

The Warning Letters presented in this chapter were chosen to provide examples of the types of Warning Letters issued for violations of FDA laws. A complete list of Warning Letters issued is available on FDA's web site at: <http://www.fda.gov/foi/warning.htm>.

Bioresearch Monitoring

Warning Letter Issued to Clinical Investigator Conducting Cystic Fibrosis Study

FDA Inspection Disclosed that Clinical Investigator Failed to Protect the Rights, Welfare, and Safety of Human Subjects in Clinical Study

On June 7, 2005, the FDA's Center for Drug Evaluation and Research's (CDER), issued a Warning Letter to Clark Bishop, M.D., Utah Valley Institute of Cystic Fibrosis, Utah Valley Regional Medical Center, Provo, Utah. The Warning Letter was issued

following an FDA investigation of a clinical study. The inspection was conducted between January 27 and 30, 2004, and February 2 and 5, 2004. Dr. Bishop served as the sponsor and clinical investigator of this clinical study involving patients with Cystic Fibrosis.

This inspection was conducted as part of the FDA's Bioresearch Monitoring (BIMO) Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

The Warning Letter advised Dr. Bishop that he was in violation of the Federal, Food, Drug, and Cosmetic Act (the Act) and FDA regulations governing the use of investigational new drugs, by initiating a clinical investigation without an investigational new drug application (IND) in effect, and by failing to meet the obligations of a sponsor and an investigator under applicable regulations.

The Warning Letter identified the following violations:

- Failure to conduct the study under an IND.
- Failure to protect the rights, safety and welfare of subjects.

Departures from the protocol apparently occurred without provision of the required notice to the IRB of such a change in the research. Not only did these violations directly

increase the level of risk associated with the study, they also appeared to have prevented the IRB from effective oversight, potentially further exacerbating the risks posed to study subjects. The examples of violations included, but were not limited to:

- Failure to promptly report to the IRB all unanticipated problems involving risk to human subjects.
- Failure to provide an informed consent document that contained all the basic elements of informed consent.
- Failure to adequately document informed consent.

Warning Letter Issued to Gene Logic, Inc., Regarding Research Procedures

On January 28, 2005, CDER issued a Warning Letter to Gene Logic, Inc., Gaithersburg, Maryland. FDA conducted a BIMO inspection of this nonclinical laboratory between October 6 and 17, 2003.

The Warning Letter advised the firm of the following observations:

- Gene Logic's testing facility management failed to assure that mixtures of test and control articles were appropriately tested for stability, strength, and uniformity.
- Final study reports failed to include strength, purity, and stability data for the test and control articles in final study reports.
- Final study reports failed to include a description of all circumstances that may have affected the quality or integrity of data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
- The study director failed to assure that the protocol contained documentation indicating that the protocol had been approved by the sponsor.
- The study director failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study.

The Warning Letter stated, "Following our review of the establishment inspection report and related documents, including your letter dated October 27, 2003, we conclude that you violated FDA regulations governing the conduct of nonclinical laboratory studies."

Counterfeit Drugs

*Combating Counterfeit Drugs***FDA Announced New Initiative Involving the Use of Radiofrequency Identification Technology**

Radiofrequency Identification Technology (RFID) Makes it Easier to Ensure Drugs Are Authentic and Creates a Record of Chain of Custody

On November 15, 2004, FDA announced increased efforts to improve the safety and security of the nation's drug supply through the use of radio frequency identification (RFID)

technology. FDA launched this effort by publishing a Compliance Policy Guide, Section 400.210, for implementing RFID feasibility studies and pilot programs that are designed to enhance the safety and security of the drug supply. This action continues FDA's commitment to promote the use of RFID by the U.S. drug supply chain by 2007.

RFID technology makes it easier to ensure that drugs are authentic, and it also creates an electronic pedigree, or record of the chain of custody, from the point of manufacture to the point of dispensing. Electronic pedigrees will improve patient safety and protect the public health by allowing wholesalers and retailers to rapidly identify, quarantine, and report suspected counterfeit drugs and conduct efficient, targeted recalls.

FDA considers electronic pedigrees to be a type of "electronic safety net" which utilizes technology that allows illicit drug transactions to be rapidly identified and, potentially, transmitted to the FDA thereby improving FDA's ability to conduct investigations of suspected counterfeiting or diversion of prescription drugs.

RFID is a state-of-the-art technology that uses electronic tags on product packaging to allow manufacturers and distributors to more precisely keep track of drug products as they move through the supply chain. It is similar to the technology used for tollbooth and fuel purchasing passes.

These actions are key steps in implementing a major recommendation of [FDA's report](#), issued February 18, 2004, titled "Combating Counterfeit Drugs." The report recommended that RFID technology be in widespread use throughout the pharmaceutical industry by 2007.

In a related action, the FDA announced that it was creating an internal "RFID Workgroup" whose charge is to monitor adoption of RFID in the pharmaceutical supply chain, pro-actively identify regulatory issues raised by the use of this new technology, and develop straightforward processes for handling those issues.

The full text of the Press Release is available at:
<http://www.fda.gov/bbs/topics/news/2004/NEW01133.html>.

FDA Issued Warning about Counterfeit Drugs Purchased in Mexico

Pharmacies in Mexican Border Towns Offer Counterfeit Lipitor, Viagra, and "Generic Evista"

On May 10, 2005, FDA issued a warning to the public about the sale of counterfeit versions of Lipitor, Viagra, and an unapproved product promoted as "generic

Evista" to U.S. consumers at pharmacies in Mexican border towns.

FDA advised that consumers who have any of these counterfeit products should not use them and should contact their healthcare provider immediately. FDA warned consumers that prescription drugs purchased in foreign countries are not regulated by FDA and do not carry the same FDA assurances of safety, effectiveness, and manufacturing quality as drugs purchased within the United States.

Counterfeit versions of Lipitor (a cholesterol-lowering drug), Viagra (a treatment for erectile dysfunction), and Evista (a treatment and prevention medication for osteoporosis in postmenopausal women) can pose significant risks to consumers. Counterfeit Lipitor that contains no active ingredient or not enough active ingredient could present a long-term risk for the various complications of high cholesterol, such as heart disease.

The counterfeit Lipitor purchased in Mexico was associated with several reports of high cholesterol in consumers who had used the product. Counterfeit Viagra that contains little or no active ingredient would be less effective than a legitimate product or altogether ineffective. Women who take the substandard generic Evista product that contains no active ingredient may be at risk for developing osteoporosis or for having their osteoporosis progress.

The "generic Evista" was analyzed by FDA in coordination with the National Association of Boards of Pharmacy and was found to contain **no** active ingredient. The counterfeit Lipitor and counterfeit Viagra were analyzed by Pfizer, Inc. and were also found to contain no active ingredient.

The "generic Evista" product was purchased from Agua Prieta, Sonora, Mexico and is labeled as "Raloxifeno, fenilox, 50 tabletas, 60 mg", made or distributed by Litio and labeled as manufactured in Monterrey, Nuevo Leon, Mexico. The label has red triangles across the top and bottom.

