
Chapter 3 – Center for Drug Evaluation and Research

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The Warning Letters presented in this chapter were chosen to provide examples of the types of Warning Letters issued for violations of FDA laws. The hyperlinks provided may change and to locate the archived Warning Letters go to <http://www.fda.gov/foi/warning.htm>.

Bioresearch Monitoring

Clinical Investigator Received Warning

On May 28, 2008, the Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Office of Compliance (OC), Division of Scientific Investigations (DSI) issued a Warning Letter to Arturo Corces, M.D., Miami, Florida. Between March 20 and April 26, 2007, FDA officials conducted an inspection of clinical investigations conducted by Dr. Arturo Corces. The FDA's investigation was conducted as part of its Bioresearch Monitoring (BIMO) Program to ensure that data submitted in support of New Drug Applications (NDAs) are scientifically valid and accurate. The investigation revealed serious non-adherence to the statutory requirements and Federal regulations governing the conduct of clinical investigations.

Violations included:

- Failure to personally conduct or supervise the clinical investigations;
- Failure to meet informed consent requirements that information given to the subject or the subject's representative shall be in a language understandable to the subject or the representative; and
- Failure to maintain adequate drug disposition records.

The clinical investigator responded in writing to FDA's inspectional findings in a letter dated June 14, 2008, and CDER regarded the response as adequate.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6837c.pdf

Clinical Investigator Received Warning

On October 26, 2007, CDER's OC's DSI issued a Warning Letter to Dr. Alan Rapoport, of Stamford, Connecticut. The inspection was conducted between May 1 and June 5, 2007, as part of the BIMO Program. The investigation revealed non-adherence to the statutory requirements and FDA regulations governing the conduct of clinical investigations. Violations included:

- Failure to ensure that the investigations were conducted according to the signed investigator statement;
- Failure to maintain adequate and accurate case histories on each subject involved in the trial; and
- Failure to obtain informed consent.

The full text of FDA's Warning Letter to Dr. Rapoport is available on FDA's Website at: http://www.fda.gov/foi/warning_letters/archive/s6582c.htm

Drug Sponsor Received Warning

On October 23, 2007, CDER's OC's DSI issued a Warning Letter to Sanofi-Aventis, of Bridgewater, New Jersey. FDA conducted an inspection of Aventis Pharmaceuticals' (Aventis) role as a sponsor of a study of an investigational new drug, Ketek. The investigation revealed non-adherence to the statutory requirements and FDA regulations governing the conduct of clinical investigations. Violations included:

- Failure to secure investigator compliance with the investigational plan and applicable FDA regulations;
- Failure to ensure proper monitoring of the clinical investigation; and
- Failure to select qualified investigators and provide investigators with the information needed to conduct the study properly.

To view the full text of the Warning Letter, go to:
<http://www.fda.gov/cder/warn/2007/07-HFD-45-1002.pdf>

Applicant Failed to Provide Data to FDA

On January 18, 2008, CDER's OC's DSI issued a Warning Letter to Mr. Kenneth Collins, President and Chief Executive Officer (CEO) of Replidyne, Inc., located in Louisville, Colorado. FDA conducted inspections of Replidyne, Inc., initially between July 19 and August 8, 2006, and for a follow-up inspection, between September 11 and October 17, 2006. The investigation was part of FDA's BIMO Program.

After review of the establishment inspection reports (EIRs), the documents submitted with that report, the firm's written responses (dated September 11, 2006, and February 8, 2007) to the inspectional observations, and the documents for the clinical investigators that were inspected for the NDA, FDA concluded that Replidyne, Inc., did not adhere to the applicable statutory requirements and regulations governing an applicant's responsibilities concerning submission of data and information to the FDA.

Replidyne, Inc., refused to make available the underlying raw data from the investigation for the FDA's audit, and failed to provide adequate descriptions and analyses of any other data or information relevant to the evaluation of the safety and effectiveness of the drug product obtained by the applicant from any source. In addition, Replidyne, Inc., submitted data from several clinical investigative research sites in support of an NDA, but did not adequately verify the integrity of the data at those sites.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/archives/s6638c.htm

Investigational Review Board Failed to Comply with Regulations

On February 25, 2008, CDER's OC's DSI issued a Warning Letter to Dr. Alfred E. Abuanza, Chief Medical Officer at West Jefferson Medical Center (West Jefferson), in Marrero, Louisiana. FDA inspected the Investigational Review Board (IRB) at West Jefferson between July 23 and July 26, 2007, to determine whether the IRB procedures for the protection of human subjects complied with the Code of Federal Regulations (CFR) Parts 50 and 56.

CDER concluded that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. Violations of FDA regulations included:

- Failure to excuse a member from participating in the initial review of a project in which the member had a conflicting interest, except to provide information requested by the IRB;
- Failure to review proposed research at convened meetings at which a majority of the members of the IRB were present, including at least one member whose primary concerns were in nonscientific areas (for other than expedited reviews);
- Failure to conduct continuing review of research at intervals of not less than once per year; and
- Failure to determine, at the time of initial review, that studies involving children are in compliance with 21 CFR Part 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations."

The FDA will conduct additional follow-up inspections to ensure that adequate corrective actions have been implemented.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6717c.htm

BIMO Drug-Device Combination Product

On June 30, 2008, CDER's OC's DSI issued a Warning Letter to Robert Cohen, President and CEO of Travanti Pharma, Inc., in Mendota Heights, Minnesota, after an inspection to review the firm's practices as the sponsor of a clinical investigation of an investigational device-drug combination product. The inspection took place between February 19 and 28, 2008, as part of the FDA's BIMO Program.

The investigation revealed non-adherence to the statutory requirements and FDA regulations governing the conduct of clinical investigations. Violations included:

- Failure to submit an Investigational New Drug (IND) for the conduct of clinical investigations with an investigational new drug;
 - Failure to obtain an investigator statement, Form FDA 1572, before permitting an investigator to participate in an investigation; and
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- Failure to select a monitor qualified by training and experience to monitor the progress of the investigation.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6854c.htm

Postmarketing Adverse Drug Experience

On March 25, 2008, the FDA sent a Warning Letter to Jean-Pierre Garnier, Ph.D., CEO of GlaxoSmithKline (GSK), located in Research Triangle Park, North Carolina. The letter referred to an inspection conducted August 20 through November 13, 2007. The inspection focused on the firm's compliance with postmarketing adverse drug experience reporting requirements and other postmarket reporting requirements relating to Avandia, approved by FDA on May 25, 1999.

The inspection revealed that the firm failed to adequately report multiple postmarketing studies involving Avandia in mandatory periodic and/or NDA annual reports. FDA considered the firm's initial response to the inspection report inadequate because the response did not explain how the firm will ensure it had submitted to FDA all mandatory postmarketing reports and other information concerning its approved drug products. FDA expected the corrective actions to include a comprehensive evaluation of the firm's reporting of postmarketing studies for all drug products for which the firm holds an approved application.

GSK representatives met with FDA officials on June 26, 2008, to discuss their remediation plan to address the FDA Warning Letter. The firm's completed, promised, and remedial corrective actions appeared adequate to FDA.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6714c.htm

Counterfeit Drugs

FDA Issued Warning Regarding Counterfeit Drugs

On August 8, 2008, the FDA issued a warning to consumers who filled prescriptions at The Medicine Shoppe pharmacies located at 8035A Liberty Road

and 5900 Reisterstown Road in Baltimore, Maryland. The warning indicated that consumers may have received drugs that were either expired or suspected counterfeit. The FDA was particularly concerned because a number of the drugs dispensed were labeled for the treatment of serious diseases and the use of these products could result in adverse effects for patients.

The products in question include:

- Lisinopril (20 mg)
- Guaifenesin/Dextromethorphan (600 mg and 1000 mg)
- Gabapentin (100 mg, 300 mg, and 400 mg)
- Metoprolol (50 mg)
- Nifedipine (30 mg)
- Diclofenac Sodium (30 mg)
- Glucophage (500 mg Extended Release)
- Glucovance (125 mg and 500 mg)
- Glipizide/Metformin (2.50 mg/250 mg)
- Furosemide (20 mg)
- Tamoxifen Citrate (10 mg)
- Metformin HCl ER (500 mg)
- Calcitrol (0.25 µg)

The FDA had no evidence that any other Medicine Shoppe pharmacies outside of the 8035A Liberty Road and 5900 Reisterstown Road facilities were involved. Because the listed drugs may have been counterfeit, the safety and efficacy was in question. The FDA has strongly advised consumers who filled prescriptions for these drugs at these two pharmacy locations to contact the prescribing physician immediately for new prescriptions. Consumers in possession of the above listed prescription drugs from these pharmacies were advised to call the FDA for further information on how to dispose of the drugs.

