



Vol. 40, No. 30  
Aug. 4, 2008

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**Correction:** In “J&J Submits sNDA for Risperdal Consta” in the July 28 issue, the sentence reading “The drug contains the same active ingredient as Risperdal but is taken in a pill form every two weeks” should have said, “... by injection every two weeks.”

## FDA Globalization Bill Evolving Into New GMP Legislation

As Congress continues its work on the FDA Globalization Act, a bill originally aimed at increasing FDA inspections of manufacturing facilities, the legislation is evolving into a new GMP law.

The first discussion draft of the bill, which included documentation requirements and fees for imported drug ingredients and facility registration to defray the cost of overseas inspections, was released earlier this year (*WDL, May 5*). A new second draft of the legislation was released last week by the House Energy and Commerce Committee.

Under the second draft of the bill, drugmakers must manufacture pharmaceuticals under quality risk management plans, and firms must conduct periodic audits to monitor suppliers. The bill also describes elements that risk management plans should contain.

*(See Globalization, Page 2)*

## Amgen ESAs Get Labeling Restrictions, New Warning

The FDA is requiring Amgen to modify physician labeling for its erythropoiesis stimulating agents (ESAs) Aranesp, Epogen with a revised boxed warning and a new restricted indication, using language that Amgen opposed.

The agency used authority it gained through the FDA Amendments Act of 2007 to order the company to make the changes — the first time the agency has invoked its new powers under that act to order a company to change physician labeling, according to Richard Pazdur, director of the FDA’s Office of Oncology Drug Products.

Amgen has five days to appeal the order or 15 days to update the labels. The company said it would communicate the new labels to physicians soon.

The revised boxed warning and indications section of physician labeling for Aranesp (darbepoetin alfa) and Epogen (epoetin alfa) —

*(See ESAs, Page 10)*

## Globalization, from Page 1

“A quality risk management plan ... shall address risk assessment, risk control, risk communication and risk review,” the draft bill states. Such plans would need to require pharmaceutical companies to use vendor qualification programs for raw materials and ingredient suppliers, as well as for third-party contract manufacturers they want to use.

Quality risk management plans would have to be periodically revised and updated and would “define responsibilities and communication processes for manufacturing, quality control and quality assurance activities” with respect to suppliers and contractors, the bill states.

In addition, risk management plans must have effective systems “to detect any hazard that has been, or is reasonably likely to be, present in or on the drug,” including appropriate specifications and test methods to verify the quality, identity, purity and strength of drug ingredients, according to the new draft.

HHS would have the authority to issue regulations mandating additional requirements for risk management plans as it sees fit if new rules are deemed necessary to protect public health.

The commissioner of the FDA would have subpoena authority for testimony and documentary evidence in connection with any hearing, investigation or other proceeding involving a violation of the Food, Drug and Cosmetic Act (FDCA). The power also would apply to investigations “to determine if a person is in compliance with a standard or other requirement of the act,” the bill states.

The bill also would impose a maximum life sentence for knowingly counterfeiting drugs when they lead to death. In other cases, knowingly counterfeiting a drug would carry a maximum 20-year sentence and a fine not to exceed \$250,000 for each count.

When a firm fails to have a quality risk management plan in place, penalties for introducing drugs that are adulterated or misbranded

would carry a fine of \$15,000 per day, with total fines not to exceed \$1 million for all violations adjudicated in a single proceeding, the bill states.

The bill also would codify the federal government’s extraterritorial jurisdiction over FDCA violations for imported drugs — an authority that HHS Secretary Michael Leavitt requested from Congress (*WDL*, March 3).

A copy of the drug-related portions of the new FDA Globalization Act draft can be accessed at [www.fdanews.com/ext/files/Revised FDAGA Draft Drug Safety Title.pdf](http://www.fdanews.com/ext/files/Revised_FDAGA_Draft_Drug_Safety_Title.pdf). — Christopher Hollis

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## Lawmakers Propose Bill To Fund Academic Detailing

Lawmakers have introduced a bill that would fund nonprofit and government programs to develop unbiased educational materials about the safety, effectiveness and cost of prescription and nonprescription drugs, and train and deploy educators to provide the information to prescribers.

It would provide grants to produce educational materials on prescription, generic and OTC products. It also would provide 10 grants or contracts to train and send such healthcare professionals as pharmacists and nurses to physicians’ and other health providers’ offices to distribute and discuss the information.