Counterfeit Lipitor and Viagra were purchased in the Mexican border towns of Juarez, Los Algodones, Nogales, and Tijuana. The counterfeit Lipitor and counterfeit Viagra products were labeled only in English, whereas legitimate Mexican pharmaceuticals are usually labeled in Spanish. In addition, the counterfeit Lipitor was provided in round white plastic bottles; however, authentic Lipitor in Mexico is sold only in boxes of blister packs.

FDA and Mexican federal health officials are continuing to work together to address the issue of counterfeit human drug products, especially along our common border. Federal health officials in Mexico's Federal Commission for the Protection from Sanitary Risks (COFEPRIS) have undertaken several specific operations to target illegal drugs, including counterfeit drugs, in Mexican drug stores. These operations, throughout Mexico, including the areas that border on the U.S., have resulted in the suspension of 19 pharmacies and the confiscation and recall of over 105 tons of medicines.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01357.html>.

FDA Issued Alert about Recall of Counterfeit "Lipitor" Sold in the United Kingdom

On July 29, 2005, FDA alerted U.S. residents to the recent recall of a batch of counterfeit "Lipitor" (atorvastatin) sold in the United Kingdom (U.K.). The medicine is used to treat high cholesterol. The counterfeit Lipitor 20mg tablets were recalled in the U.K. on July 28, 2005. Health authorities in the U.K. stated that initial results of tests performed on the counterfeit drugs did not indicate that this product posed an immediate risk to patients. However, they advised that patients stop taking the drug and return it to the pharmacy where they obtained it. U.K. pharmacies were advised to return all remaining stock of this batch to Pfizer Ltd., the manufacturer of Lipitor.

Consumers who purchased FDA-approved Lipitor products through legitimate U.S. pharmacies should not have received any of these counterfeit tablets and were not subject to this recall. But some U.S. residents may have obtained prescription drugs from the U.K. through on-line or storefront operations that do not supply legitimate, FDA-approved products, or through state-run drug importation programs that facilitate the purchase of unapproved foreign drugs. Consumers who purchase drugs through these arrangements may have received these counterfeit products.

The affected product is 20 mg "Lipitor" and is sold in packages of 28 tablets. The drug packages are marked with batch number 004405K1 and an expiration date of "11 2007." The batch number can be found on the end of the box next to the expiration

date and on the foil backing of the drug's blister pack. Legitimate U.K. Lipitor also has this same batch number.

FDA advised that because the recalled Lipitor is fake, there is no guarantee of its quality or effectiveness. U.S. patients who have the identified U.K. drugs should stop using them and should consult their physician or pharmacist if they have any questions or concerns. Patients should resume treatment as soon as they can obtain from their doctors or pharmacists a legitimate supply of Lipitor or an equivalent medicine. When patients resume taking the drug, they should take only the daily dose prescribed and not try to make up for missed doses.

Lipitor belongs to a class of drugs known as "statins." In addition to Lipitor, a number of low-cost FDA-approved generic versions of these drugs are available to consumers. FDA advised consumers who were interested in these options to discuss them with their physicians.

The full text of the Press Release is available at:
<http://www.fda.gov/bbs/topics/NEWS/2005/NEW01216.html>.

Good Manufacturing Practices

Consent Decree of Injunction - Propharma, Inc.

**Following November 2004 Consent
Decree Firm Made Corrections - FDA
Inspections Found Firm in Compliance**

United States v. Propharma, Inc., (S.D. Fla.). On November 23, 2004, U. S. District Judge Celica Altonaga, entered a Consent Decree of Permanent Injunction requiring

Propharma, Inc., and two of its officers to take necessary corrective steps to ensure that its pharmaceutical manufacturing operations are conducted in compliance with current good manufacturing practice (CGMP) and the labeling and new drug provisions of the Federal Food, Drug, and Cosmetic Act (Act).

The firm, based in Miami, Florida, manufactures multiple prescription and over-the-counter drug products, consisting mainly of cough and cold liquids, nasal sprays, and ear drops. Under the Decree, Propharma shut down its operations until FDA was satisfied that the deficiencies had been addressed.

The Decree also provided that if Propharma failed to comply with the CGMP regulations, FDA could order the company to take a variety of actions to remedy the deficiencies, including ceasing manufacturing and related operations at the plant, and recalling relevant products.

Pursuant to the Decree, three FDA inspections of Propharma were conducted in January/February 2005, May 2005 and October 2005. Based upon the findings of the October 2005 inspection, and the corrections of the inspectional findings from the January/February 2005 and the May 2005 inspections, the firm was deemed to be in compliance with the requirements set forth in the Decree. Florida District notified the firm on October 20, 2005, that operations at their Miami, Florida facility could resume.

GlaxoSmithKline - Seizures and Subsequent Consent Decree

FDA Found Problems with GSK's Prescription Drugs - Paxil^{CR} and Avandamet
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Seizures. On March 4, 2005, in response to ongoing concerns about manufacturing quality, FDA and the U.S. Department of Justice initiated seizures of Paxil^{CR} and

Avandamet. GlaxoSmithKline (GSK) manufactures these drugs. FDA determined that manufacturing practices for the two drugs failed to meet the standards laid out by FDA that ensure product safety, strength, quality and purity. Paxil CR is approved to treat depression and panic disorder. Avandamet is used to treat Type II diabetes.

The Agency initiated these seizure actions based on concerns that GSK's violation of manufacturing standards may have resulted in the production of poor quality drug products that could potentially pose risks to consumers. Among the violations noted during FDA's inspection was the finding that the Paxil^{CR} tablets could split apart and patients could receive a portion of the tablets that lacked any active ingredient, or alternatively a portion that contained active ingredient and did not have the intended controlled-release effect. Additionally, FDA found that some Avandamet tablets did not have an accurate dose of rosiglitazone, an active ingredient in this product.

Background

FDA issued a Warning Letter to GSK Cidra, Puerto Rico, in July 2002, identifying numerous significant CGMP violations found during a February/April 2002 inspection. The letter requested that the violations be corrected and stated that failure to correct the violations may result in regulatory action, including seizure and/or injunction. Although a limited follow-up FDA inspection in October 2002, found that some specific corrections were acceptable, the subsequent FDA inspections in November/December 2003 and September/November 2004, revealed continuing significant CGMP violations. FDA concluded that the firm's data and corrective plans were not adequate to correct the CGMP violations. The firm also initiated recall of some, but not all, lots of the two products.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/news/2005/NEW01162.html>.

Consent Decree: On April 28, 2005, FDA announced that GSK (through its U.S. subsidiaries SB Pharmco Puerto Rico, Inc., GlaxoSmithKline Puerto Rico Inc., and SmithKline Beecham Corporation), had signed a Consent Decree with FDA to correct manufacturing deficiencies at its Cidra, Puerto Rico, facility.

The Consent Decree was initiated based on FDA's continued concerns that GSK's violation of manufacturing standards may have resulted in the production of drug products that could potentially pose risks to consumers.

The Decree required GSK to post a penal bond of \$650,000,000, contingent upon GSK either successfully reconditioning drugs seized in March 2005, or destroying them and paying costs to the government.

FDA urged patients who use these two drugs to continue taking their medication and to talk with their health care provider about possible alternative products until the manufacturing issues have been resolved.