To read the full text of the FDA Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2008/NEW01873.html>.

Current Good Manufacturing Practice/Adulteration

Changzhou SPL Warning Letter for CGMP Violations

On April 18, 2008, the FDA's Center for Drug Evaluation and Research, OC, issued a Warning Letter to Dr. Yan Wang, General Manager of Changzhou SPL

Company, in Wujin City, Changzhou, China. The firm was inspected February 20 through 26, 2008, following recalls by Baxter of heparin sodium U.S. Pharmacopeia (USP) and crude heparin sodium used in the manufacture of sterile dosage forms due to contamination issues.

Significant Current Good Manufacturing Practice (CGMP) deficiencies were noted during this initial inspection of the SPL facility, including: no critical processing steps identified for the manufacturing process; stepwise removal of impurities was not evaluated; no impurity profile established for heparin sodium USP active pharmaceutical ingredient (API); no evaluation of degradation of the API during stability; use of crude heparin sodium lots from an unacceptable vendor workshop used to produce several lots of heparin sodium USP API for the U.S. market; and test methods used in testing heparin sodium USP and crude heparin sodium materials have not been evaluated for suitability of use.

The firm submitted two responses dated March 17 and April 15, 2008, which were deemed inadequate. Subsequently, the Warning Letter was issued to the firm citing the following deficiencies:

- Failure to evaluate the effectiveness of critical processing steps designed to remove impurities;
- Failure to identify critical processing parameters; use of crude material from an unacceptable workshop used in the manufacture of heparin sodium USP API shipped to the U.S.;
- Failure to verify under actual conditions some USP compendial test methods; and
- Failure to document that the tanks used in the final processing steps were observed with unidentified material adhering to the surfaces even though the equipment was labeled clean.

The firm is currently on Import Alert (IA) under IA 66-40 for all heparin products.

FDA Issued Warning Letters and an Import Alert to Ranbaxy Laboratories Citing Serious Manufacturing Deficiencies

The FDA on September 16, 2008, issued two Warning Letters to Ranbaxy Laboratories Ltd., of the Republic of India, and an IA for generic drugs produced by Ranbaxy's Dewas and Paonta Sahib plants in India. FDA inspected the pharmaceutical manufacturing facilities on January 28 through February 12 and March 3 through 7, 2008, respectively.

The Warning Letters identified the Agency's concerns about deviations from CGMP regulations. Because of the extent and nature of the violations, the FDA issued an Import Alert, under which U.S. officials may detain at the U.S. border any API (the primary therapeutic components of a finished drug product), and both sterile and non-sterile finished drug products manufactured at these Ranbaxy facilities offered for import into the United States (U.S.).

The problems FDA investigators identified at these two Ranbaxy plants relate to deficiencies in the company's drug manufacturing process. The actions were proactive measures that the FDA undertook in order to assure that all drugs that reach the American public are manufactured according to CGMP requirements. The action did not involve removing products from the market because the FDA had no evidence to date that Ranbaxy had shipped defective products. The FDA continues to monitor the situation.

The current announcement did not impact products from Ranbaxy's other plants. FDA had inspected those facilities and, to date, the facilities had met CGMP requirements for drug manufacturing.

Earlier, the FDA informed Ranbaxy that until the firm resolved the deficiencies at each of these two facilities and the plants came into compliance with CGMP requirements, FDA would recommend denial of approval of any NDAs and Abbreviated New Drug Applications (ANDA) that list the Paonta Sahib or Dewas plants respectively as the manufacturer of APIs or finished drug products. Ranbaxy is one of the largest foreign suppliers of generic drugs to the U.S.

The FDA Import Alert covers more than 30 different generic drug products (http://www.fda.gov/cder/drug/infopage/ranbaxy/ranbaxy_list.htm) produced in multiple dosage forms and dosage amounts (i.e., 25 mg, 50 mg, and 100 mg) at these two locations. The FDA evaluated whether these actions would create any potential drug shortages in the U.S., and determined that with one exception, other suppliers could meet market demand. Because Ranbaxy was

the sole supplier to the U.S. of one drug product, Ganciclovir oral capsules (an antiviral drug), to avoid creating a shortage of the drug, the FDA did not detain shipments of this product, and planned to arrange for additional oversight and controls until the company resolved the manufacturing issues.

CDER said with this action FDA was sending a clear signal that drug products intended for use by American consumers must meet FDA standards of safety and quality. The FDA notified other agencies and health care professionals so that appropriate action could be taken to advise patients as needed.

Following the two inspections, the Agency evaluated the findings, Ranbaxy's responses, and the firm's overall inspectional history. The evaluation was complex due to the scientific and technical issues at both sites and the identified deficiencies. Ultimately, FDA concluded that the firm's responses were not adequate and that Warning Letters were the appropriate regulatory response.

This represents the second time in less than three years FDA issued a Warning Letter to Ranbaxy. In 2006, FDA cited Ranbaxy for violations of U.S. CGMP regulations at the Paonta Sahib facility.

To read the full text of the FDA Warning Letters:

http://www.fda.gov/foi/warning_letters/s6922c.htm

http://www.fda.gov/foi/warning_letters/s6923c.htm

Northeast Pharmaceutical Received Warning Letter for Poor Compliance with CGMP

On October 31, 2007, FDA's Center for Drug Evaluation and Research, OC, issued a Warning Letter to Mr. Liu Zhen, President and General Manager of Northeast Pharmaceutical Factory, in Shenyang, Liaoning, China. An inspection of the facility on August 27 through 30, 2007, revealed significant deviations from CGMPs in the manufacture of API.

On October 1, 2007, the firm responded to the observations. FDA said the firm's response did not adequately address the following:

- Failure to maintain manufacturing facilities and equipment to prevent API contamination;
 - Failure to test stability samples at the scheduled intervals; and
-

- Failure of the Quality Control Unit (QCU) to oversee and evaluate manufacturing and laboratory controls.

The Warning Letter referred to a guidance document entitled "Q7A Good Manufacturing Practice Guidance of Active Pharmaceutical Ingredients (API)" (ICH CGMP Guidance), prepared under the auspices of the International Conference on Harmonisation (ICH) Committee on Technical Requirements for Registration of Pharmaceuticals for Human Use. The ICH CGMP guidance describes CGMP for manufacturing of API to help ensure that all API meet the standards for quality and purity they purport or are represented to possess. Although the ICH CGMP Guidance does not impose requirements, FDA considers its recommendations, as well as alternatives intended to accomplish the same goals, provide an equivalent level of assurance that a firm's API have been manufactured, processed, packed, and held accordance with CGMP.

To obtain the ICH CGMP Guidance for reference, refer to the following Website:
<http://www.fda.gov/cder/guidance/4286fnl.htm>

To view the full text of the Warning Letter, go to
http://www.fda.gov/foi/warning_letters/archive/s6566c.htm

Seizure of Drugs and Dietary Supplements Due to Unsanitary Conditions and Unapproved Status

At the request of the FDA, on October 31, 2007, U.S. Marshals seized more than \$300,000 worth of product, including NC Solution, an antifungal product, and other drugs for human or animal use, dietary supplements, and ingredients to make those products. These products were seized because some lacked FDA approval and all were maintained under grossly unsanitary conditions by General Therapeutics Corp., of St. Louis, Missouri. All of the finished products and raw materials were deemed adulterated. The FDA considered NC Solution to be a drug because it was intended for the use in the diagnosis, cure, or treatment of disease in people or animals. NC Solution was also a new drug because it was not generally recognized as safe and effective for its intended uses.

This action was the culmination of concerted efforts by the FDA to get the firm to follow the law when it comes to manufacturing safe products for consumers. In August and September, FDA inspectors found that the company was still manufacturing drugs and dietary supplements under unsanitary conditions, including findings of insects and rodent filth on and around manufacturing

equipment despite warnings by FDA of similar serious violations in 1999. Following the 1999 inspection, a company official told the FDA in January 2000 that the firm would stop manufacturing drugs.

The FDA's action against the company was consistent with the Agency's initiative on unapproved drugs which pose potentially harmful risks to consumers.