To ensure the information is unbiased, the bill would bar grant recipients from receiving financial support from drug manufacturers whose products they review.

Sen. Herb Kohl (D-Wis.), chairman of the Special Committee on Aging, is co-sponsoring the bill, and Reps. Henry Waxman (D-Calif.), chairman of the House Committee on Oversight and Government Reform, and Frank Pallone (D-N.J.) are introducing it in the House of Representatives.

In a written statement announcing his bill, Kohl cited an April editorial in the *Journal of the*

(See **Detailing**, Page 12)

## GAO Says FDA Oversight of Off-Label Drug Promotion Is Not Systematic

The FDA takes an average of seven months from the time it begins drafting to issue regulatory letters asking drugmakers to cease violative off-label drug promotions — and companies cited for serious violations take an average of four months to act, according to a new government study.

Although the agency issued 42 regulatory letters in calendar years 2003–2007 for violations of its rules for off-label promotions, it referred none to the Justice Department, which settled 11 civil and criminal actions involving such violations during that time, the Government Accountability Office (GAO) finds in its report, “FDA’s Oversight of the Promotion of Drugs for Off-Label Uses.” The settlements were for actions brought to Justice’s attention by sources other than the FDA, the GAO says.

Responding to a request by Sen. Chuck Grassley (R-Iowa), the GAO examined how the FDA oversees promotion of off-label uses and what actions were taken to address the practice.

The agency manages off-label promotion primarily by reviewing some of the materials it receives from drugmakers, but it does not have enough staff, does not systematically prioritize its reviews and “lacks a standardized tracking system to manage its review,” the GAO says.

It also says it recommended in its 2006 study of the agency’s oversight of direct-to-consumer advertising that the FDA institute a standardized tracking system to review promotions, a recommendation it reiterates for off-label promotions (*WDL*, Dec. 18, 2006).

It concludes that “limitations in FDA’s oversight process make it unlikely that all off-label violations are detected.”

Part of the agency’s problem is the growing number of annual submissions of final promotional materials — from about 40,000 in 2003 to

more than 68,000 last year, according to figures supplied by the FDA for the report. Division of Drug Marketing, Advertising, and Communications staff told the GAO that the agency “can only review a small portion of [these] final materials,” the report says.

Of the 42 letters citing off-label promotion, 31 stemmed from a review of submissions, and 14 letters indicate that the FDA identified at least one violative promotion through monitoring and surveillance activities.

Half of all letters were for promotions targeted to physicians and other medical professionals. GAO’s study also showed that 21 letters were for violations involving such materials as professional journal ads and exhibit panels, which target the same two audiences. “Seven letters were issued for promotions directed at consumers and the remaining 14 letters were about promotions to both medical professionals and consumers,” the report says.

A copy of the GAO report is available at [www.gao.gov/new.items/d08835.pdf](http://www.gao.gov/new.items/d08835.pdf). — David Grant

## FDA Sets PDUFA Fees For Fiscal 2009

The FDA has increased its user fee rates for drug applications by about 6 percent for fiscal 2009 under the Prescription Drug User Fee Act (PDUFA).

The new rates will become effective Oct. 1 and remain in effect through Sept. 30, 2009.

Applications requiring clinical data will have a fee of \$1,247,200, according to the FDA notice published in the Aug. 1 *Federal Register*. Applications not requiring clinical data and supplements requiring clinical data will have fees of \$623,600.

The establishment fee for fiscal 2009 will be \$425,600. The FDA estimates that 35 establishment fee waivers will be made in fiscal 2009 —

(See **User Fee**, Page 6)



