibility. All of the admixtures have been tested for short-term chemical compatibility by assaying for the concentration of acetylcysteine after mixing.

[2] The active ingredient in the PRODUCT AND/OR AGENT was also assayed after mixing.
Some of the admixtures developed minor physical changes which were considered to be insufficient to rate the admixture **Incompatible**. These are listed in footnotes 3, 4, and 5.

[3] A strong odor developed after storage for 24 hours at room temperature.

[4] The admixture was a slightly darker shade of yellow than a control solution of the PRODUCT AND/OR AGENT.

[5] A light tan color developed after storage for 24 hours at room temperature.

[6] Entries are final concentrations. Values in parentheses relate volumes of Mucomyst® solutions to volumes of test solutions.

The supplying of these data should not be interpreted as a recommendation for combining Mucomyst with other drugs. The table is not presented as positive assurance that no incompatibility will be present, since these data are based only on short-term compatibility studies done in the Mead Johnson Research Center. Manufacturers of drug products may change formulations. This could alter compatibilities. These data are intended to serve only as a guide for predicting compounding problems.

If it is deemed advisable to prepare an admixture, it should be administered as soon as possible after preparation. Do not store unused mixtures.

HOW SUPPLIED Mucomyst® 20% acetylcysteine solution. Sterile.

NDC 0087-0570-03	Cartons of three 10 ml. vials, 1 plastic dropper.
NDC 0087-0570-09	Cartons of three 30 ml. vials.
NDC 0087-0570-07	Cartons of twelve 4 ml. vials.

Mucomyst®-10 10% acetylcysteine solution. Sterile.

NDC 0087-0572-01	Cartons of three 10 ml. vials, 1 plastic dropper.
NDC 0087-0572-02	Cartons of three 30 ml. vials.
NDC 0087-0572-03	Cartons of twelve 4 ml. vials.

REFERENCES A bibliography on Mucomyst will be supplied on request.

Mead Johnson PHARMACEUTICAL DIVISION
MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A.

 Date of Printing: May, 1978

IN VITRO COMPATIBILITY[1] TESTS OF ACETYLCYSTEINE

PRODUCT AND/OR AGENTS	MANUFACTURER (TRADEMARK)	COMPATIBILITY RATING	RATIO TESTED[4] ACETYLCYSTEINE	RATIO TESTED[4] PRODUCT OR AGENT
ANESTHETIC, GAS				
Halothane U.S.P.	Ayerst (Halothane)	Compatible	20%	Infinite
Nitrous Oxide U.S.P.	National Cylinder Gas Company	Compatible	20%	Infinite
ANESTHETIC, LOCAL				
Cocaine HCl	Merck	Compatible	10%	5%
Lidocaine HCl	Astra (Xylocaine HCl)	Compatible	10%	2%
Tetracaine HCl	Winthrop (Pontocaine HCl)	Compatible	10%	1%
ANTIBACTERIALS	(A parenteral form of each antibiotic was used)			
Bacitracin[2,3] (mix and use at once)	Upjohn	Compatible	10%	5,000 U/ml
Cephaloridine[2,4]	Lilly (Loridine)	Compatible	10%	46 mg/ml
Chloramphenicol Sodium Succinate	Parke, Davis (Chloromycetin)	Compatible	20%	20 mg/ml
Disodium Carbenicillin[2] (mix and use at once)	Roerig (Geopen)	Compatible	10%	125 mg/ml
Gentamicin Sulfate[2]	Schering (Garamycin)	Compatible	10%	20 mg/ml
Kanamycin Sulfate[2]	Bristol (Kantrex)	Compatible	10%	167 mg/ml
(mix and use at once)		Compatible	17%	85 mg/ml
Lincomycin HCl[2]	Upjohn (Lincocin)	Compatible	10%	150 mg/ml
Neomycin Sulfate[2]	Upjohn (Mycifradin Sulfate)	Compatible	10%	100 mg/ml
Novobiocin Sodium[2]	Upjohn (Albamycin)	Compatible	10%	25 mg/ml
Pencillin G Potassium[2]	Lilly (Buffered Potassium	Compatible	10%	25,000 U/ml
(mix and use at once)	Pencillin G)	Compatible	10%	100,000 U/ml
Polymyxin B Sulfate[2]	Burroughs Wellcome (Aerosporin)	Compatible	10%	50,000 U/ml
Rolitetracycline[2] (mix and use at once)	Bristol (Syntetrin-IM)	Compatible	10%	87.5 mg/ml
Sodium Cephalothin	Lilly (Keflin)	Compatible	10%	110 mg/ml
Sodium Colistimethate[2] (mix and use at once)	Warner-Chilcott (Coly-Mycin M)	Compatible	10%	37.5 mg/ml
Vancomycin HCl[2]	Lilly Vancocin HCl)	Compatible	10%	25 mg/ml
Amphotericin B	Squibb (Fungizone Intravenous)	Incompatible	4-15%	1.0-4.0 mg/ml
Chlortetracycline HCl[2]	Lederle (Aureomycin HCl)	Incompatible	10%	12.5 mg/ml
Erythromycin Lactobionate	Abbott (Erythrocin Lactobionate-IV)	Incompatible	10%	15 mg/ml
Oxytetracycline HCl	Pfizer (Terramycin IV)	Incompatible	10%	12.5 mg/ml
Sodium Ampicillin	Bristol (Polycillin-N)	Incompatible	10%	50 mg/ml
Tetracycline HCl	Lederle (Achromycin)	Incompatible	10%	12.5 mg/ml