To read FDA's Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01736.html>

FDA Warns Transdermal Drug Manufacturer Noven Pharmaceuticals About Not Conforming to CGMP

On January 4, 2008, Florida District issued a Warning Letter to Robert C. Strauss, President, CEO and Chairman of Noven Pharmaceuticals, located in Miami, Florida. The FDA conducted an inspection on June 11-14, 19-22, 25-26, 28-29, and July 2, 2007, which revealed significant CGMP problems in transdermal drug products manufactured at the site.

The Warning Letter cited the firm for failure to establish scientifically sound and appropriate specifications and the failure to assure that the transdermal patch meets applicable standards of identity, strength, quality, and purity. Observations included failure to have appropriate specifications and to establish an expiration date that assures the drug product has acceptable release characteristics. The firm provided a written response dated July 23, and an updated response dated October 16, 2007, to the FDA. The responses were not adequate in that the FDA needed more information about the actions taken by the firm to correct identified deficiencies. Also, FDA was concerned that the underlying system problems resulting in the violations had not been fully addressed.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6632c.htm

Warning Letter Issued for Marketing of Unapproved Drugs and for Not Conforming to CGMP for Drugs

On November 7, 2007, the FDA's New England District issued a Warning Letter to Amerifit Brand, Inc., of Cromwell, Connecticut. The FDA inspection of the

facility on April 10 to May 10, 2007, documented significant deviations from the CGMP for drug products.

The FDA investigator found the test methods used in, and procedures and controls used for; the manufacture, processing, and holding of the drugs did not conform to CGMP. Amerifit Brand, Inc., failed to assure that they have the identity and strength, and meet the quality and purity characteristics, which the drugs were represented to possess.

The Warning Letter cited CGMP deficiencies with final drug product and incoming material testing and disposition. The firm failed to establish appropriate specifications, document quality programs, store drug products under appropriate conditions, and have adequate record procedures.

Additionally, the firm was marketing new drugs in violation of the Act. Until an FDA-approved application is in effect for these new products, the FDA considers these prescription drugs misbranded because the labeling failed to bear adequate directions for use.

Although there were numerous drug products marketed before the enactment of the Act in 1938 and its amendment in 1962, the FDA believed that it was unlikely that the currently marketed products such as the ones the firm manufactures were grandfathered or otherwise not a new drug. The grandfather clauses have been construed very narrowly by the courts, and drug products on the market would not be entitled to grandfather status if the drugs differed from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population.

(See the appendix of the FDA's Marketed Unapproved Drugs - Compliance Policy Guide (CPG), <http://www.fda.gov/cder/guidance/6911fnl.htm>, lines 323-329.)

Further, it was FDA's view that companies claiming that the products are grandfathered bear responsibility to fully document the products' grandfathered status. Any company marketing products on this basis should have available documentation to demonstrate the market presence of the product prior to the enactment of the new drug requirements that were established in 1938 and 1962. Amerifit Brand, Inc. should discontinue manufacturing and distributing any and all new drugs, until an FDA-approved application is in effect. Amerifit Brand, Inc., should take prompt action to correct the CGMP deviations cited for any of

the other products that may be legally marketed without an approved application.

Additionally, FDA may withhold approval of requests for export certificates or approval of pending NDAs listing the facility as a manufacturer until the above violations were corrected. A reinspection of the facility may be necessary.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6713c.htm

Making False and Misleading Claims on the Internet

Warning: FDA Warned Companies Importing and Marketing Drugs Over the Internet

On March 6, 2008, the FDA issued Warning Letters to seven U.S. companies and one foreign individual for marketing unapproved and misbranded drugs over the Internet to U.S. consumers for the prevention and treatment of sexually transmitted diseases (STDs).

CDER stated that some of the products falsely claimed to have "FDA Approval" and some claimed to be "more effective" than conventional medicine. The products posed a serious health threat to unsuspecting consumers who did not know that these products were not FDA-approved and had not been proven safe or effective. STDs are very serious diseases, and these products gave consumers a false sense of security that they were protected from STDs.

The products claimed to prevent or treat a variety of STDs, including herpes, chlamydia, human papillomavirus infections, cervical dysplasia, and human immunodeficiency virus/acquired immunodeficiency syndrome. The FDA considered these U.S. and imported products to be unapproved new drugs being marketed in violation of the Act. The drugs were also misbranded under the law because the drugs lacked proper directions for use by consumers. In addition, some of the products were misbranded because of false and misleading claims.

Examples of claims that these products made include "Treatment Kills all Herpes Viruses WITHOUT having to use conventional drugs or medications," "Greatest STD Protection Without Condoms," (SlicPlus) and "The active

ingredient in our product is FDA certified to destroy 99.9992 percent of all pathogenic organisms [i.e.] Chlamydia" (OXi-MED).

To view the full text of the Warning Letters:

http://www.fda.gov/foi/warning_letters/s6680c.htm - Aviralex Int.

http://www.fda.gov/foi/warning_letters/s6681c.htm - Aidance Skincare

http://www.fda.gov/foi/warning_letters/s6682c.htm - Health-science-report

http://www.fda.gov/foi/warning_letters/s6683c.htm - NeumaLife

http://www.fda.gov/foi/warning_letters/s6684c.htm - IMULUX, LLC

http://www.fda.gov/foi/warning_letters/s6685c.htm - Saferex Laboratories

http://www.fda.gov/foi/warning_letters/s6686c.htm - McKinnon, Blair

FDA Warned Individuals and Firms Selling Fake Cancer "Cures" on Internet Sites

In June 2008, FDA sent Warning Letters to 28 U.S. companies and two foreign individuals marketing a wide range of products fraudulently claiming to prevent and cure cancer. As of September 18, 2008, the FDA has issued an additional five warning letters to other companies selling fake cancer "cures", bringing the total number of fake cancer products addressed in Warning Letters to 187.

The complete list of fake cancer "cure" products and their manufacturers along with the Warning Letters and a consumer article on health scams can be found at: <http://www.fda.gov/cder/news/fakecancercures.htm>.

While promotions of bogus cancer "cures" have always been a problem, the Internet has provided a medium for them to flourish. These Warning Letters are an important step to ensure that consumers do not become the victim of false "cures" that may cause greater harm to their health.

The products contained ingredients such as bloodroot, shark cartilage, coral calcium, cesium, ellagic acid, Cat's Claw, an herbal tea called Essiac, and mushroom varieties such as Agaricus Blazeii, Shitake, Maitake, and Reishi.

The products claimed to cure, treat, mitigate or prevent disease, and have not been shown to be safe and effective for the labeled conditions of use. The products are unapproved new drugs marketed in violation of the Act.

Examples of fraudulent claims for these products included:

- "Treats all forms of cancer"
- "Causes cancer cells to commit suicide!"
- "80% more effective than the world's number one cancer drug"
- "Skin cancers disappear"
- "Target cancer cells while leaving healthy cells alone"
- "Shrinks malignant tumors"
- "Avoid painful surgery, radiotherapy, chemotherapy, or other conventional treatments"

To learn about the Federal Trade Commission's "Operation False Hope" and its efforts to educate consumers about health scams, go to www.ftc.gov/curious.

To read about efforts in Canada to educate consumers about health scams, go to <http://www.competitionbureau.gc.ca/epic/site/cb-bc.nsf/en/02614e.html>.

FDA Sent Warning Letter for Misleading Website and Newsletter Promotional Material

The FDA Division of Drug Marketing, Advertising, and Communications (DDMAC) issued a Warning Letter on December 13, 2007, to Kurt Orlofski, CEO of Morton Grove Pharmaceuticals, Inc., in Morton Grove, Illinois, for promotional pieces for Lindane Shampoo.

The Websites promoting Lindane Shampoo (http://www.alliantpharma.com/alliant_products.html and <http://www.lindane4lice.com>) and a promotional piece entitled *The Nit Picking News* (LINS 06-602) were misleading in that they omitted and/or minimized the most serious and important risk information associated with the use of Lindane Shampoo, particularly in pediatric patients, included a misleading dosing claim, and overstated the efficacy of Lindane Shampoo.

The FDA says that Lindane Shampoo was plainly labeled as second line treatment, suitable only when other, safer treatments failed or were not tolerated. The materials on the Website conveyed little sense of this limitation and little about the magnitude and nature of the risks associated with the drug.

The materials appeared to downplay the significant risks associated with Lindane Shampoo use and encouraged wider use, with less care, than is appropriate under approved labeling.