## SPOTLIGHT ON CONGRESS

Legislative Update		
Bill and Sponsor	Brief Description	Status
S. 1145, H.R. 1908 — Patent Reform Act of 2007 Sen. Patrick Leahy (D-Vt.), Rep. Howard Berman (D-Calif.)	<b>Patents</b> — Amends Title 35 of the U.S. Code to provide for patent reform.	S. 1145 placed on Senate Legislative Calendar Jan. 24. H.R. 1908 placed on the Senate Legislative Calendar Sept. 11, 2007.
H.R. 5605, S. 2029 — Physician Payments Sunshine Act of 2008 Sen. Chuck Grassley (R-Iowa), Rep. Peter A. DeFazio (D-Ore.)	<b>Gift Disclosure</b> — Amends Title XI of the Social Security Act to provide for transparency in the relationship between physicians and manufacturers of drugs, devices or medical supplies for which payment is made under Medicare, Medicaid or SCHIP.	H.R. 5605 introduced March 13, 2008, and referred to House Energy and Commerce Health Subcommittee and House Committee on Ways and Means; S. 2029 referred to Senate Finance Committee Sept. 6, 2007.
H.R. 380, S. 242 — Pharmaceutical Market Access and Drug Safety Act of 2007 Rep. Rahm Emanuel (D-Ill.), Sen. Byron Dorgan (D-N.D.)	<b>Importation</b> — Allows individuals to order medications from outside the U.S. when ordering from an FDA-registered and approved Canadian pharmacy. Also allows U.S.-licensed pharmacists and wholesalers to import FDA-approved medications from a number of major nations and pass along the savings to their customers.	Hearing held in the Senate Commerce, Science and Transportation Committee March 7, 2007. H.R. 380 referred to the Commerce, Trade and Consumer Protection Subcommittee Feb. 2, 2007.
S. 1951, H.R. 3700 — Fair Medicaid Drug Payment Act of 2007 Sen. Max Baucus (D-Mont.), Rep. Frank Pallone (D-N.J.)	<b>Access to Generics</b> — Amends Title XIX of the Social Security Act to ensure and foster continued beneficiary access to generic drugs under the Medicaid program by setting pharmacy reimbursement based on retail acquisition cost and to promote the use of generic drugs.	S. 1951 referred to the Senate Finance Committee Aug. 2, 2007. H.R. 3700 referred to the House Subcommittee on Health Nov. 8, 2007.
S. 3046, H.R. 6270 — Access, Compassion, Care, and Ethics for Seriously Ill Patients Act Sen. Sam Brownback (R-Kansas), Rep. Diane Watson (D-Calif.)	<b>Investigational Access</b> — Amends Section 561 of the Federal Food, Drug, and Cosmetic Act to enable the FDA to conditionally approve and patients to use investigational drugs or devices for treatment before general marketing begins.	S. 3046 introduced in Senate May 21, 2008; H.R. 6270 introduced June 12 in House and referred to House Ways and Means Committee and House Energy and Commerce Committee.
S. 316, H.R. 1432 — Preserve Access to Affordable Generics Act Sen. Herb Kohl (D-Wis.), Rep. Henry Waxman (D-Calif.)	<b>Reverse Payments</b> — Prohibits brand drug companies from compensating generic drug companies for delaying the entry of a generic drug into the market.	Hearings held on S. 316 in the Judiciary Subcommittee on Antitrust, Competition Policy and Consumer Rights March 7, 2007. H.R. 1432 referred to the Commerce, Trade and Consumer Protection Subcommittee March 12, 2007.
H.R. 4083, S. 2311 — Non-Prescription Drug Modernization Act Rep. Henry Waxman (D-Calif.), Sen. Edward Kennedy (D-Mass.)	<b>OTC Drugs</b> — Amends the Federal Food, Drug and Cosmetic Act to provide for the amendment or repeal of monographs, to expand the FDA's authority to regulate drug advertising and for other purposes.	H.R. 4083 referred to House Energy and Commerce Committee Nov. 6, 2007. S. 2311 referred to Senate Health, Energy, Labor and Pensions Committee Nov. 6, 2007.
H.R. 5629 — Pathway for Biosimilars Act Reps. Anna Eshoo (D-Calif.), Joe Barton (R-Texas)	<b>Biologics</b> — Amends the Public Health Service Act to establish a pathway for the licensure of biosimilar biological products, and for other purposes.	H.R. 5629 referred to the Committee on Energy and Commerce, and in addition to the Committee on the Judiciary March 13, 2008.
Food and Drug Administration Globalization Act of 2008 — discussion draft (no bill number as not yet introduced) Reps. John Dingell (D-Mich.), Frank Pallone (D-N.J.), Bart Stupak (D-Mich.)	<b>FDA Authority</b> — Adds authorities to create registry for foreign and domestic food, drug and device facilities, restrict and destroy imports, and recall drugs, and to require registration fees, country-of-origin labeling, manufacturer testing of ingredients, and biennial inspection of all drug facilities.	Hearings held in Energy and Commerce Committee 4/24 (food provisions), 5/1 (drug provisions) and 5/14 (device and cosmetic provisions) with intent to markup thereafter.
H.R. 5839 — Safeguarding America's Pharmaceuticals Act of 2008 Reps. Steve Buyer (R-Ind.), Jim Matheson (D-Utah), Mike Rogers (R-Mich.), Gene Green (D-Texas)	<b>Drug pedigree</b> — Require drugs to have standard national identifiers and pedigrees, and HHS to establish drug-tracking system.	Referred to the Energy and Commerce Committee April 17, 2008.