IN VITRO COMPATIBILITY[1] TESTS OF ACETYLCYSTEINE

PRODUCT AND/OR AGENTS	MANUFACTURER (TRADEMARK)	COMPATIBILITY RATING	RATIO TESTED[4] ACETYLCYSTEINE	RATIO TESTED[4] PRODUCT OR AGENT
BRONCHODILATORS				
Isoproterenol HCl[2]		Compatible	3.0%	0.5%
Isoproterenol HCl[2]		Compatible	10%	0.05%
Isoproterenol HCl[2]		Compatible	20%	0.05%
Isoproterenol HCl	Winthrop (Isuprel 1%)	Compatible	13.3% (2 parts)	.33% (1 part)
Aerolone Compound	Lilly	Compatible	13.3% (2 parts)	(1 part)
Bronkosol	Breon	Compatible	13.3% (2 parts)	(1 part)
Epinephrine HCl	Parke, Davis (Adrenalin HCl 1:100)	Compatible	13.3% (2 parts)	.33% (1 part)
CONTRAST MEDIA				
Iodized Oil U.S.P.	Fougera (Lipiodol)	Incompatible	20%/20 ml	40%/10 ml
DECONGESTANTS				
Phenylephrine HCl[2]		Compatible	3.0%	.25%
Phenylephrine HCl	Winthrop (Neo-Synephrine HCl Nasal Solution, 0.5%)	Compatible	13.3% (2 parts)	.17% (1 part)
ENZYMES				
Pancreatic Dornase (mix and use at once)	Merck (Dornavac)	Compatible	16.7%	8,000 U/ml
Chymotrypsin	Armour	Incompatible	5%	400 γ/ml
Trypsin	Armour	Incompatible	5%	400 γ/ml
SOLVENTS				
Alcohol		Compatible	12%	10-20%
Propylene Glycol		Compatible	3%	10%
STEROIDS				
Dexamethasone 21-Phosphate	Merck (Decadron Phosphate)	Compatible	16%	0.8 mg/ml
Prednisolone 21-Phosphate[5]	Merck (Hydeltrasol)	Compatible	16.7%	3.3 mg/ml
OTHER AGENTS				
Hydrogen Peroxide		Incompatible	(All ratios)	
Sodium Bicarbonate, U.S.P.		Compatible	20% (1 part)	4.2% (1 part)

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REFERENC

MEA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

13-601/S029

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-160

2. NDA NUMBER: 13-601

3. NAME AND ADDRESS OF APPLICANT *(City and State)*: Mead Johnson and Company, Evansville, Indiana 47721

4. AF NUMBER: 7-111

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
5029	6-21-78

6. NAME OF DRUG: Mucomyst

7. NONPROPRIETARY NAME: N-acetylcysteine

8. SUPPLEMENT(S) PROVIDES FOR: addition of a statement to the package insert indicating that sodium bicarbonate is compatible with Mucomyst

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES

10. PHARMACOLOGICAL CATEGORY: mucolytic agent

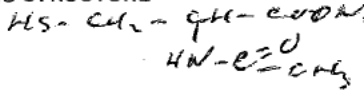
11. HOW DISPENSED: ☑ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): 4, 10 and 30 ml vials of sterile solutions

14. POTENCY *(Iso)*: 10% and 20% solutions for use in aerosol dispensers

15. CHEMICAL NAME AND STRUCTURE



16. RECORDS AND REPORTS

CURRENT: ☑ YES ☐ NO

REVIEWED: ☑ YES ☐ NO

17. COMMENTS: Applicant wishes to add a statement to the compatibility section of the package insert to the effect that equal parts of Mucomyst and sodium bicarbonate (4.2%) USP are compatible.

He has mixed equal parts of Mucomyst (20%) with Sodium Bicarbonate for Injection (4.2%) USP and stored at 1, 4 and 8 days at 25°C and at 5°C. Assay for acetylcysteine HCl was normal. Color, clarity and odor was normal. The pH went to 7.9 and stayed unchanged.