The package insert or product labeling (PI) included contraindications and warnings for the elderly, nursing mothers and pediatric patients. Coinciding with the addition of the boxed warning to the PI for Lindane Shampoo and Lindane Lotion, FDA released a Public Health Advisory in March 2003, addressing the significant potential toxicity associated with the use of topical formulations of Lindane Lotion for the treatment of scabies and Lindane Shampoo for the treatment of lice. An FDA Talk Paper was released at the same time discussing the significance of the risk from a public health perspective given the prevalence of head lice and scabies, which occur mostly in school-aged children.

The significant risks are further emphasized in the Medication Guide for Lindane Shampoo. The Medication Guide is a labeling feature reserved for products that the FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information.

To view the full text of the Warning Letters:

http://www.fda.gov/foi/warning_letters/s6604c.htm

Internet Selling of Illicit Street Drug

On January 31, 2008, the FDA sent a Warning Letter to Ms. Jennifer Gulla of Laguna Niguel, California, for marketing the product "Blow" on her Website. "Blow" is marketed as an alternative to an illicit street drug and is intended to affect the structure or function of the body. "Blow" is well known street drug terminology for illicit cocaine, and the term may suggest that the product has effects on the body similar to cocaine.

The FDA had become aware of the proliferation of various products that were being manufactured, marketed, or distributed as alternatives to illicit street drugs. FDA is concerned that these products pose a potential threat to the public health. Some street drug alternatives are being marketed as dietary supplements. FDA does not believe that street drug alternatives are intended to be used to augment the diet, to promote health, or to reduce the risk of disease.

Accordingly, street drug alternatives do not qualify as dietary supplements. In March of 2000, FDA made available guidance for industry on street drug

alternatives. This document contains additional information and is available at: <http://www.fda.gov/cder/guidance/3602fnl.htm>.

FDA considers "Blow" a drug because it was intended to affect the structure or function of the body of man or other animals. Moreover, this product is a new drug because it was not generally recognized as safe and effective for its labeled uses. The sale of "Blow" without an approved application violates the law.

To view the full text of the Warning Letters:

http://www.fda.gov/foi/warning_letters/s6674c.htm

Misleading Claims

FDA Issued Warning Letter to Wyeth for Overstating Drug Efficacy

The FDA's DDMAC issued a Warning Letter on December 10, 2007, to Robert Essner, Chairman and CEO of Wyeth Pharmaceuticals, Inc., in Philadelphia, Pennsylvania. The FDA reviewed a professional journal ad submitted by Wyeth for Effexor XR® (venlafaxine HCL) tablets. The journal ad was misleading because it: overstated the efficacy of Effexor XR®; made unsubstantiated superiority and other claims; and minimized the risks associated with the use of Effexor XR®. According to FDA's approved PI, Effexor XR® is indicated, among other things, for the treatment of major depressive disorder.

Effexor XR® use is associated with a number of serious risks. The PI for Effexor XR® includes a black box warning regarding suicidality in children and adolescents. Furthermore, there are numerous warnings associated with Effexor XR® use, including clinical worsening and suicide risk, the need to screen patients for bipolar disorder, the potential for interactions with monoamine oxidase inhibitors, serotonin syndrome, sustained hypertension, and mydriasis. The PI for Effexor XR® also contains precautions concerning discontinuation of Effexor XR®, insomnia and nervousness, changes in weight, changes in height, changes in appetite, activation of mania/hypomania, hyponatremia, seizures, abnormal bleeding, serum cholesterol elevation, and use in patients with concomitant illness.

The journal ad claimed that "In an open-label study of patients who failed previous antidepressant treatment, nearly 60% achieved remission when changed to Effexor XR®." This claim was misleading because it suggests that Effexor XR® was more effective than had been demonstrated by substantial

evidence or substantial clinical experience. In addition, by implying that Effexor XR® can successfully treat patients who had not responded to other antidepressant treatments, the claim misleadingly suggested that Effexor XR® was superior to other antidepressant treatments when this had not been demonstrated by substantial evidence or substantial clinical experience.

The study provided no information about whether Effexor XR® was superior to prior failed therapy because study subjects were not randomized for the prior failed therapy. Because improvement in depression can occur over time, subjects in the Effexor XR® arm of the study who responded well to treatment might have responded just as well had they continued on the prior failed therapy. Other claims in the ad cited no supporting references but added to the misleading implication discussed above, claiming that Effexor XR® was more effective than other antidepressants.

The journal ad additionally overstated Effexor XR®'s effectiveness when it claimed, "In the PREVENT™ study, the probability of preventing a new episode of depression was 92% with Effexor XR® in the second maintenance year versus 55% with placebo." This claim misleadingly overstated the probability of preventing a new episode of depression with Effexor XR® in the second maintenance year because it is based on a study that is inadequate to support this claim. Specifically, by selecting only patients who responded to Effexor XR® to continue to the next phase of treatment, and by failing to properly account for potential recurrent depressive episodes in those patients who discontinued Effexor XR®, the study design is biased in favor of Effexor XR® treatment.

DDMAC requested that Wyeth immediately cease the dissemination of violative promotional materials for Effexor XR®.

To view the full text of the Warning Letter, go to http://www.fda.gov/foi/warning_letters/s6603c.htm

Over-the-Counter Products

FDA Seized Dietary Supplements Marketed as New Drugs

On October 9, 2007, at the request of the FDA, U.S. Marshals seized \$71,000 of goods from FulLife Natural Options, Inc., of Boca Raton, Florida, which marketed and distributed Charantea Ampalaya Capsules and tea.

The Complaint, filed by the U.S. Attorney's Office for the Southern District of Florida, charged the products were in violation of the drug and misbranding provisions of the Act because the products were labeled as dietary supplements and were being promoted by FullLife for use in treating serious conditions, such as diabetes, anemia, and hypertension. The claims were evident in the products' labeling, including promotional literature and FullLife's Internet Website.

The Agency takes seriously its responsibility to protect Americans from unapproved drugs. The FDA considered these products to be unapproved new drugs because they made claims related to the prevention or treatment of diseases in the products' labeling. Before a new drug product may be legally marketed, it must be shown to be safe and effective, and approved by FDA. This action protects consumers who may rely on unapproved products and unsubstantiated claims associated with these products when making important decisions about their health.

To read the full text of the Compliance Policy Guide Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs, go to:

http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg440-100.html.

To read FDA's Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01723.html>.

Marketing Claims

GlaxoSmithKline Received Warning Letter for Three Healthcare Practitioner Letters

On November 21, 2007, CDER's DDMAC issued a Warning Letter to GlaxoSmithKline of Triangle Research Park, North Carolina after reviewing three Healthcare Practitioner letters which were part of the launch campaign for Tykerb.

The FDA stated the letters were misleading in that they omitted and minimized the most serious and important risk information for Tykerb and selectively presented efficacy information for Tykerb, thereby overstating the efficacy of the drug. The materials, which were disseminated to healthcare professionals during the product's launch and formed the basis of their first impressions of the drug, suggested to healthcare professionals that Tykerb was safer and more effective than had been demonstrated.

DDMAC requested that GlaxoSmithKline immediately cease the dissemination of violative promotional materials for Tykerb. FDA requested a written response to their Warning Letter stating whether GlaxoSmithKline intended to comply with the request, listing all violative promotional materials for Tykerb, and explaining the plan for discontinuing use of such materials. Because the violations described are serious, FDA also requested that the 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 audience(s) that received the violative promotional materials.

To view the full text of the Warning Letter, go to http://www.fda.gov/foi/warning_letters/s6585c.htm

Professional Mailer Includes Misleading Information

On April 18, 2008, CDER's DDMAC sent a Warning Letter to David R. Bethune, CEO of Zila Pharmaceuticals, Inc., (Zila) in Phoenix, Arizona. FDA reviewed a professional mailer for Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse (Peridex®) submitted by Zila. The professional mailer includes a letter, a brochure, and the approved PI for Peridex.

The promotional pieces in the mailer are false or misleading because they present efficacy claims for Peridex® but fail to communicate any information about the risks associated with its use, make unsubstantiated superiority claims, fail to use the required established name, overstate the efficacy and omit material facts, and broaden the indication. These promotional materials also make false or misleading representations about a competitive product.