Under the terms of this Decree the company agreed to take measures to ensure that its Cidra facility and the two drugs, Paxil^{CR} and Avandamet, fully comply with CGMP requirements and to ensure that ongoing shipments have the quality attributes they are required to possess. The Decree also requires that all corrections and the firm's compliance with CGMP requirements be certified by a third-party expert. Additionally, FDA will continue to monitor these activities through its inspections.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/news/2005/NEW01176.html>.

Consent Decree of Injunction - Kiel Laboratories, Inc.

Lengthy Violative History of Non-Compliance with CGMPs Resulted in Consent Decree of Permanent Injunction
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On June 14, 2005, a Consent Decree of Permanent Injunction and a Complaint for Injunction were filed against Kiel Laboratories, Inc., Gainesville, Georgia.

The injunction involved the company and three individuals. Kiel operates primarily as a contract manufacturer of prescription and OTC drugs. The prescription drugs are primarily for the treatment of pediatric and adult pulmonary and respiratory diseases. The

firm had an extensive violative history involving their failure to comply with drug current good manufacturing practices (CGMPs).

Repeat observations documented during FDA inspections included failure to investigate any unexplained discrepancies in the batch, failure to reject drug product that did not meet specifications, failure to withhold from use each lot of components that did not meet specifications, failure to have adequate procedures for production and process controls, failure to establish an adequate quality control unit, failure to validate their laboratory methods, and failure to establish an adequate stability program that could support the expiration dates placed on their products.

Under the terms of the Consent Decree the defendants are permanently restrained and enjoined from manufacturing, processing, packing, labeling, holding, and distribution of any drugs unless and until the defendants comply with the terms of the Consent Decree.

The defendants are required to hire an expert to perform a comprehensive inspection of the defendants' facilities and to determine if the facilities, methods, and controls used to manufacture, process, package, label, hold, and distribute drugs are in compliance with CGMP regulations. In addition, defendants are required to recall certain specified drugs.

Court Ordered Injunction - Pharmakon Labs

On July 27, 2005, FDA announced a permanent injunction shutting down operations at Pharmakon Labs of Florida. The company manufactured and distributed cough and cold liquids, tablets and caplets. Following inspections by FDA and a trial in U.S. District Court, Judge Richard A. Lazzara found that drug products sold by Pharmakon Labs, Inc., and two officers (the defendants) did not meet current good manufacturing practice (CGMP) standards and other legal requirements, including new drug approval requirements.

Judge Lazzara stated that he was "simply unwilling as a court of equity to place the health, safety, and welfare of the general public at risk in order to accommodate the economic well-being of Defendants." Thus, the defendants were ordered to stop manufacturing and distributing drugs until they complied with CGMP standards to the satisfaction of FDA and obtain marketing approvals.

The defendants have had a long history of continued violations of the Federal Food, Drug, and Cosmetic Act. The government's initial complaint alleged numerous manufacturing violations documented in four inspections dating back to 2001. FDA later added charges related to Pharmakon's manufacture and distribution of unapproved new drugs, as part of the Agency's longstanding policy to seek relief for all legal violations by a firm at the same time.

The full text of the Press Release is available at:
<http://www.fda.gov/bbs/topics/NEWS/2005/NEW01211.html>.

FDA Issued Nationwide Alert on IV Flush Brand of Heparin or Sodium Chloride Intravenous Catheter Flushes

Outbreaks of *Pseudomonas fluorescens* Infections in Patients Might Have Been Associated with Heparin Flushes

On February 4, 2005, FDA reissued a nationwide alert against the use of all lots of preloaded syringes containing either heparin or sodium chloride intravenous

catheter flushes manufactured by the IV Flush, LLC and distributed by Pinnacle Medical Supply, of Rowlett, Texas, because new cases of infections that may be associated with the use of these unapproved and possibly contaminated products had been reported.

Previously, on January 31, 2005, FDA warned consumers and institutions who had these preloaded syringes containing heparin or sodium chloride intravenous flushes to not use them and immediately return them to the IV Flush, LLC or the original distributor.

After that initial warning, FDA was informed of a cluster of *Pseudomonas fluorescens* (*P. fluorescens*) infections in patients that may have been associated with the heparin flushes.

The heparin and sodium chloride containing intravenous flushes were sold to distributors who redistributed to other medical distributors and hospitals. Some of the intravenous flushes may have been provided to patients for home use. They can be identified by the syringe label, which reads in part: "IV Flush Dallas, TX."

IV Flush, LLC, notified its distributors by phone and letter and requested those distributors to contact their customers. The company arranged for return of all recalled products.

P. fluorescens is an infrequent cause of infection, but has been reported to cause outbreaks of pseudobacteremia, i.e., presence in a blood culture in the absence of clinical evidence of bloodstream infection. *P. fluorescens* has also been reported as the cause of procedure-related infections and infections resulting from transfusion with contaminated blood components.

The full text of the Press Release is available at:
<http://www.fda.gov/bbs/topics/news/2005/NEW01154.html>.

**Class I Recall: Central Admixture Pharmacy Service
Recalled All Its Injectable Products**

On September 17, 2005, FDA notified healthcare professionals and hospitals about a product recall involving all injectable products manufactured by Central Admixture Pharmacy Services, Inc. (CAPS) of Lanham, Maryland due to concerns regarding the sterility of these injectable products. CAPS distributed the affected injectable products to hospitals in Maryland, Delaware, Washington, D.C., and Virginia.

Gram negative rods were identified in several lots of Cardioplegia solution manufactured by CAPS. Non-sterility of injectable products could represent a serious hazard to health that could lead to life-threatening injuries and death.

The following products distributed up to September 16, 2005, were affected by this action:

- Cardioplegia solutions including: Cardioplegia, Cold Cardioplegia, Warm Cardioplegia, Blood Cardioplegia 1, Blood Cardioplegia 2, Cardioplegia Base 1, Cardioplegia Base 2, Cardioplegia Base, Cardioplegia Reperfusion, Cardioplegia High Potassium, Cardioplegia Low Potassium, Cardioplegia #1, Cardioplegia #2, Cardioplegia #3; Maintenance Cardioplegia, Enriched Cardioplegia, Cardioplegia Hot Shot, Cardioplegia Base Enriched
- Oxytocin injectable products including: Oxytocin Infusion, Oxytocin 20 units, Oxytocin 30 units, Oxytocin D5 ½ NS, Oxytocin in Lactated Ringers
- Promethazine
- Magnesium-containing injectable products including: Magnesium 1 GM, Magnesium 2 GM, Magnesium Sulfate 2 GM, Magnesium 4 GM, Hydration-Magnesium in D5W, Magnesium Infusion, Magnesium in Lactated Ringers
- Heparin Replacement
- Antibiotic Irrigation Bag and Bottle
- Bupivacaine 0.25 % and 0.5%, Pain Bags (Bupivacaine 0.25 %)
- Dialysate solutions including: Citrate Dialysate, Heparin Dialysate, Pediatric Dialysate, Hydration Dialysate #1, Hydration Dialysate #2, CRRT Dialysate, CVVHD (Dialysate) 300, CVVHD (Dialysate) 342, CVVHD Pediatric Formula (Normocarb), CVVHD Formalin #1, CVVHD Formalin #2, CVVHD Formalin #3, CVVHD Non-Standard, CVVHD D5W, CVVHD ½ NS, CVVHD NS
- Total Parenteral Nutrition (TPN) products including: TPN-Day, TPN-Day 1 Neonatal Stock Solution
- Diltiazem (Cardizem)
- Norepinephrine (Levophed)
- Cefazolin

Although CAPS directly notified known hospital customers of the recall, FDA urged hospitals, physicians, and health care workers to examine their supplies for any CAPS of Lanham, Maryland, injectable products, immediately discontinue their use, and quarantine the products.