## SPOTLIGHT ON THE FDA

### Upcoming FDA Advisory Committee Meetings

Committee and Date	Agenda	Contacts
<b>August 14-15</b> — Risk Communication Advisory Committee	Discussion of the scientific basis for translating principles of risk communication into practice in situations of emerging and uncertain risk.	For more information, go to <a href="http://edocket.access.gpo.gov/2008/E8-17304.htm">edocket.access.gpo.gov/2008/E8-17304.htm</a> .

## Merck Resolves Warning Letter, Awaits FDA Approval of Supplements

Merck has resolved a warning letter citing GMP violations at its vaccine operations in West Point, Pa., and resolved supply constraints for bulk varicella, which had affected the sale of certain vaccines.

During its second-quarter earnings call, the company said that the FDA closed out a warning letter that claimed bulk drug substances for many of Merck's vaccines were adulterated (*WDL*, May 5). The letter resulted from an inspection that cited 49 Form 483 observations, all but 12 of which were resolved before the letter was issued, the company said.

"On July 10, Merck received a letter from the FDA closing out its recent inspection at the West Point manufacturing facility. As a result, any filed sBLAs which were held up due to the inspection can now move through the agency's normal review and approval process," Merck CEO Dick Clark said.

"Concerning supplements, we have at least two supplements with the FDA concerning Gardasil [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] and they will move through the [review] process," he said.

Merck told *WDL* the supplements are for expanded labeling for Gardasil. The company will respond this month to an FDA complete response letter for the use of the vaccine in women 27–45 years of age.

The company said Gardasil sales would fall \$500 million short of previous expectations, primarily because women age 19–26 go to physicians who normally do not administer vaccines.

Judicial Watch, a conservative public advocacy group, has been publicizing adverse event data in a campaign against Gardasil, claiming that safety concerns need to preclude mandates by states to vaccinate children with the product (*WDL*, May 28, 2007).

But the FDA and the Centers for Disease Control and Prevention (CDC) are reaffirming the positive risk-benefit profile of the vaccine. "Based on ongoing assessments of vaccine safety information, FDA and CDC continue to find that Gardasil is a safe and effective vaccine," the agencies say in a statement released this week.

More than 16 million doses of the vaccine have been distributed in the U.S. Of the 9,749 adverse events reported to the FDA's Vaccine Adverse Event Reporting System before June 30, 6 percent — which included 20 patient deaths, cases of Guillain-Barre syndrome and blood clots — were considered serious, the agencies said.

Merck also said it has resolved supply issues related to producing bulk varicella, a virus used for several vaccines, including ProQuad, a

(See **Merck**, Page 12)

## FDA Focuses on REMS Of Amgen sBLAs

The FDA has been focusing its attention on proposed risk evaluation and mitigation strategies (REMS) for Amgen's pending applications for Nplate and Enbrel.

"The establishment of ... REMS programs is becoming increasingly important in our interactions with the FDA," Roger Perlmutter, Amgen executive vice president of R&D, said earlier this week during the firm's second-quarter earnings call.

The agency has a special focus on its assessment of the REMS for chronic thrombocytopenia purpura treatment Nplate (romiplostim), he said. The FDA recently missed its deadline to issue a decision on Nplate, but the company is optimistic that one will be made shortly (*WDL*, July 28).

Amgen's REMS for its Enbrel (etanercept) sBLA to treat pediatric psoriasis may be a key factor in the agency's review, considering comments from the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee members,

(See **REMS**, Page 8)

## User Fee, from Page 3

the same as in 2008 — with 10 waivers coming from the orphan drug exemption in the FDA Amendments Act, which reauthorized PDUFA. Establishment fees are assessed annually for each establishment that manufactures a prescription drug.

The product fee for fiscal 2009 will be \$71,520. The FDA estimates that 2,450 products will be billed for product fees in fiscal 2009.