The FDA says that promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Both the letter and brochure provided in the professional mailer make numerous efficacy claims for Peridex®, including claims that it is "the gold standard in gingivitis treatment," an "ideal solution for your growing dental practice," and "a proven way to combat gingivitis." However, these promotional materials entirely omit risk information for Peridex®, including the contraindication, warnings, precautions, and most frequently reported adverse events from the PI. FDA noted that the PI is included in the envelope along with the letter and brochure, but the inclusion of the PI is not sufficient to provide appropriate qualification or pertinent information for the claims made in the letter and brochure. For pieces to be non-

misleading, they must contain risk information in each part as necessary to qualify any safety or effectiveness claims made.

DDMAC requested that Zila immediately cease the dissemination of violative promotional materials for Peridex®.

To view the full text of the Warning Letter, go to http://www.fda.gov/foi/warning_letters/s6751c.htm

Warning Letter for Labeling Claims on Magnet

On May 1, 2008, CDER's DDMAC sent a Warning Letter to Ludwig Hantson, Head of Pharma North America and CEO of Novartis Pharmaceuticals Corporation, in East Hanover, New Jersey. The FDA reviewed labeling claims on a Partial Seizure Lenticular Magnet (TPL-OT-0167-A) (magnet) for Trileptal® (oxcarbazepine) Tablets and Oral Suspension (Trileptal®) submitted by Novartis Pharmaceuticals Corporation (Novartis). The magnet was violative because it omitted the full indication for Trileptal® and omitted information about the risks associated with its use. These violations were concerning from a public health perspective because they may encourage the use of Trileptal® in circumstances other than those for which the drug had been shown to be safe and effective and suggested that Trileptal® was safer and more effective than had been demonstrated.

DDMAC requested that Novartis immediately cease the dissemination of violative promotional materials for Trileptal®.

To view the full text of the Warning Letter, go to http://www.fda.gov/foi/warning_letters/s6765c.htm

Pharmacy Compounding

FDA Issued Warning Letters to Pharmacy Operations Regarding False and Misleading Claims

In January 2008, the FDA sent letters warning nine pharmacy operations that the claimed safety and effectiveness of their so-called "bio-identical hormone replacement therapy" or "BHRT" products was unsupported by medical evidence, and was considered false and misleading by the Agency. FDA is

concerned that unfounded claims like these mislead women and health care professionals.

The pharmacy operations improperly claimed that the drugs, which contain hormones such as estrogen, progesterone, and estriol (which is not a component of an FDA-approved drug and has not been proven safe and effective for any use), were superior to FDA-approved menopausal hormone therapy drugs and prevented or treated serious diseases, including Alzheimer's disease, stroke, and various forms of cancer.

The FDA was concerned that the claims for safety, effectiveness, and superiority that the pharmacy operations were making could mislead patients, as well as doctors and other health care professionals. Compounded drugs are not reviewed by the FDA for safety and effectiveness, and FDA encourages patients to use FDA-approved drugs whenever possible. The Warning Letters stated that the pharmacy operations violate federal law by making false and misleading claims about the hormone therapy. Pharmacy operations receiving Warning Letters used the terms "bio-identical hormone replacement therapy" and "BHRT" to imply that their drugs were natural or identical to the hormones made by the body. FDA regards the use of the term "bio-identical" as a marketing term implying a benefit for the drug for which there is no medical or scientific basis.

Pharmacy operations also made unsupported claims that the drugs were better than FDA-approved menopausal hormone therapy drugs and could be used to prevent and treat serious diseases such as Alzheimer's disease, stroke, and various forms of cancer. In addition, the pharmacy operations compounded hormone therapy drugs that contained estriol. No drug product containing estriol has been approved by FDA and the safety and effectiveness of estriol is unknown.

FDA's action did not target pharmacists who practice traditional pharmacy compounding and who did not make false or misleading claims about compounded products. Traditional pharmacy compounding typically involves preparation of a drug for an individual patient by a pharmacist in response to a valid prescription from a licensed practitioner. This compounding follows a practitioner's decision that his or her patient has a special medical need that cannot be met by FDA-approved drugs. FDA's current view on human drug compounding is addressed in its compounding Compliance Policy Guide, available at <http://www.fda.gov/cder/pharmcomp/default.htm>.

FDA also responded to a citizen petition from Wyeth, in Madison, New Jersey, asking the FDA to take regulatory action against compounding pharmacy

operations that produce compounded "BHRT" drugs. Health care providers, consumer groups, and other stakeholders have also raised concerns about "BHRT" drugs.

Warning Letters and Q and A's are available at:

<http://www.fda.gov/cder/pharmcomp/default.htm>.

Warning Letter Issued to Newman Inc., dba Medi-Stat

On June 24, 2008, FDA sent a Warning Letter to Newman Inc., dba Medi-Stat, of Mobile, Alabama, regarding the production of a large volume of standardized transdermal, prescription products in anticipation of receiving prescriptions.

The pharmacy operation engaged in the commercial-level distribution of standardized drug products, employed a team of sales representatives to visit physicians' offices, and provided promotional material and drug product samples to physicians.

In addition, the labeling of the firm's transdermal products included false and misleading claims regarding treatment of diseases such as osteoarthritis, complicated neuropathic pain, fibromyalgia, and neuroma. The FDA is not aware of substantial evidence consisting of adequate and well-controlled clinical investigations supporting these claims.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6836c.pdf

Warning Letter Issued to Farmacia La Salud, Inc., Regarding Compounding Copies, or Near Copies, of Commercially Available, FDA-Approved Drugs

On March 26, 2008, FDA issued a letter to Farmacia La Salud, Inc., warning that the production volume of the firm exceeded the practices associated with traditional extemporaneous compounding and that the firm operation is more akin to a drug manufacturer. The firm compounded several inhalation solution drugs that are copies, or essentially copies, of commercially available, FDA-approved drugs. The firm was also not in conformance with the Puerto Rico Department of Health requirements.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6723c.pdf

Marketing of Unapproved Drugs

FDA Issues Warning Letter to Jen-On Herbal Science International for Marketing Claims

On October 12, 2007, the FDA sent a Warning Letter to Jen-On Herbal Science International, Inc., City of Industry, California, for the product H S Joy of Love. The statements in the inserts that accompany H S Joy of Love described the intended use of the product to diagnose, cure, mitigate, treat, or prevent disease, or to affect the structure or function of the body.

The H S Joy of Love product contains piperadino vardenafil, an analog of vardenafil. Vardenafil is the active pharmaceutical ingredient in Levitra®, an FDA-approved drug that is used to treat erectile dysfunction (ED).

The product labeling did not declare that this product contained piperadino vardenafil. Further, an insert stated "clinical experiments prove that Joy of Love is the only natural health product that can improve potency and energy instantly without causing any side effects." This statement falsely asserted that the product did not have the potential to cause side effects, even though piperadino vardenafil likely exhibits similar pharmacological action to vardenafil. FDA regards compliance with its NDA approval and over-the-counter (OTC) drug monograph requirements to be integral to drug safety. Without this foundation of compliance, it is not possible to ensure that consumers and the health care community are provided with established and emerging drug safety information so that they can make the best possible medical decisions about the safe and effective use of drugs.

A description of the new drug approval process can be found on FDA's Internet Website at <http://www.fda.gov/cder/reulatory/applications/default.htm>

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6731c.htm

FDA Issued Warning Letter to Health Freedom Nutrition for Marketing Claims

On October 18, 2007, FDA sent a Warning Letter to Health Freedom Nutrition, in Reno, Nevada, citing inspectional deficiencies from an inspection on January

30 and February 2 and 6, 2007. The inspection was conducted to determine the firm's compliance with the Act and applicable implementing regulations. Based on the claims found in their labeling and on their Website, the FDA determined that many of the products were promoted for conditions that cause the products to be drugs.

Some of the products were intended to be used in some manner other than ingestion. Because the products were not ingested, the products failed to meet the definition of food or dietary supplements.

Linolenic Ester Cream contains ingredients that were not evaluated as topical analgesics under the OTC Drug Review, nor is FDA aware of any OTC marketing history in the U.S. for the listed ingredients as topical analgesics. Linolenic Ester Cream falls outside of the OTC Review and was a new drug.

TransMist Natural Progesterone Spray was subject to final regulations covering topically applied hormone-containing drug products for OTC human use. The product contained a therapeutic claim that caused the product to be classified as a new drug.

In addition, both of the products were misbranded in that they were drugs manufactured in a facility that was not registered.