The full text of the Press Release is available at:

<http://www.fda.gov/medwatch/safety/2005/safety05.htm#CAPS>.

FDA Issued Nationwide Alert on One Lot of Pharmedium Services Magnesium Sulfate Solution

On March 18, 2005, FDA issued a nationwide alert against the use of Pharmedium Services Magnesium Sulfate 1 gram in 50mL D5W (piggyback) IV solution, lot number 100504900049 and expiration date April 4, 2005. This product is manufactured by PharMEDium Services of Houston, Texas, and may be contaminated with *Serratia marcescens*, a bacteria that can cause serious, life-threatening illness in patients with compromised immune systems.

This product is frequently administered intravenously to patients undergoing cardiac surgery and was apparently distributed to several hospitals around the country. The product has been associated with at least 5 cases of *Serratia marcescens* infection in a hospital in New Jersey. All patients responded to treatment with antibiotics and reportedly are recovering well.

On April 8, 2005, the firm announced a recall of all strengths of 50 ml admixtures of Magnesium Sulfate in 5% Dextrose solution due to a lack of sterility assurance for these products.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/news/2005/NEW01166.html>.

FDA Advised Public of Nationwide Recall of All Drugs from Able Laboratories

Concerns Regarding Quality Assurance of Drugs Resulted in Nationwide Recall

On May 27, 2005, FDA took action to ensure that the public was fully aware that Able Laboratories of Cranbury, New Jersey, was conducting a nationwide recall of all of its manufactured drugs (mostly generic prescription drugs, including drugs containing acetaminophen), because of serious concerns that they were not produced according to quality assurance standards. Able Laboratories ceased all production.

The list of names of the recalled drugs and their imprint codes are available on FDA's website at <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01182.html>. The imprints are marks (usually letters and numbers) found on the surfaces of drugs. FDA advised consumers that if they had one of the drugs listed with one of the corresponding imprint codes, the drug is covered by the Able Laboratories recall.

Liquid products being recalled may be identified by the lot numbers printed on their packaging.

It is important to note that this recall only applied to the drugs produced by Able Laboratories, and not to the same drugs produced by other manufacturers.

FDA Issued Public Health Advisory on the Fentanyl Patch

On July 15, 2005, FDA issued a Public Health Advisory regarding the safe use of transdermal fentanyl patches in response to reports of deaths in patients using this potent narcotic medication for pain management. In addition, a patient information sheet and an alert to healthcare professionals were issued identifying several important safety precautions for the use of fentanyl transdermal patches. These safety precautions include but are not limited to patient education regarding signs of overdose, proper patch application, use of other medications while using the patch, safeguards for children, and proper storage and disposal.

The Agency has been examining the circumstances of product use to determine if the reported adverse events may be related to inappropriate use of the patch or factors related to the quality of the product. FDA concluded that it was possible that some patients and their health care providers may not be completely aware of the dangers of these potent narcotic drug products and the important recommendations regarding their safe use. The Agency is working closely with the manufacturers of fentanyl patches to fully evaluate the risks associated with their use and to develop a plan to help patients avoid

accidental fentanyl overdose.

For more information, go to: <http://www.fda.gov/cder/drug/infopage/fentanyl/default.htm>

FDA Approved Updated Labeling for Viagra, Cialis, and Levitra Regarding Risk of Sudden Vision Loss

Post-Marketing Reports of Sudden Vision Loss Prompted FDA's Action

On July 8, 2005, FDA approved updated labeling for Cialis, Levitra, and Viagra to reflect a small number of post-marketing reports of sudden vision loss, attributed to

NAION (non arteritic ischemic optic neuropathy), a condition where blood flow is blocked to the optic nerve.

FDA advised patients to stop taking these medicines, and call a doctor or healthcare provider right away if they experienced sudden or decreased vision loss in one or both eyes. Further, patients taking or considering taking these products should inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION. Such patients are at an increased risk of developing NAION again.

At this time, it is not possible to determine whether these oral medicines for erectile dysfunction were the cause of the loss of eyesight or whether the problem was related to other factors such as high blood pressure or diabetes, or to a combination of these problems. The new labeling information is available along with additional information for healthcare providers and consumers online at:

Viagra (<http://www.fda.gov/cder/consumerinfo/viagra/vIAGRA.htm>)

Levitra (<http://www.fda.gov/cder/drug/infopage/vardenafil/default.htm>)

Cialis (<http://www.fda.gov/cder/drug/infopage/cialis/default.htm>)

Importation of Prescription Drugs

Court Halted Illegal Importation of Rx Drugs - Canada Care Drugs

**Court Order Gave FDA
Inspection Authority Regarding
Defendants**

On December 16, 2004, the U.S. District Court for the Southern District of New York issued an Order of Preliminary Injunction that enjoined Canada Care Drugs, Inc. (Canada Care) and two individuals (the defendants) from causing the importation of drugs, receiving commissions from the importation of drugs, and advertising or promoting any importation service.

The court order gave FDA inspection authority to ensure that the defendants did not continue to violate the law. In addition, the order required the defendants to send their customers a letter notifying them that their importation business violated the law and that the safety, purity, and efficacy of drugs obtained through the defendants cannot be assured.

The court order followed a civil complaint filed by the government against these defendants on November 29, 2004, based on an FDA investigation of Canada Care's illegal importation operations.

FDA's investigation found products that posed a risk to the public health. FDA made two undercover purchases of the FDA-approved drugs Neurontin and Sporanox through Canada Care. Instead of Neurontin, FDA received unapproved drugs called APO-Gabapentin and Novo-Gabapentin. These unapproved drugs purchased through the defendants posed a public health threat, because FDA cannot assure the safety and efficacy of unapproved drugs that are not subject to the FDA's oversight.

Also, unapproved new drugs are more likely to be contaminated, counterfeit, inherently ineffective, or contain different amounts of the active ingredients from similar drugs that have been reviewed and approved by the FDA.

The shipment of Sporanox that was sent by the foreign pharmacy also posed a potentially serious health threat. The foreign pharmacy sent three packages of Sporanox at one time. Therefore, patients receiving the drugs could have taken all 84 tablets without consulting their doctor in between "pulse" treatments - an action that could have exposed them to serious and even fatal side effects.

FDA's Press Release also cautioned patients to take Sporanox in treatment "pulses" of one week, and then wait three weeks before resuming another pulse treatment. Between treatments, patients should consult their doctors to determine whether the treatment

should be terminated either because it is no longer necessary or because they are experiencing liver or heart side effects.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01337.html>.

Order of Injunction - Genendo Pharmaceutical N.V

Drug Importer Enjoined from Further Importation of Unapproved "New" Drugs

On August 22, 2005, U.S. District Judge James F. Holderman entered an Order of Permanent Injunction against Genendo Pharmaceutical N.V., a drug importer located in Curacao,

Netherlands, Antilles. The Order held that Genendo violated the Federal Food, Drug, and Cosmetic Act when it imported name-brand drugs that were labeled in foreign languages and manufactured and/or packaged in facilities not identified in FDA-approved new drug applications (NDAs).