Just as for fiscal 2008, the FDA estimates that 70 products will receive waivers or reductions in fiscal 2009, including 30 exemptions from fees for orphan drugs.

As in previous fiscal years, revenue from each of the three fee categories will provide one-third of all fee revenue, according to the FDA.

The total drug fee revenue for fiscal 2009 is projected to be \$510,665,000 after adjustments for inflation and workload charges, an 11 percent increase from the \$459,412,000 that

the agency expected to collect this fiscal year (*WDL*, Oct. 15, 2007).

Congressional criticism of PDUFA has been growing. Rep. Maurice Hinchey (D-N.Y.) called it “a big fat mistake that needs to be corrected” and “an open invitation to corruption” during February hearings before the House Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, which funds the FDA (*WDL*, March 3).

The administration’s fiscal 2009 budget request calls for PDUFA user fees of \$346,612,000 for FDA center activities and \$6,916,000 for field activities, according to the agency’s program resource table.

The PDUFA budget includes \$35 million in user fees for drug safety in fiscal 2009, compared with \$25 million in the current fiscal year.

The FDA’s notice on prescription drug user fee rates can be seen at [www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-N-0427-n.pdf](http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-N-0427-n.pdf).

— Martin Gidron

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**FDANEWS**

## FDA Offices Agree to Emphasize Safety in Approving Drug Names

The way in which the FDA approves proposed drug names is changing as the agency increases its focus on drug safety through preventing medication errors.

The Division of Medication Error Prevention (DMEDP) is taking the lead in regulatory actions related to proprietary name review and medication error prevention, Susan Proulx, president of Med-ERRS, said at an FDAnews audio-conference last week.

Under a memorandum of agreement signed this month between the FDA's Office of New Drugs and Office of Surveillance and Epidemiology (OSE), "there will be more transparency, and DMEDP will have more say," Proulx said.

DMEDP may get the final say on whether a proposed drug name can be approved rather than the reviewing division, she added. The goal is to improve drug safety by decreasing the risk of medication errors caused by name confusion.

The Division of Drug Marketing, Advertising and Communications (DDMAC) will continue to check promotional issues, such as overstatement of efficacy or minimization of risk, before DMEDP reviews a proposed drug name. "If DDMAC decides to reject a name for promotional reasons, it won't even go to DMEDP for a more comprehensive review," Proulx said.

DMEDP's mission is to prevent medication errors caused by look-alike or sound-alike drug names, confusing modifiers to trademarks, use of the same trade name for different drugs in different countries and confusingly similar packaging and labeling for different drugs or dosages.

For example, many medication errors were caused by the similarity between the trade names of Xanodyne Pharmaceuticals' Amicar (aminocaproic acid), an inhibitor of fibrinolysis, and GlaxoSmithKline's Omacor (omega-3 acid

ethyl esters), which is used to reduce high triglyceride levels, Proulx said.

"The names are similar looking and sounding, and they also have overlapping dosage strengths," she said. As a result, the FDA required Glaxo-SmithKline to change Omacor's U.S. trade name to Lovaza, but it remains Omacor in other countries.

DMEDP tries to stop problems before they start by using reviews by a panel of experts; name simulation studies; risk assessment, including failure mode and effects analysis; and phonetic and orthographic computer analysis (POCA) — computer software that searches databases of drug names.

The POCA software will be made available to the public by the end of this year or sometime next year, Proulx said.

The FDA is running a pilot program testing methods that may reduce the potential for drug name confusion. It is funded under the latest version of the Prescription Drug User Fee Act (PDUFA IV), and drugmakers can volunteer to participate (*WDL*, June 2).

To increase the chances of getting a proposed drug name approved, Proulx recommended that manufacturers:

- Stay up to date on PDUFA IV activities;
- Use such experts as trademark development companies, safety-testing companies and legal counsel to develop and test drug names;
- Subject proposed names to due diligence, including legal and safety screening;
- Check outside the U.S. for matches to a proposed name, which is important if a drug is to be marketed internationally;
- Not let the marketing department fall in love with a proposed name — be willing to consider alternatives;
- Not submit a proposed name to the FDA and withdraw it later; and
- Only submit to the FDA drug names that are completely "clean" from a legal and safety standpoint. — Martin Gidron

**REMS**, *from Page 5*

who convened last month to discuss the proposed indication.