It is the firm's responsibility that they are in compliance with the Act and its implementing regulations.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/archive/s6557c.htm

FDA sent Warning Letter to Heartland Products for Labeling, Promotional Materials and Internet Claims

The FDA on October 22, 2007, sent a Warning Letter to Heartland Products, Inc., in Valley City, North Dakota, citing inspectional deficiencies found at their facility during an inspection conducted on February 1 and 2, 2007. A review of the product labeling, promotional materials and Websites showed serious violations.

Many of the product claims on the Website caused the products to be drugs. Because these products were not generally recognized as safe and effective when used as labeled, they were classified as new drugs. A new drug may not

be legally marketed in the U.S. without an approved NDA. 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. Further, the products were misbranded in that the labeling for the drugs failed to bear adequate directions for use.

Additionally, the FDA determined that the facility was subject to the registration requirement and implementing regulations. FDA advised Heartland Products, Inc., of these requirements during the inspection. FDA records indicated that, to date, this facility has not been registered with FDA.

The responsible official of a facility that manufactures, processes, packs, or holds food for human or animal consumption in the U.S. is responsible for ensuring that the overall operation and the products distributed are in compliance with the law.

FDA regulations are available on FDA's Website at www.fda.gov.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6558c.htm

Recall of 'True Man Sexual Energy' and 'Energy Max' Dietary Supplement

On November 1, 2007, FDA requested a recall of True Man Sexual Energy Nutrient Capsules and Energy Max Energy Supplement Men's Formula Capsules, illegal drug products that contained potentially harmful, undeclared ingredients. The products, often advertised as "all natural" alternatives to approved ED drugs, could interact with medications and cause dangerously low blood pressure. The products contained substances that have similar structures to active ingredients in approved prescription drugs.

Chemical analysis had shown that Energy Max contained a thione analog of sildenafil, a substance similar to the active ingredient in the approved ED drug Viagra®. In addition, FDA investigators found that True Man contained the same analog or an analog of vardenafil, the active ingredient in Levitra®, another approved ED treatment. Neither of the analogs used in True Man or Energy Max were components of FDA-approved drug products.

The FDA issued an alert on May 10, 2007, advising consumers not to buy or use True Man or Energy Max products because consumers may not know that the ingredients can interact with medications and dangerously lower their blood pressure.

To read FDA's Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01737.html>

Sentence for Woman Who Claimed to Cure "Lou Gehrig's Disease"

On December, 19, 2007, the FDA Office of Criminal Investigations (OCI) today announced that a New Jersey woman had been sentenced to 33 months in prison for falsely claiming that she could cure amyotrophic lateral sclerosis (ALS), commonly called "Lou Gehrig's Disease."

The FDA's OCI aggressively pursues those that provide false hope to patients by making unproven medical claims to unsuspecting patients, many with serious or life-threatening conditions who are desperate for a medical cure.

Elizabeth Lerner, a.k.a. "Elizabeth Cooperman," of Egg Harbor City, New Jersey, and her co-conspirator Charlene C. DeMarco, a former doctor of osteopathy in Egg Harbor City, were convicted in December 2006 of all charges contained in an 11-count federal indictment. The indictment included one count of conspiracy to commit mail and wire fraud, three counts of mail fraud, six counts of wire fraud, and one count of money laundering.

Evidence showed that from October 2002 until November 2004, DeMarco and Lerner agreed to defraud ALS patients and their families by claiming they could treat ALS patients with stem cell therapy, even though they knew they could not. The defendants falsely told their patients and their families that DeMarco had previously received FDA approval to treat ALS.

To read the full text of the Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01760.html>.

FDA Warned Consumers Not to Use "Blue Steel" and "Hero" Products

On March 25, 2008, the FDA advised consumers not to purchase or use "Blue Steel" or "Hero" products marketed as dietary supplements throughout the U.S. because they were considered unapproved drugs and had not been proven to be safe or effective. The products contained undeclared ingredients.

The products were promoted and sold over the Internet for the treatment of ED and for sexual enhancement. The products were touted as "all natural" and labeled as dietary supplements. However, Blue Steel and Hero products do not

qualify as dietary supplements because the products contain undeclared and unapproved substances that are similar in chemical structure to sildenafil, the active ingredient in Viagra®, an FDA-approved prescription drug for ED.

The undeclared ingredients in the products may interact with nitrates found in some prescription drugs (such as nitroglycerin), and can lower blood pressure to dangerous levels. Consumers with diabetes, high blood pressure, high cholesterol, or heart disease often take nitrates. ED is a common problem in men with these medical conditions. Because they may have been advised against taking ED drugs, these men may seek products like Blue Steel and Hero because the products were marketed as "all natural" or as not containing the active ingredients in approved ED drugs. Also, the product labels for these dietary supplements did not list the ingredients.

For more information, visit:

<http://www.fda.gov/consumer/updates/erectiledysfunction010408.html>.

To read the full text of the Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01809.html>.

Authorities Seized Unapproved Drugs Marketed as "Natural Supplements"

U.S. Marshals seized more than 14,000 dosage units of Shanghai Regular, Shanghai Ultra, Super Shanghai, Naturalë Super Plus, and Lady Shanghai. Labeled as natural supplements, the seized products were all marketed to treat ED, impotency, and/or to provide sexual enhancement.

The seized products, valued at more than \$100,000, contain undeclared active ingredients found in FDA-approved prescription drugs for ED or in similar substances. Use of these products may result in serious side effects and may interact in dangerous ways with medications that a consumer may already be taking.

Shanghai Distributors, Inc., of Coamo, Puerto Rico, packaged and distributed the seized products which originated in China. Although the products' labels stated the products were natural supplements, the products were drugs and their sale was illegal without FDA approval. Before a new drug product may be legally marketed, the drug must be shown to be safe and effective.

In response to a consumer complaint, the FDA conducted an inspection of Shanghai Distributors, Inc., in November 2007. The FDA's investigation and

testing revealed that the seized products contained active drug ingredients found in FDA-approved ED prescription drugs and/or a substance with a structure similar to such drugs that may cause similar side effects and drug interactions. None of the drug ingredients were listed on the labels of any of the seized products.

Despite being advised of the findings and the potential adverse health risk posed by the seized products, and that regulatory action was possible, the company did not take any action to correct the violations. The FDA issued a press release on December 28, 2007, advising consumers not to buy or use the products. Prior to the seizure, the Puerto Rico Department of Health embargoed the seized products to protect the citizens of Puerto Rico and to support the FDA's enforcement actions.

The FDA reaffirms its policy that when a drug and a dietary ingredient are combined into a single dosage form, the combination is deemed a drug, which requires an approved NDA. The Agency notes that neither product was the subject of an approved NDA.

To read the full text of the Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01817.html>

FDA Seized Xiadafil™ VIP Tabs After Company Refuses to Recall Product

On May 27, 2008, the FDA requested that SEI Pharmaceuticals, of Miami, Florida, recall all Xiadafil™VIP Tabs sold in eight tablet bottles (Lot # 6K029) or blister cards of two tablets (Lot # 6K029-SEI) because the products contained a potentially harmful, undeclared ingredient that may dangerously affect a person's blood pressure and can cause other life-threatening side effects.

Although labeled as a dietary supplement and touted as "all-natural," Xiadafil™ VIP Tabs were an illegally marketed drug that contained a potentially harmful undeclared ingredient. FDA chemical analysis revealed that Xiadafil™ VIP Tabs contained hydroxyhomosildenafil, which is an analog of sildenafil, the active ingredient in Viagra®, an FDA-approved prescription drug for ED.

The undeclared ingredient may interact with nitrates found in some prescription drugs (such as nitroglycerin) and can lower blood pressure to life-threatening levels. Consumers with diabetes, high blood pressure, high cholesterol, or heart disease often take nitrates. ED is a common problem in men with these medical conditions.

The safety and effectiveness of Xiadafil™ VIP Tabs is unknown. The product was promoted, sold over the Internet, given away as free samples at trade shows, and sold in health food stores nationwide.

On May 13, 2008, Florida officials issued a "stop sale" action at SEI's distribution facility. This action required the firm to hold, intact, violative Xiadafil™ VIP Tabs found on-hand at the facility. The State of Florida's action to control the supply of the product, coupled with the formal request by FDA to recall this product from the marketplace, further reduced the likelihood that unsuspecting consumers would use this potentially dangerous product.

Alternative products like Xiadafil™ VIP Tabs were often sought out because they were marketed as "all natural" or as not containing the active ingredients in approved, prescribed ED drugs. Because the manufacturing source of the active ingredients in many of these alternative products is unknown, consumers should also be aware that the safety, efficacy, and purity of these ingredients have not been verified by the FDA.