In determining that the drugs imported by Genendo were unapproved new drugs, the court specifically noted that "[t]o be introduced into interstate commerce under the cover of an FDA-approved NDA . . . drugs must comply with all requirements of that NDA."

In addition to enjoining Genendo from further importation of unapproved new drugs, the court ordered the condemnation of a shipment of Lipitor that the United States seized in 2003, after it was imported by Genendo. At trial, the government established that the seized Lipitor was not fully compliant with the approved NDA for Lipitor, because it was packaged in a Brazilian facility that was not identified in the NDA and was labeled in Portuguese (the approved NDA for Lipitor does not encompass Portuguese labeling).

The court rejected Genendo's argument that the imported drugs lose their unapproved status when they are sent to a repackager before distribution to consumers under an exemption for repackagers. The court noted that accepting Genendo's argument regarding the exemption "would necessarily lead to the evisceration of the protections afforded by the new drug approval process."

Internet Enforcement

FDA Issued Advisory Regarding Purchase and Use of Carbolith 150 Milligram Capsules, an Unapproved Product that Might be Substandard

On December 8, 2004, FDA issued an advisory to consumers about a Canadian recall of Carbolith (Lithium Carbonate) 150 mg capsules distributed in Canada by Valeant Canada Limited. Although Carbolith is not an FDA-approved product, several Internet websites advertised Carbolith for sale to U.S. consumers. Carbolith 150 mg capsules are used in the treatment of manic-depressive illness, a serious psychiatric condition. The company's testing led to the conclusion that the product may not deliver adequate amounts of the drug to ensure effective treatment.

As a precaution, Health Canada advised individuals taking Carbolith 150 mg capsules to continue taking their medication and to consult their health care professional as soon as possible. This product has been available to the Canadian public with a prescription from physicians.

FDA advised that U.S. consumers who purchased this drug through the Internet and took it for the treatment of manic-depressive illness could experience adverse events associated with lowered blood lithium levels. These events could include a worsening of manic-depressive illness.. A worsening of this condition could result in symptoms associated with mania (such as motor hyperactivity, delusions of grandeur, poor judgment and aggressiveness) and depression or suicidal thoughts, which may require hospitalization.

Additionally, consumers who may have taken the Carbolith product for several weeks or more may experience toxic effects when they switch to a lithium carbonate product that delivers adequate amounts of the drug. Mild toxicity could result in tremors of the hands, thirst and more frequent urination, drowsiness, ringing in the ears and blurred vision. More severe toxicity could result in confusion, muscle twitching, vomiting, diarrhea, seizures, coma and death.

Because lithium carbonate requires careful, closely monitored dosing and periodic blood tests to measure the level of the drug in the blood, FDA advised U.S. consumers who have taken Carbolith 150 mg capsules to continue to take the product and consult their health care provider as soon as possible so that an alternative medication can be prescribed.

FDA urged consumers and health care professionals to report adverse reactions associated with Carbolith 150 mg capsules to FDA's MedWatch program online www.fda.gov/medwatch/report.htm, fax (800-332-0178) or phone (800-332-1088) and

to Health Canada by toll-free telephone at (866) 234-2345 or by toll-free fax at (866) 678-6789.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01330.html>.

Warning Letter Issued to Purest Colloids, Inc., for Mesosilver™, Mesogold™, and Mesocopper™

Therapeutic Claims Caused Products To Be Unapproved "New" Drugs

On December 2, 2004, FDA's New Jersey District Office issued a Warning Letter to Purest Colloids, Inc., Westhampton, New Jersey. FDA issued the Warning Letter based on a review the firm's web site at the Internet address: <http://www.purecolloids.com>. FDA's review found violations of the Federal Food, Drug, and Cosmetic Act (Act) based on the promotion of the products Mesosilver™, Mesogold™, and Mesocopper™. These products were being promoted on the web site for conditions that caused the products to be drugs. The therapeutic claims on this web site established that the products were drugs because they were intended for use in the cure, mitigation, treatment, or prevention of disease. The marketing of these products with these claims is in violation of the Act.

Examples of some of the claims observed on the Pures Colloids web site included, but were not limited to, the following:

- **Mesosilver™**

"Silver promotes the production of new cells, thus increasing the rate of wound healing."

"[R]ecognized as one of the most potent antidotes for food poisoning."

- **Mesogold™**

"Word of gold's power to relieve the pain of arthritis was passed down through the centuries and even today it is used in the treatment of rheumatoid arthritis, its efficacy confirmed by modern medical research."

- **Mesocopper™**

"A variety of inorganic copper preparations were found to be effective in treating chronic adenitis, eczema, impetigo, scorphulosis, tubercular infections, lupus, syphilis, anemias, chorea and facial neuralgia."

". . .subcutaneous and intravenous injections of.. .colloidal copper softened and degenerated carcinomas transplanted into mice."

The Warning Letter advised the firm of the following: (1) Mesosilver™, Mesogold™, and Mesocopper™ were not generally recognized as safe and effective for the above referenced conditions and therefore, the products were "new drugs" under section 201(p); (2) new drugs may not be legally marketed in the U.S. without prior approval from FDA; and, (3) FDA approves a new drug on the basis of scientific data submitted by a drug sponsor to demonstrate that the drug is safe and effective. In addition, Mesosilver™, Mesogold™, and Mesocopper™ were misbranded, because their labeling failed to bear adequate directions for the conditions for which they were offered.

Over-the-Counter Products

Seizure of OTC Topical Antifungal Products at Salon Sciences Co./International/Cosmerica, Laboratories, Inc.

On June 15, 2005, FDA investigators from the Florida District Office accompanied the U.S. Marshals Service in a seizure of over-the-counter topical antifungal products, Fungi Septic and Fungi FIX, including their components and labeling.

OTC Anti-Fungal Products Lacked FDA Approval

The products were located at Salon Sciences International/Cosmerica Laboratories, Inc. (Salon Sciences), Fort Lauderdale, Florida. The articles were seized, because the products had never received approval by FDA and were therefore unapproved new drugs.

In addition, the drugs were misbranded, because they failed to bear adequate directions for use. The products were manufactured in an establishment that was not registered and not listed as required by 21 U.S.C. 360(j).

After a January 2001 inspection, FDA issued a Warning Letter to Salon Sciences in July 2001, advising the firm that Fungi Septic was a misbranded drug and an unapproved new drug. The letter requested that the violations be corrected and stated that failure to correct

the violations may result in regulatory action, including seizure and/or injunction. The firm responded. FDA replied to the firm, and a subsequent FDA inspection in December 2001, revealed that the firm had not made adequate labeling changes

A subsequent FDA inspection of Salon Sciences on September 22, 23, and October 13, 2004, revealed the Fungi Septic labeling had been revised somewhat, but was still unacceptable and that the firm had added a new product, Fungi FIX, with similarly violative labeling. An FDA sample collected on November 19, 2004, and an FDA inspection in the Spring of 2005, also found that the firm continued to use the same violative labeling for both products.