Although the committee voted 8–5, recommending the biologic be approved for the pediatric indication, several members wanted to limit it to patients with only severe forms of the disease because of the risks associated with Enbrel, such as bacterial sepsis and tuberculosis (*WDL*, June 23).

The company submitted an sBLA last September for Enbrel to treat moderate-to-severe plaque psoriasis in children age 4–17, and the FDA requested more information regarding the proposed REMS for the indication. Amgen plans to submit it in the near future, Perlmutter said.

During the committee meeting, the company proposed a REMS that included a prescriber checklist to make sure patients are screened for tuberculosis and hepatitis B and that their immunizations are up to date. It also proposed a patient medication guide and a starter kit to ensure patients and their guardians are educated about the product's risks.

Amgen told the committee that sales representatives would only promote Enbrel for the pediatric indication to dermatologists and that no direct-to-consumer ads would be used. Education of pediatricians and dermatologists would be voluntary under the proposed REMS.

The company reported \$1.69 billion in U.S. sales of Enbrel during the first half of 2008, an increase of 15 percent above the same period last year. Amgen had said the dermatology market is important for the growth of the product.

“In the dermatology segment, Enbrel continues to get the majority of first-line biological use for psoriasis and maintains a strong position in the segment, holding approximately 70 percent dollar share during the quarter,” George Morrow, vice president of Global Commercial Operations, said. — Christopher Hollis

**USP Reminds Levothyroxine Makers of Updated Monograph**

The U.S. Pharmacopeia (USP) is urging manufacturers outside the U.S. to adopt the new monograph for levothyroxine sodium, which tightens potency specifications.

USP released the new monograph in January. The new potency requirement, which takes effect October 2009, is 95 percent to 105 percent throughout a product's shelf life. It was tightened from 90 percent to 110 percent.

The FDA revised the specification last year after evaluating data from all levothyroxine sodium products. It found variable stability profiles and shelf lives for different versions of the drug, a concern for patients who use the thyroid replacement therapy and may get prescription refills made with different potencies by different manufacturers. — Christopher Hollis

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## Unapproved Expectorant Product Seized

Officials from the FDA and U.S. Marshal's Service have seized \$24.2 million worth of unapproved new drugs from St. Louis-based KV Pharmaceutical.

Agents acted after U.S. Attorney Catherine Hanaway filed a civil forfeiture suit and obtained a warrant from the U.S. District Court for the Eastern District of Missouri to seize the unapproved products.

"American consumers are entitled to have safe and effective drugs," Hanaway said. "The majority of the products being seized were made after the FDA required an end to their production."

Earlier this year, the FDA inspected several of KV's plants and found that the company was not complying with an agency enforcement notice warning that drugs in time-release format containing guaifenesin, an expectorant, must be approved to ensure the safe and effective release of the active ingredients.

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## FDA Goes After Dietary Supplements With Undeclared Ingredients

U.S. marshals acting for the FDA seized two lots of Miami-based SEI Pharmaceuticals' Xiadafil VIP tablets that the company refused to recall at the request of the agency.

"Today's seizure action shows that FDA will take enforcement action to protect the public from dietary supplements that contain prescription drug ingredients that are potentially harmful to consumers," Margaret Glavin, associate commissioner of the FDA's Office of Regulatory Affairs, says in a written statement.

The FDA's chemical analysis of Xiadafil VIP tablet lots 6K029 and 6K029-SEI found that the product contained an undeclared ingredient, hydroxyhomosildenafil, the agency's statement says. The chemical is similar to sildenafil, the active ingredient in Viagra (sildenafil citrate), which is approved to treat erectile dysfunction (ED).

In May 2007, the agency told 20 companies to cease marketing unapproved drug products containing guaifenesin before Aug. 27, 2007, and to stop shipping them before Nov. 26, 2007.

KV continued to manufacture and distribute the unapproved drugs, according to the U.S. attorney's office. The company also made other unapproved new drugs, including products for cough, cold, topical wound healing, skin bleaching and gastrointestinal conditions, the office said.

The seized products had been held under embargo by the state of Missouri and are subject to destruction.

In a statement, KV calls the seizure an inventory disposal that concludes discussions with the FDA regarding the agency's guidance on products containing guaifenesin. It adds that it will continue to cooperate with the FDA in bringing this matter to resolution.