On July 24, 2008, U.S. Federal Marshalls seized nearly \$74,000 worth of Xiadafil™ VIP tablets. The seizure action protected the public from dietary supplements containing prescription drug ingredients that are potentially harmful.

For more information, visit:

www.fda.gov/consumer/updates/erectedysfunction010408.html.

To read the full text of the Press Releases, go to:

[FDA Requests Recall of Xiadafil VIP Tabs](#)

Combination Enforcement Activities

The FDA intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the Act against a drug or firm that also violates another provision of the Act, even if there are other unapproved versions of the drug made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates Current Good Manufacturing Practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation *and* the violation of section 505 of the Act (21 U.S.C. 355). This policy efficiently

preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action. See *U.S. v. Sage Pharmaceuticals, Inc.*, 210 F.3d 475, 479-80 (5th Cir. 2000).

CGMP for Finished Pharmaceuticals

Warning Letter Issued for CGMP Violations, Marketing Unapproved Prescription Drugs, and Misbranding OTC Drugs

On May 8, 2008, the FDA's Dallas District sent a Warning Letter to Larry Gremminger, R.Ph., President, Elge, Inc., in Richmond, Texas. An inspection conducted January 14 through February 14, 2008, revealed that the methods for the manufacture, processing, packing or holding of product did not conform to CGMP regulations. The firm was also marketing new drugs and misbranded drugs in violation of the Act.

Violations of CGMP regulations included:

- Failure of the Quality Control Unit (QCU) to follow written procedures;
 - Failure to conduct complete investigations;
 - Failure to conduct adequate identity testing for API containing tannates;
 - Failure to provide 100% of the labeled amount of active ingredient for drug products containing tannates;
 - Failure to conduct accelerated stability studies as necessary;
 - Failure to correct deficiencies in dissolution testing and establishing specifications;
 - Failure to qualify reference standards used in the testing of products containing tannates;
 - Failure to maintain stability indicating testing methods; and
 - Failure to establish the reliability of the supplier's analysis.
-

Elge, Inc., manufactures numerous prescription drug products and products for OTC use. Some of the firm's prescription cough and cold products were unapproved new drugs because they were not generally recognized as safe and effective for their labeled uses. Additionally, these products were misbranded because the drugs were prescription drugs and the labeling failed to bear adequate directions for use. Prescription drugs must have adequate written directions for use so that a layman could use the products safely for the intended uses. Several products that were manufactured inappropriately bear the Rx (prescription) legend but were OTC drug products based on their formulation and directions for use as described in the monograph covering "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC Human Use."

The FDA considered the response dated March 26, 2008, addressing the deviations from the inspection observations as inadequate because the firm failed to provide sufficient information to fully assess the adequacy of the proposed corrective actions. Furthermore, the information submitted to address many of the inspectional observations only indicated that the observations will be corrected; however, a specific timeframe for implementing the proposed corrective actions was not indicated.

To view the full text of the Warning Letter, go to http://www.fda.gov/foi/warning_letters/s6771c_2.htm

Federal Agents Seized More Than \$24 Million in Unapproved New Drugs

On July 30, 2008, the FDA and the U.S. Marshals Service seized \$24.2 million worth of unapproved new drugs from KV Pharmaceutical Company, of St. Louis, Missouri.

The seizure followed an inspection of several of the company's plants where an FDA investigator found that the company was not complying with an FDA enforcement notice as well as manufacturing unapproved new drugs such as products for cough, cold, topical wound healing, skin bleaching, and gastrointestinal conditions, as well as narcotic drug products.

Consumers need to be confident that the drugs and medical products they use are safe and effective, and the FDA will take the necessary measures to ensure safety and effectiveness throughout the lifecycle of the products, including keeping the product from reaching the marketplace should conditions warrant this action.

In a routine inspection of KV Pharmaceutical's facilities in early 2008, the FDA found the company was violating its May 29, 2007, notice requiring companies to stop manufacturing all timed-release drug products containing guaifenesin, including combination drug products which contain guaifenesin because they were unapproved new drugs. FDA took the action as part of its effort to ensure that all drugs marketed in the U.S. have the required FDA approval and that they are safe, effective, of good quality, and appropriately labeled. For products in timed-release form, the approval includes making sure that the product releases its active ingredients at the correct rate. Improperly manufactured timed-release products may release the active ingredients too quickly, too slowly, or not at all, making the product unsafe or ineffective.

The inspection also exposed the company's manufacturing and distribution of other unapproved drug products. The action addressed numerous unapproved drug products manufactured and distributed by the company. The seized drugs had been held under embargo by the State of Missouri. Since the time of the embargo, KV Pharmaceutical had been cooperating with FDA officials.

In June 2006, the FDA issued a guidance document title, "Market Unapproved Drugs - Compliance Policy Guide" (CPG). This CPG makes clear that companies may not market drugs that require approval without first establishing, through applications for approval, that the products are safe and effective.

The link to the CPG guidance is at:

<http://www.fda.gov/cder/Guidance/6911fnl.htm>.

FDA Obtains Permanent Injunction Against Scientific Laboratories, Inc.

The FDA announced on May 16, 2008, that Scientific Laboratories Inc., and its president, Rajeshwari Patel, and CEO, Amit Roy, signed a consent decree of permanent injunction and are barred from manufacturing and distributing drug products until they bring their manufacturing operations into compliance with the law and obtain approval for their products.

Scientific Laboratories is a contract manufacturer and distributor of various prescription cough and cold products. The government's complaint, filed by the U.S. Department of Justice, alleged violations of the Act. The company failed to seek required FDA approval for some of its products and failed to comply with CGMP requirements.

The unapproved new drugs manufactured by the firm have not undergone FDA review for safety and efficacy and may pose potential health risks. The FDA had warned Scientific Laboratories against violating the Act and about the risk of enforcement action if it failed to take corrective measures.

The FDA will take action against companies and their executives who violate the law and endanger public health. The FDA will carefully monitor the provisions of this injunction as well as investigate and take action against other marketers of unapproved drugs.

The consent decree barred the defendants from manufacturing and distributing any drug until they obtain required FDA approval and fully comply with CGMP requirements. The defendants must destroy any illegal drugs. The consent decree also allows the FDA to order the defendants to shut down in the event of future violations. It also subjects the defendants to liquidated damages in the amount of \$5,000 per day if they fail to comply with any of the provisions of the decree and an additional sum of \$5,000 for each violation, up to \$1 million per year.

In June 2006, the FDA issued a guidance document titled, "Marketed Unapproved Drugs - Compliance Policy Guide" (CPG). The CPG clearly states that companies may not market drugs that require approval without first establishing that the products are safe and effective, and it also explains that FDA may take action against manufacturers and marketers of unapproved drugs that violate other provisions of the Act, including CGMP requirements.

The decree was signed Thursday, May 8, 2008, by Judge William D. Quarles, Jr., in the U.S. District Court for the District of Maryland.

To read the full text of the Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01837.html>

For information about FDA's ongoing efforts on marketing unapproved drugs go to: <http://www.fda.gov/cder/drug/unapproved%5Fdrugs/>

For CDER's Website on Compliance with CGMP go to:

<http://www.fda.gov/cder/dmpq/>

New Drugs Claimed as Grandfather Drugs

On November 16, 2007, the Cincinnati District Office issued a Warning Letter to Thomas Murphy, President, Ben Venue Laboratories, Inc., located in Bedford, Ohio. The firm was inspected May 7 through June 15, 2007. The inspection revealed significant deviation from CGMP regulations and that the firm was producing drug products that do not have FDA approval.

The following CGMP deviations were cited:

- Failure to establish written control procedures to monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product; and
- Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed.

The firm was producing Levothyroxine Sodium for Injection, Colchicine Injection USP, Ephedrine Sulfate Injection USP, Papaverine HCl Injection USP, and Caffeine and Sodium Benzoate Injection. According to FDA investigators, the firm believed that these products were grandfathered as unapproved drugs. It is FDA's view that companies claiming that their products are grandfathered bear responsibility to fully document their products' grandfathered status. Any company marketing products on this basis should have available documentation to demonstrate the market presence of the product prior to the enactment of the new drug requirements that were established in 1938 and 1962.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6579c.htm

Warning Letter for CGMP for Finished Pharmaceuticals and New Drug

On July 24, 2008, the FDA issued a Warning Letter to G & W Laboratories, in South Plainfield, New Jersey, after an inspection conducted December 3 through December 20, 2007, revealed significant deviations from the CGMP for finished pharmaceuticals regulations. The firm was also cited for manufacturing unapproved new drugs.