Applicant has submitted PPL with this addition to compatibility section of package insert.

18. CONCLUSIONS AND RECOMMENDATIONS: Approve Supplement.

cc: NDA 13-601/S-029
HFD-~~160, Doc. Room~~/HFD-160
R/D IOneson 7/10/78
R/D Init. RAJerussi 7/25/78
fx pd 9/1/78

SEP 0 1 1978

RAJ 7/25/78

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
IRVING ONESON	I Oneson	7-10-78

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

13-601/S029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 13-601

Mead Johnson Research Center
Attention: Jay K. Gunther, Ph.D.
Evansville, IN 47721

JUN 27 1978

Gentlemen:

We acknowledge receipt of your supplemental application for the following:

Name of drug: (Mucomyst and Mucomyst-10)

NDA number: 13-601

Supplement number: S-029 Labeling

Date of supplement: June 21, 1978

Date of receipt: June 23, 1978

All communications concerning this NDA should be addressed as follows:

Bureau of Drugs HFD-160
Attention: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

Gary H. Boyer

Gary H. Boyer
Acting Supervisory Consumer
Safety Officer
Division of Surgical-Dental
Drug Products
Bureau of Drugs

cc: NDA Orig.
HFD-160
R/D by: DPaulsgrove(HFD-160)6/26/78
R/D Init. by: GHBoyer 6/27/78
PGWalters 6/27/78
F/T 6/27/78:jw Doc. Room

SUPPLEMENT ACKNOWLEDGEMENT

DPaulsgrove
6-27-78

PGW 6/27/78

15243

NDA NO. 13-601 REF. NO. S-029 LF

NDA SUPPL FOR Labeling

Mead Johnson RESEARCH CENTER / EVANSVILLE, INDIANA 47721 TELEPHONE (812) 426-6000

June 21, 1978

Division of Surgical Dental
Drug Products
Respiratory Anesthesia Drugs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Reference: NDA #13-601 (Mucomyst and Mucomyst-10)

Gentlemen:

We are pleased to submit a supplemental New Drug Application which proposes a revision to the compatibility section of the package insert for the Mucomyst and Mucomyst-10 products. The only change that will be made is the addition of a statement indicating that sodium bicarbonate is compatible with these products.

We have included in this submission the data that supports this change and printed copies of the revised labeling. These data are fully convincing and we trust we may look forward to a prompt review and approval.

Very truly yours,

MEAD JOHNSON & CO.

Jay K. Gunther

Jay K. Gunther, Ph.D.
Associate Director
Drug Regulatory Affairs

eb

Attachments
(in triplicate)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

15244

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

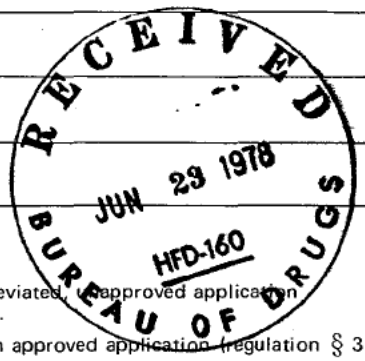
(Title 21, Code of Federal Regulations, § 314.1)

Name of applicant Mead Johnson & Company

Address Evansville, IN 47721

Date June 21, 1978

Name of new drug Mucomyst and Mucomyst-10



☐ Original application (regulation § 314.1).

☐ Amendment to original, unapproved application (regulation § 314.6)

☐ Abbreviated application (regulation § 314.1(f)).

☐ Amendment to abbreviated, unapproved application (regulation § 314.6).

☒ Supplement to an approved application (regulation § 314.8).

☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §201.100 (21 CFR 201.100). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §314.8 of the new-drug regulations.

Attached hereto, submitted in the form described in §314.1(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, and expanded summary and evaluation as outlined in §314.1(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it it is to be advertised or represented, in accord with §201.100 (21 CFR 201.100). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of nay such advertising for a prescription drug (see §310.300 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and control applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper, identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing

history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the sutitability of the analytical method used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §310.3(g), from the batches(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for inital marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §310.3(g) of the new-drug regulations, from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug; *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Drugs and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and in vitro studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or other wise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clincial observations and laboratory examinations made, full information

concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of HEW. 5600 Fishers Lane, Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §310.9 of the new-drug regulations, about related drugs; a bibliography will suffice. Include the evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

h. In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320, Subpart B).

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §314.8 of the new-drug regulations concerning supplemental applications.

14. [Reserved]

15. The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §6.1 of this chapter.

Mead Johnson & Co.

(Applicant)

Per Jay K. Gunther

(Responsible official or agent)

Associate Director
Drug Regulatory Affairs

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Tittle 18, sec. 1001.)

Note: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.