A copy of the FDA's guidance is available at [www.fda.gov/cder/guidance/6911fn1.htm](http://www.fda.gov/cder/guidance/6911fn1.htm).  
— Elizabeth Jones

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The agency says it has not approved Xiadafil VIP for ED or any other drug use and the product's safety and effectiveness are unknown. Mark Hirsch, a medical team leader in CDER's Division of Reproductive and Urologic Products, says on the FDA's website that "taking sildenafil in addition to certain prescription drugs containing nitrates may lower blood pressure to an unsafe level."

Following its analysis of the tablets, the FDA had initiated an inspection April 22 at SEI and informed the company of the product's potential adverse health risks. Florida state officials then issued a "stop sale" action May 13 at SEI's distribution facility to keep the illegal product out of the marketplace, according to the FDA.

The agency says it asked the company to recall the tablets May 27. Although SEI committed to halting distribution, it refused to recall the

(See **Xiadafil**, Page 12)

## ESAs, from Page 1

both indicated to treat chemotherapy-induced anemia — warn that physicians who expect to cure their patients' cancer with myelosuppressive therapy should not also prescribe ESAs.

Amgen wanted the boxed warning and new restricted indication to state that, when the anticipated outcome of myelosuppressive therapy is to cure the disease, ESAs are only indicated to treat anemia when red blood cell transfusion is not an option, according to an FDA labeling change order letter sent last week.

The letter ordered changes to both drugs' dosage and administration labeling. The new labels must state that dosing needs to be initiated when hemoglobin levels are less than or equal to 10 g/dL. Amgen's proposed statement — “except where the patient is unable to tolerate this degree of anemia due to co-morbid conditions,” which it wanted to immediately follow the 10 g/dL dosing instruction — was rejected by the FDA.

In its letter, the agency said Amgen's proposed statements on the use of ESAs when myelosuppressive therapy is anticipated to cure

cancer suggested that the product was approved for use in such situations. But “clinical studies supporting the approval of [the ESAs] were conducted in patients with metastatic disease without the potential for cure,” the agency says.

The FDA also said the proposed language “when red blood cell transfusion is not a treatment option” is not a commonly understood and accepted criteria in the practice of transfusion medicine. In discussions with an external expert, neither the FDA nor the consultant could identify a situation when a transfusion was not an option, the letter says.

Amgen's proposed dosing statements were not accepted because they undermine other dosing directions to administer the product to maintain the lowest hemoglobin level needed to avoid red blood cell transfusions, the letter says.

“You have not identified co-morbid conditions in which maintenance of hemoglobin levels of 10.0-12.0 g/dL results in improved survival or decreased serious morbidity,” the letter says.

The labeling change order for Aranesp can be accessed at [www.fda.gov/cder/drug/infopage/RHE/aranesp/signed.pdf](http://www.fda.gov/cder/drug/infopage/RHE/aranesp/signed.pdf). — Christopher Hollis

## Third Annual FDA Inspections Summit *Getting it Right the First Time, Every Time* Bethesda North Marriott Hotel & Conference Center Bethesda, Maryland (Washington, DC) • Oct. 15–17, 2008

**Warning:** In the wake of Baxter's heparin scandal, the FDA is aggressively pursuing tighter controls for drug safety, including new offices, stricter preapproval inspection requirements and the establishment of a five-year drug safety plan.

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**FDANEWS**

## Baxter Promotional eMail Gets FDA Untitled Reply

Baxter Healthcare's Feiba VH, a hemophilia therapy, is misbranded because the company disseminated a "clinical thank you email" that made misleading safety and efficacy claims, according to an FDA untitled letter.

The July 7 letter, posted last week on the agency's website, was issued by the Division of Case Management in CBER's Office of Compliance and Biologics Quality. It requests that Baxter stop using the email and any similar communications.

Feiba VH (anti-inhibitor coagulant complex, vapor-heated) is indicated for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and hemophilia B patients with inhibitors. The biologic is a freeze-dried sterile human plasma component with Factor VIII inhibitor bypassing activity.

The alleged violative efficacy claim in the email says the product, "controlled 78 percent of bleeds with three or fewer infusions — 60 percent of which were controlled with one infusion within 12 hours."

The FDA says the assertion overstated the product's efficacy because the claim was not consistent with physician labeling. "In 130 (78 percent) of the episodes, hemostasis was achieved with one or more infusions ... of these, 36 percent were controlled with one infusion within 12 hours," according to the labeling's clinical pharmacology section.