The firm responded to the cited violations on January 15 and January 31, 2008. The responses were incomplete in that the firm stated it would complete additional analyses for preservative testing. However, the response lacked timeframes for completion.

The CGMP deviations concerned failure to establish appropriate statistical criteria where appropriate for batch release, failure to validate scale-up, specifically regarding mixing times, failure to reject in-process material not meeting specifications, poor maintenance of the manufacturing facility disrepair, incomplete investigation into the presence of black particles in finished product, water sample microbial test failure, and failure to test validation lots for preservative content uniformity.

During the inspection, the firm supplied FDA with information about the manufacture of two prescription drugs: Chloral Hydrate Rectal Suppository and Anucort-HC. These are drugs because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. The drugs are "new drugs" because the drugs are not generally recognized as safe and effective for their labeled uses. A new drug may not be introduced into or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for the drug. The firm does not have any FDA-approved applications on file for these drug products.

To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/s6874c.htm

Combination Warning Letter to Pharmaceutical Company

After an inspection of Midland Pharmaceutical LLC, a manufacturing facility located in Kansas City, Kansas, between July 24 and September 5, 2007, the FDA issued a Warning Letter citing numerous deviations from CGMP for finished pharmaceuticals.

On November 12, 2007, the firm responded to the violations noted during the inspection but the response was unacceptable because it did not adequately address the following: the process validation deficiencies; the impact of analytical method changes; root cause into out of specification (OOS) results; the status; and the disposition of returned drug products.

The firm also violated the Act by introducing into commerce "new drugs" that did not have FDA approval.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6769c.htm

Warning Letter to U.S. Apothecary Labs

On December 18, 2007, the FDA's Los Angeles District Office issued a Warning Letter to James McDaniel, President, U.S. Apothecary Labs, in Sante Fe Springs, California. The inspection of the firm was reopened on August 9, 2007, for the purpose of collecting a sample. The inspection conducted at the end of July 2007 revealed significant deviations from the CGMP regulations.

The inspection revealed that the firm was manufacturing RadBlock™ – an unapproved new drug that may not be legally marketed in the U.S. without an approved NDA. Although Section 802 of the Act [21 U.S.C. § 382] permits the export of certain unapproved new drugs if specific requirements are met, Section 802(f)(1) of the Act [21 U.S.C. 382] prohibits exportation of drugs that are not manufactured in substantial conformity with CGMP regulations. RadBlock™ is not in substantial compliance with CGMP regulations as CGMP deficiencies included failure to conduct finished product testing before release; lots released without QCU approval; undefined test methods and sampling plans for finished product testing; lack of data to support three year expiration date; reserve sample sizes not defined; failure to validate manufacturing process; no testing of incoming raw materials; and inadequate CGMP training.

The firm responded twice to the FDA's observations, but the responses were deemed inadequate in that they did not adequately address all of FDA's concerns. The firm's responses lacked an explanation for how the testing justified the declaration that the tablets' "weight variation meets USP requirements." Weight variation is the method used to demonstrate uniformity of dosage units. The assay is used in the actual weight variation calculation. Also, the firm's test results only stated "a range of tablet weights is reported." The response also failed to address whether the firm evaluated the contract laboratory's findings that the test method was inadequate.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6707c.htm

Vintage Pharmaceuticals Receives Warning Letter

On February 1, 2008, the FDA's New Orleans District Office sent a Warning Letter to Vintage Pharmaceuticals, LLC, of Huntsville, Alabama, after an inspection on July 16-20, 23-25, and August 8, 2007, revealed significant violations of the CGMP regulations and that the firm is marketing unapproved new drugs.

In a letter to FDA, Vintage responded to each of the deviations found during the inspection. FDA found that that the response failed to promise adequate corrections and the Warning Letter was issued.

The Warning Letter cited the firm for various CGMP deviations such as inadequate investigations into microbiological test failures; failure to follow microbial test procedures; use of unvalidated microbial testing methods; failure to follow the retesting procedures; unjustified use of alternative test methods; and environmental monitoring deficiencies.

The Warning Letter also listed unapproved new drugs that were being marketed by Vintage in violation of the Act.

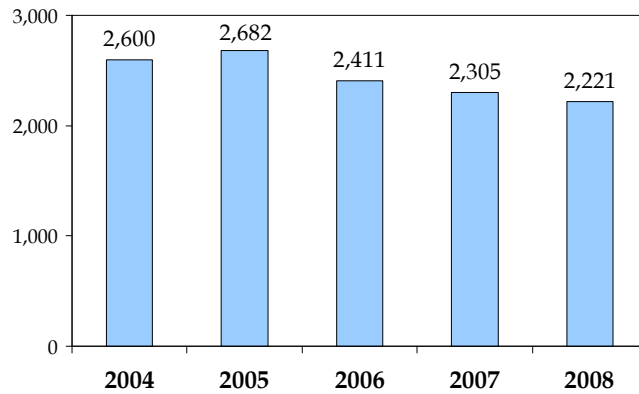
Following receipt of the Warning Letter, in meetings and correspondence, Vintage management promised extensive corrections. FDA has been monitoring the firm's progress and has found that significant corrections have been made.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6667c.htm

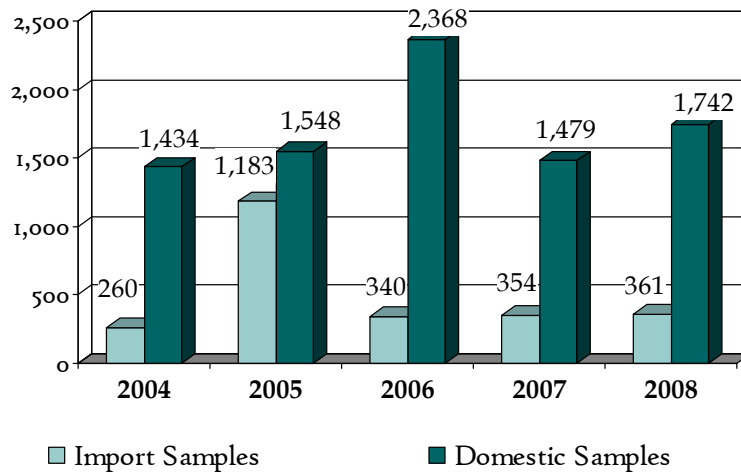
Enforcement Statistics



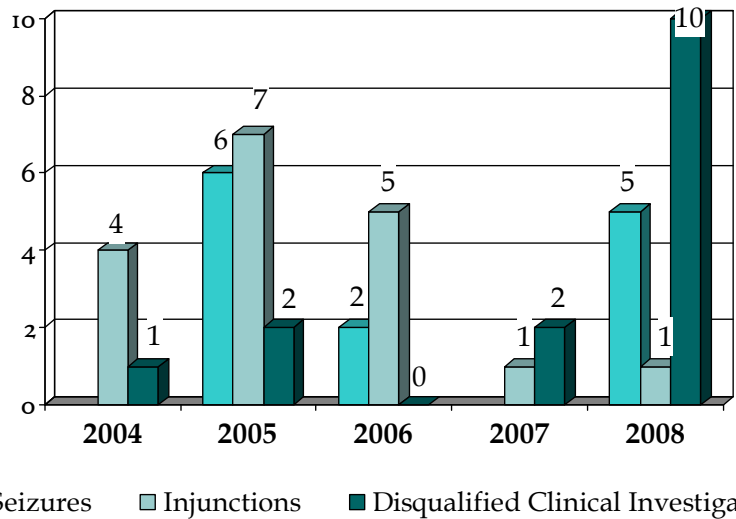
Center for Drug Evaluation and Research
FDA Foreign and Domestic Inspections
Fiscal Years 2004 - 2008



Center for Drug Evaluation and Research
Surveillance: Import and Domestic Samples
Fiscal Years 2004 - 2008



Center for Drug Evaluation and Research
Enforcement Activity
Fiscal Years 2004 - 2008



NB: These data are not comparable to those reported in FY07 as partial seizures have been assigned to one Center. A single seizure may involve more than one Center's products.

Center for Drug Evaluation and Research
Five-Year Total Product Recall Statistics
Fiscal Years 2004 - 2008