FDA Announced Nationwide Recall of Infants' Oral Drops

On August 1, 2005, FDA announced that Perrigo Company had initiated a voluntary nationwide recall of all lots of concentrated infants' oral drops that were packaged with a dosing syringe bearing only a "1.6 mL" mark containing *acetaminophen*; *acetaminophen, dextromethorphan HBr, and pseudoephedrine HCl*; or *dextromethorphan HBr, and pseudoephedrine HCl*.

The dosing syringe could be confusing in determining the proper dose for infants under 2 years of age as directed by a doctor and could lead to improper dosing, including overdosing. The following products were recalled to the retail level:

- Cherry Flavor Infant Pain Reliever 160 mg Acetaminophen (0.5 ounce and 1.0 ounce)
- Grape Flavor Infant Pain Reliever 160 mg Acetaminophen (0.5 ounce and 1.0 ounce)
- Cherry Flavor Cough and Cold Infant Drops (0.5 ounce)
- Cherry Flavor Decongestant and Cough Infant Drops (0.5 ounce)

The directions on the bottle and carton labeling for infants ages 2-3 years and weighing 24-35 pounds allowed safe and effective dosing for this age and weight group. However, these products were also intended for use by children younger than 2 years and weighing less than 24 pounds. The labeling directed consumers to ask a doctor for dosing directions for this age and weight group.

The oral dosing syringe enclosed with these products was not marked so as to accurately measure doses less than 1.6 mL when prescribed by physicians for infants younger than 2 years and weighing less than 24 pounds. These products were provided with a dropper, not the oral dosing syringe, and the dropper had two markings on it ("0.4 mL" and "0.8 mL").

The single mark on the current syringe along with the changeover from the dropper to this syringe caused confusion among consumers and health-care professionals and could lead to improper dosing. Taking more than the recommended dose (overdose) of acetaminophen could cause liver damage. FDA advised that consumers who had questions should discuss this with their doctor to accurately determine proper dosage.

FDA also advised that, in using an alternative over-the-counter product, parents and doctors should thoroughly discuss the specifics about the product and the dosing device, particularly the labeling and marking, so that the proper dose could be measured and administered correctly.

The confusion of the dosing syringe was noted after a physician filed a complaint with the American Academy of Pediatrics.

The recalled products were sold nationally at retail chains under the following store-brand labels: American Fare, Best Choice, Brooks, Berkley & Jensen, CVS, Dollar General, Eckerd, Equaline, Equate, Family Dollar, Food Lion, Good Neighbor, GoodSense, Healthy Generations, Health Pride, Hy-Vee, Kroger, Leader, Longs, Major, Medicine Shoppe, Meijer, Parklane, Publix, Rite Aid, Safeway, Shop Rite, Sunmark, Target, Today's Health, Top Care, Walgreen, Western Family, and Winn Dixie.

[The agency subsequently determined the recall to be a Class II Recall.]

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/answers/2005/ans01364.html>.

FDA Issued Warning Against Abuse of Dextromethorphan

FDA Expressed Concern Over Abuse of Cough and Cold Remedy, Dextromethorphan (DXM)
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On May 20, 2005, FDA issued a Talk Paper discussing the Agency's concern about the abuse of dextromethorphan (DXM), a synthetically produced ingredient found in many over-the-counter (OTC)

cough and cold remedies. The Agency is working with other health and law enforcement authorities to address this serious issue and warned the public of potential harm, after five reported deaths of teenagers that might have been associated with the consumption of powdered DXM sold in capsules.

Although DXM, when formulated properly and used in small amounts, can be safely used in cough suppressant medicines, abuse of the drug can cause death as well as other serious adverse events such as brain damage, seizure, loss of consciousness, and irregular heart beat.

DXM abuse, though not a new phenomenon, has developed into a disturbing new trend which involves the sale of pure DXM in powdered form. This pure DXM is often encapsulated by the “dealer” and offered for street use.

DXM has gradually replaced codeine as the most widely used cough suppressant in the United States. It is available OTC in capsule, liquid, liquid gelatin capsule, lozenge, and tablet forms. When ingested at recommended dosage levels, DXM is generally a safe and effective cough suppressant.

Additional information about the dangers of DXM use and abuse can be found at the following Substance Abuse and Mental Health Services Administration National Clearinghouse for Alcohol and Drug Information links.

<http://store.health.org/catalog/mediaDetails.aspx?ID=371>,
<http://www.family.samhsa.gov/get/otcdrugs.aspx>.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.HTML>.

Pharmacy Compounding

Third Circuit Court Ruled in Favor of FDA in Wedgewood Pharmacy Case

The Court Agreed with FDA that the Exemption in the Statute Excluded Only Records, Not Inspection of the Facility, and that Wedgewood Did Not Meet the Requirements of Limited Inspection

In the Matter of Establishment

Inspection... Wedgewood Pharmacy, (3d Cir.).

On September 1, 2004, in a precedential decision, the Third Circuit Court of Appeals (Judges McKee and Buckwalter) affirmed a ruling that Wedgewood Pharmacy, a compounding pharmacy, was subject to full inspection by FDA. Wedgewood argued that it was exempt from FDA inspection and denied

due process when FDA obtained an *ex parte* administrative warrant. Although the Federal Food, Drug, and Cosmetic Act (Act) provides traditional pharmacies with a limited exemption from full FDA inspection, FDA asserted in its warrant application that Wedgewood did not qualify for the exemption, because Wedgewood was not operating strictly as a retail business, as is required for the statutory exemption.

FDA found that Wedgewood was engaged in making large quantities of drugs without prescriptions, utilizing large-scale mixing tanks. FDA argued that Wedgewood was, therefore, engaged in manufacturing drugs rather than the traditional practice of

pharmacy and, therefore, subject to full inspection. Wedgewood argued that it met the statutory exemption and was not subject to FDA inspection at all.

The court agreed with FDA that the exemption in the statute excluded only records, not inspection of the facility, and that Wedgewood did not meet the requirements of the limited inspection. The court also found that the ex parte administrative warrant obtained by FDA did not violate Wedgewood's right to due process.

Warning Letter Issued to Lincare, Inc., and Reliant Pharmacy Services, Inc.

On December 9, 2004, FDA issued a Warning Letter to Lincare, Inc., and Reliant Pharmacy Services, Inc., Clearwater, Florida. The letter was issued following an FDA inspection of Reliant Pharmacy in South Haven, MS on June 16-18, 2004. During the inspection, the FDA investigator documented serious violations of the Federal Food, Drug, and Cosmetic Act (Act).

Based on FDA's inspection, the Agency determined that the firm's operation was akin to that of a drug manufacturer. Relevant findings included, but were not limited to, the following:

- The firm's acetylcysteine products were the same strengths (10% and 20%) as those available commercially. The commercial products were available as 10ml and 30ml multidose vials, whereas the firm's products were available as 0.5ml and 5ml single dose vials. FDA did not view the availability of single-dose vials as a meaningful distinction between the firm's products and commercially available products.
- The strengths and sizes of the firm's budesonide products were the same as the commercially available products. The Agency acknowledged the commercially available products were suspensions and the firm's products were solutions, but FDA did not regard this as a meaningful distinction and the firm's records failed to document patient-specific medical need for the compounded solutions.
- From June 1, 2003, to May 31, 2004, the firm dispensed large volumes of these individual doses of different compounded products, to patients in many states.