The claim that 78 percent of bleeds were controlled with three or fewer infusions also omits contextual information, the agency says. Bleeds are controlled within 36 hours and by omitting that information, "the overall presentation of the claim misleadingly suggest[s] that 60 percent of the bleeds were controlled within 12 hours, which is false," the letter says.

The alleged misleading safety claims in the email concern the following statement: "Feiba is well tolerated in 96 percent [to] 100 percent of

infusions with a low thrombotic event incidence (0.008 percent)."

The FDA says the "well tolerated" claim minimizes the fact that serious thrombotic events can occur with the product, for which physician labeling warns of thromboembolic events particularly when high doses of the drug are administered. The labeling also states that patients need to be monitored for disseminated intravascular coagulation and symptoms of acute coronary ischemia.

Another problem with the claim is that the reference Baxter used to support the 0.008 percent thrombotic event rate was based on an analysis of postmarketing events, which the FDA does not consider substantial evidence.

Baxter told *WDL* it would revise the claims and is working closely with the FDA to address the agency's concerns. It said it would submit revised promotional materials to the FDA for pre-clearance. — Christopher Hollis

## FDA Approves Generic Versions Of Depakote

The FDA has approved the first generic versions of Abbott's Depakote delayed-release tablets, 125, 250 and 500 mg.

The generic tablets will have the same safety warnings as Depakote (divalproex sodium), including a boxed warning that cautions about the risk of liver damage and pancreatitis, according to the FDA. The warning also will highlight the risk of birth defects.

Sun Pharmaceutical, Genpharm, Nu-Pharm, Upsher-Smith Laboratories, Sandoz, Teva Pharmaceuticals USA, Dr. Reddy's Laboratories and Lupin Limited all received approval to market the generic drug.

Depakote is approved by the FDA to treat seizures, bipolar disorder and migraine headaches. Sales of the drug were strong in the second quarter, earning \$414 million worldwide, according to Abbott. — Elizabeth Jones

## Detailing, from Page 2

American Medical Association that highlighted improper drugmaker influence on physicians. The April issue contained two articles that concluded Merck withheld mortality data on its painkiller Vioxx (rofecoxib) before its approval and that company employees guest-authored and ghostwrote medical literature for the drug (*WDL*, April 21).

“This bill will provide an important alternative to the way doctors currently get their information about drugs — from the drug companies themselves. This practice seems to be fraught with conflicts of interest,” Kohl says in the statement.

“Many doctors learn about new drugs from drug company salespersons who may not be objective,” Durbin says in the statement. “Studies confirm that when unbiased health professionals armed with educational materials provide guidance to doctors, they are more likely to purchase the best drug for the patient instead of the best deal for the pharmaceutical company.”

The senate bill, S.3396, may be accessed at [www.fdanews.com/ext/files/academicdetailing\\_bill.pdf](http://www.fdanews.com/ext/files/academicdetailing_bill.pdf). — Martin Gidron

## Merck, from Page 5

combination vaccine for chicken pox, measles, mumps and rubella (MMR).

Subpotent bulk varicella had led to shortages of ProQuad, which is not available for purchase. Instead of ProQuad, Merck is recommending separate vaccinations with its chicken pox vaccine Varivax and its MMR vaccine.

Merck implemented some manufacturing process improvements for bulk varicella and filed for FDA approval during the first quarter of 2008, the company said. The agency approved those manufacturing improvements, and supply of Varivax will not be interrupted for the foreseeable future, it added.

However, the use of bulk varicella was prioritized for Varivax, affecting the firm’s other varicella-containing vaccine Zostavax, which is used to prevent shingles.

“We prioritized Varivax particularly to ensure that we had a supply to support the second dose vaccination recommendations. As a result, we were not in the same way publicizing or promoting Zostavax,” Ken Frazier, president of Merck’s Global Human Health division, said.

There were eight- to 12-week delays for Zostavax orders as of last week, according to a vaccine supply notice posted on Merck’s website.

Merck told *WDL* it is waiting for regulatory approvals to increase its manufacturing capacity. — Christopher Hollis

## Xiadafil, from Page 9

product already on the market, the agency says. Having warned the company of possible legal actions, the FDA asked the U.S. marshals to seize the product to keep it from being sold or distributed at trade shows, the agency says.

A company spokeswoman declined to comment. — Martin Gidron

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