The Warning Letter noted that while FDA recognized some pharmacists extemporaneously compound reasonable quantities of human drugs upon receipt of valid prescriptions for individual patients, this firm produced enormous amounts of what were essentially copies of commercially available drugs. FDA determined that this practice

went beyond the scope of traditional pharmacy compounding and instead more closely resembled a drug manufacturing operation.

The Warning Letter also noted that the firm's inhalation solutions were "drugs" and "new drugs" respectively. As such, they may not be introduced or delivered for introduction into interstate commerce, because they lacked approved applications. Also, since the firm manufactured and dispensed drugs in a manner that exceeded traditional pharmacy compounding, the firm was not exempt from the registration and drug listing requirements of the Act. Thus, these drug products were misbranded, because they were not listed or manufactured in a duly registered establishment.

Warning Letter Issued to Cape Drugs for Compounding Domperidone

On July 11, 2005, CDER issued a Warning Letter to Cape Drugs, Annapolis, Maryland. The Warning Letter noted that on February 25, 2005, the owner advised FDA that he had compounded drugs containing domperidone.

The Warning Letter advised that the Agency is concerned with the public health risks associated with the compounding of domperidone. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from marketing in several countries.

Among other uses, FDA has become aware of the use of domperidone by lactating women to increase breast milk production. In several countries where the oral form of domperidone continues to be marketed, labels for the product recommend that women taking domperidone avoid breast-feeding. Because of this, FDA recommends that breastfeeding women not use domperidone to increase milk production.

Domperidone is not an active ingredient contained in any FDA-approved drug product. FDA does not sanction its use in pharmacy compounding.

The Warning Letter advised that all products compounded by the firm containing domperidone were drugs. The Warning Letter further noted that as these products were not generally recognized by qualified experts as safe and effective for their labeled uses, thus the products were "new" drugs. No approved application was in effect with respect to these products. Accordingly, the introduction or delivery for introduction into interstate commerce of "new" unapproved drugs violated the Act.

The Warning Letter also advised that these products were misbranded, because the labeling failed to bear adequate directions for their use.

Postmarketing Adverse Drug Experience Reporting

Warning Letter Issued to Mayne Pharma (USA) Inc., for Failure to File Adverse Drug Experience Reports

FDA Inspection Found that Firm Failed to File ADE's as Required
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On February 1, 2005, FDA's New Jersey District Office issued a Warning Letter to Mayne Pharma (USA) Inc., Paramus, New Jersey. FDA conducted an inspection of Marne

Pharma from September 13 through October 6, 2004. The Warning Letter stated that based on FDA's review of the inspection report, the Agency concluded that the firm violated the Act, because it failed to comply with FDA regulations which require an applicant to establish and maintain records, and to report certain adverse drug experience information for drugs for which an approved application is in effect.

The Warning Letter included, but was not limited to, the following deviations:

- Failure to submit Adverse Drug Experience (ADE) reports to the FDA.
- Failure to conduct a follow-up investigation into all serious and unexpected ADEs.
- Failure to develop adequate written procedures for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

Warning Letter Issued to Nephron Pharmaceuticals Corporation Regarding Reporting Requirements

On September 28, 2005, FDA's Florida District Office issued a Warning Letter to Nephron Pharmaceuticals Corporation (Nephron), Orlando, Florida. FDA inspected this drug manufacturing facility on March 21-28, 2005.

The inspection found significant deviations from the Postmarketing Adverse Drug Experience (PADE) reporting requirements, within the meaning of Sections 505(k) of the Federal Food, Drug, and Cosmetic Act ("the Act"). Deviations from the PADE regulations included, but were not limited to:

- Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.
- Failure to report adverse drug experience information to FDA.
- Failure to submit periodic reports of non-15 day adverse drug experiences: quarterly for one product which was approved less than three years ago and annually for three products that were approved three or more years ago.

The inspection also found deviations from the current good manufacturing practice (CGMP) requirements for drug products. The CGMP deviations caused the firm's products, Albuterol Sulfate Inhalation Solution, Ipratropium Bromide Inhalation

Solution, Racipinephrine Inhalation Solution, and Sodium Chloride Inhalation Solution, to be adulterated, in that the methods used in, or the facilities or controls used for, the manufacturing, processing, packing, storage or holding of the drug products were not operated or administered in conformity with CGMPs.

Promotional Claims/Labeling

Warning Letter Issued to Bradley Pharmaceuticals, Inc., for False and Misleading Claims on Internet

CDER Review of Professional Sales Ad Disclosed Effectiveness Claims Not Substantiated by Evidence or Clinical Experience

On November 9, 2004, CDER issued a Warning Letter to Bradley Pharmaceuticals, Inc., Fairfield, New Jersey. The Warning Letter stated that CDER had reviewed a professional sales ad for Pamine®

(methscopolamine bromide) 2.5 mg Tablets and a patient brochure for Pamine® Forte (methscopolamine bromide) 5 mg Tablets submitted by Kenwood Therapeutics (Kenwood), a Division of Bradley Pharmaceuticals, Inc. In addition, CDER reviewed the Bradley Pharmaceuticals, Inc. website that promoted Pamine at: www.bradpharm.com/pamine.htm.

The Warning Letter advised that the professional sales ad, patient brochure, and website contained numerous effectiveness claims for Pamine and Pamine Forte that to FDA's knowledge were not supported by substantial evidence or substantial clinical experience. They also omitted risk information for these drugs. Finally, the professional sales ad and website misrepresented the safety of Pamine.

FDA determined that the sales ad, brochure, and website were false or misleading under the Federal Food, Drug, and Cosmetic Act and posed a potential risk to the public health, because they suggested Pamine and Pamine Forte were safer and more effective than had been demonstrated. The Warning Letter also noted that the website was not submitted to CDER as required at the time of initial dissemination or publication.

Warning Letter Issued to Pfizer Inc. for Superiority Claims in Direct-to-Consumer Advertising

On April 13, 2005, CDER issued a Warning Letter to Pfizer Inc., New York, New York. The Warning Letter was issued following an FDA review of three direct-to-consumer (DTC) print advertisements titled "Tired of your allergy medicine not working?" (airplane), "Tired of your allergy medicine not working?" (office) and "Maybe it's time to switch allergy medicines" for Zyrtec® (cetirizine HCl) Tablets, Syrup, and Chewable Tablets submitted by Pfizer Inc.

The Warning Letter stated that these print ads made superiority claims about Zyrtec by suggesting that this product was clinically superior to some other allergy medicines. FDA stated that, to the Agency's knowledge, these claims had not been demonstrated by substantial evidence or substantial clinical experience. Therefore, these claims misbranded the firm's drug product in violation of the Federal Food, Drug, and Cosmetic Act.

Approved Product Labeling

According to the approved product labeling (PI), Zyrtec is FDA-approved for the relief of seasonal or perennial allergic rhinitis

Regulatory History

The Warning Letter noted that CDER had sent Pfizer three previous untitled letters for Zyrtec Tablets/Syrup since 1998. In addition, on July 8, 2003, CDER and the Federal Trade Commission sent a joint letter to Pfizer expressing both agencies' concerns about promotional materials that compared Zyrtec to other allergy medicines. The Warning Letter noted that for each of the ads, the text under the headline stated: "Your allergy medicine should work on all of your indoor and outdoor allergies. Really work. Why put up with a medicine that only treats outdoor allergies? Shouldn't it cover both?" Each ad also told the consumer to ask their doctor "about switching to prescription Zyrtec," "So you - and your seatmates - can feel good the whole flight" or "So you - and your co-workers - can feel good in the office," respectively.

FDA stated that it did not object to the dissemination of truthful, non-misleading statements about approved indications, such as, "No other antihistamine is approved to

treat more allergies than Zyrtec." Rather, FDA's concern was that this factual statement, which followed the other claims and visuals noted above, did not correct the impression that superior effectiveness, not merely a comparison of indications, was being promoted in these ads.

**Warning Letter Issued to Alcon Laboratories for
Unsubstantiated Superiority Claims for CIPRO® HC OTIC**

**Unsubstantiated Superiority Claims,
Omission of Risk Information, and
Overstated Efficacy Resulted in
Warning Letter**

On April 27, 2005, CDER issued a Warning Letter to Alcon Laboratories, Inc., Fort Worth, Texas. The Warning Letter advised that CDER had read the Alcon website for CIPRO® HC OTIC (ciprofloxacin hydrochloride and

hydrocortisone otic suspension).

The Warning Letter advised that the website was misleading, because it made unsubstantiated superiority claims, failed to reveal important risk information associated with the use of CIPRO® HC OTIC, and overstated the efficacy of the drug.

Therefore, based on the claims on the website CIPRO® HC OTIC was misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act. The Warning Letter noted that CDER had previously objected, in an untitled letter dated July 18, 2003, to the firm's dissemination of CIPRO® HC OTIC promotional material that made unsubstantiated superiority claims, omitted important risk information, and overstated the efficacy of the drug.

**Warning Letter Issued to Endo Pharmaceuticals Inc. for
Unsubstantiated Effectiveness Claims**

On June 28, 2005, CDER issued a Warning Letter to Endo Pharmaceuticals Inc. (Endo), Chadds Ford, Pennsylvania.

CDER reviewed two professional direct mailing pieces for Lidoderm® (Lidocaine Patch 5%) submitted by Endo and concluded that the direct mailing pieces were false or misleading for several reasons. First, they contained unsubstantiated effectiveness claims for Lidoderm; second, they omitted and minimized serious risk information associated with Lidoderm; and third, they failed to communicate an important limitation in the drug's FDA approved indication. Thus, FDA determined that the direct mailing pieces misbranded the drug.

Warning Letter Issued to Cytogen Corporation

Direct-To-Consumer Advertising Failed to Reveal Important Risk Information Associated with Cancer Drug

On July 18, 2005, CDER issued a Warning Letter to Cytogen Corporation, Princeton, New Jersey. The Warning Letter was issued based on CDER's review of a direct-to-consumer broadcast radio advertisement, patient

testimonial video, and website (www.quadrainetus.com) for Quadramet (Samarium SM 153 Lexidronam) Injection.

The Warning Letter stated that these promotional pieces overstated, to a very sick and vulnerable population, the effectiveness of Quadramet and failed to reveal and minimized important risk information associated with the use of Quadramet. Therefore, the promotional pieces misbranded Quadramet. The Warning Letter further noted that CDER had previously objected, in an untitled letter dated November 9, 2001, to the firm's dissemination of Quadramet promotional material that made unsubstantiated efficacy claims.

In addition, the Warning Letter advised that the firm's promotional pieces implied that Quadramet was more effective in treating cancer pain and more beneficial to patients receiving the drug than was demonstrated by substantial evidence or substantial clinical experience. CDER further requested that Cytogen immediately cease disseminating violative promotional materials for Quadramet that contained claims the same as or similar to those described above. Because the violations described above were serious, FDA also requested that the firm's submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in the letter to the audiences that received the violative promotional materials.

Unapproved Marketing

FDA Found Hillestad Pharmaceuticals, USA, to be Violating Injunction Against Promoting Unapproved Drugs

On October 1, 2004, FDA announced that the Agency had informed Hillestad Pharmaceuticals, USA, Inc., of Woodruff, Wisconsin, that the firm violated a court order prohibiting the company from using drug claims in the promotion of its dietary supplement products. FDA took this action after an inspection of the firm revealed that

it was promoting various dietary supplements with claims that they could treat, prevent, cure or mitigate disease -- even though none of these products had ever been shown to be safe or effective for these uses.

In its letter, FDA instructed the firm to cease these illegal practices or face further FDA action, including a possible contempt proceeding for failure to comply with the court order. The letter also directed the firm to pay liquidated damages in the amount of \$23,000.00, which reflected sales of Opti-Cran, Hi-C Level, Ginkgo Biloba, and St. John's Wort that were made in violation of the court order.

In July 2000, the company had agreed to a Consent Decree issued by the United States District Court for the Western District of Wisconsin as part of a settlement of a case FDA and the Department of Justice had brought against it for marketing unapproved new drugs -- products not shown to be safe or effective for their intended uses -- in violation of the Federal Food, Drug and Cosmetic Act. Under the terms of the Decree, the firm was required to cease making such drug claims and destroy all promotional materials containing such claims.

An FDA inspection of the firm, however, revealed that promotional materials, such as the company's monthly newsletters, contained unapproved drug claims that certain products could prevent viral and bacterial disease, or treat medical conditions such as diabetes, depression, impotence and allergies.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01316.html>.

Unapproved New Drug

FDA Issued Warning that Actra-Rx "Dietary Supplements" Contained Undeclared Prescription Drug Ingredient

On November 2, 2004, FDA issued a warning to the public not to purchase or to consume Actra-Rx or Yilishen, two products promoted and offered for sale on websites as "dietary supplements" for treating erectile dysfunction and enhancing sexual performance for men. These products in fact contained an active prescription drug ingredient. FDA also issued an Import Alert instructing FDA field personnel to stop the importation of "Actra-Rx" and "Yilishen."

A research letter published in the *Journal of the American Medical Association* described the results of a chemical analysis of Actra-Rx, finding that each capsule analyzed contained prescription-strength quantities of sildenafil. Sildenafil is the active drug ingredient in Viagra, a Pfizer prescription drug product approved in the United States for the treatment of erectile dysfunction. FDA conducted its own tests of Actra-Rx and found that the product contained prescription-strength sildenafil.

An interaction between sildenafil and certain prescription drugs containing nitrates (such as nitroglycerin) or nitrates found in illicit substances (such as amyl nitrate) may cause a significant lowering of blood pressure to an unsafe level. Consumers with diabetes, high blood pressure, high cholesterol, or heart disease often take nitrates.

Because erectile dysfunction can be a common problem in individuals with these conditions, these consumers may take Actra-Rx or Yilishen and risk experiencing serious adverse effects. FDA advised that anyone experiencing erectile dysfunction seek guidance from their health care provider before purchasing a product to treat that condition.

FDA also warned consumers who had taken Actra-Rx or Yilishen to stop taking it and consult with their health care provider regarding approved erectile dysfunction treatments, because the drugs could be dangerous to their health and even life-threatening.

The full text of the Press Release is available at:

<http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01322.html>.