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## Chapter 3 – Center for Drug Evaluation and Research

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## Bioresearch Monitoring

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 at: <http://www.fda.gov/foi/warning.htm>.

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### Clinical Investigator Receives Warning

On February 28, 2007, FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, Division of Scientific Investigations, issued a Warning Letter to Robert Michael Murray, M.D., Homewood, Alabama. On September 11 - 14, 2006, FDA officials conducted an inspection of a clinical investigation conducted by Dr. Murray. FDA's investigation was conducted as part of its Bioresearch Monitoring Program. The investigation revealed serious violations from Federal regulations, including failure to personally conduct or supervise the clinical investigation; failure to follow the investigational plan; failure to prepare and maintain adequate and accurate case histories, and failure to promptly report to the sponsor an adverse effect which may have been caused by the drug. Although the clinical investigator responded in writing to the FDA's concerns, CDER did not regard the response as adequate.

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

[http://www.fda.gov/foi/warning\\_letters/archive/b6316d.htm](http://www.fda.gov/foi/warning_letters/archive/b6316d.htm).

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### Failure to Follow Protocol Results in Warning Letter

On February 15, 2007, CDER issued a Warning Letter to Hollis J.C. Underwood, M.D., Sonoran Health Specialists, Inc., located in Scottsdale, Arizona. FDA conducted an inspection of Dr. Underwood's clinical investigation between April 26 and May 10, 2006. This inspection was part of the FDA's Bioresearch Monitoring Program. From CDER's review of the establishment inspection report and the documents submitted with that report, it was concluded that Dr. Underwood did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. Violations of FDA regulations included the following:

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- Failure to personally conduct or adequately supervise the above-referenced clinical trial;
- Failure to protect the rights, safety, and welfare of subjects;

Note: The FDA investigation determined that in at least six cases an unqualified person (lacking medical credentials) performed the physical exams required by the protocol;

- Failure to conduct the study according to the approved protocol; and
- Failure to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

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

[http://www.fda.gov/foi/warning\\_letters/archive/b6304d.htm](http://www.fda.gov/foi/warning_letters/archive/b6304d.htm).

## Counterfeit Drugs

### Counterfeit "Colgate" Toothpaste

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On June 14, 2007, the Colgate-Palmolive Company, New York, New York, warned consumers that counterfeit toothpaste falsely packaged as "Colgate" had been found in several dollar-type discount stores in four states: New York, New Jersey, Pennsylvania, and Maryland. There were indications that this product did not contain fluoride and may contain diethylene glycol (DEG). The Company stated that it does not use, nor has ever used, DEG as an ingredient in Colgate toothpaste anywhere in the world.



The counterfeit toothpaste can be easily recognized because it is labeled as "Manufactured in South Africa." Colgate does not import toothpaste into the United States from South Africa. In addition, the counterfeit packages examined had several misspellings including: "is clinically", "SOUTH AFRICA" and "South African Dental Assocation".

Counterfeit toothpaste is not manufactured or distributed by Colgate and has no connection with the Company whatsoever. Colgate worked closely with FDA to help identify those responsible for the counterfeit product. Colgate advised consumers who suspected they may have purchased counterfeit product to call its toll-free number at 1 800 468 6502.

### **FDA Issues Warning To Avoid Toothpaste Made in China**

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On June 1, 2007, the FDA issued a press release warning consumers to avoid using tubes of toothpaste labeled as made in China because of the Agency's concern that these products may contain DEG, a poisonous chemical. While FDA was not aware of any U.S. reports of poisonings from toothpaste containing DEG, FDA was concerned about potential risks from chronic exposure to DEG and exposure to DEG in certain populations, such as children and individuals with kidney or liver disease. DEG in toothpaste has a low but meaningful risk of toxicity and injury to these populations. FDA laboratories analyzed numerous samples of toothpaste from China that confirmed the presence of DEG. The FDA also issued an Import Alert (IA #66-74) to prevent toothpaste containing DEG from entering the United States and updates this Import Alert as new information becomes available. FDA's action subsequently resulted in voluntary recalls of several brands of toothpaste made in China, which were removed from the market place.

To view FDA's June 1, 2007 press release, go to:  
<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01646.html>

To view Import Alert IA #66-74, go to:  
[http://www.fda.gov/ora/fiars/ora\\_import\\_ia6674.html](http://www.fda.gov/ora/fiars/ora_import_ia6674.html).

### **FDA Issues Warning Regarding Counterfeit Drugs**

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On May 1, 2007, FDA issued a warning cautioning U.S. consumers about the dangers associated with buying prescription drugs over the internet. This warning was issued based on information the Agency received showing that 24 apparently related web sites may have been involved in the distribution of counterfeit prescription drugs.

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On three occasions in the spring of 2007, FDA received information that counterfeit versions of Xenical 120 mg capsules were obtained by three consumers from two different Web sites. Xenical is an FDA-approved drug used to help obese individuals who meet certain weight and height requirements lose weight and maintain weight loss.

None of the capsules ordered off the web sites contained orlistat, the active ingredient in authentic Xenical. In fact, laboratory analysis conducted by Roche and submitted to FDA confirmed that one capsule contained sibutramine, which is the active ingredient in Meridia, an FDA-approved prescription drug manufactured by Abbott Laboratories. While this product is also used to help people lose weight and maintain that loss, it should not be used in certain patient populations. In addition, the drug interaction profile is different between Xenical and sibutramine, as is the dosing frequency.

Other samples of drug products obtained from the websites were composed of only talc and starch. According to Roche, these two samples displayed a valid Roche lot number of B2306 and were labeled with an expiration date of April 2007. The correct expiration date for this lot number is actually March 2005. Pictures of the counterfeit Xenical capsules provided by Roche can be viewed at:

<http://www.fda.gov/bbs/topics/news/photos/xenical.html>.

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

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01623.html>.

## **Current Good Manufacturing Practices**

### **Quality Systems Approaches to Pharmaceutical Current Good Manufacturing Practice Regulations**

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On October 2, 2006, a Notice of Availability for the final guidance document on quality systems entitled "Quality Systems Approach to Pharmaceutical CGMP Regulations" was published in the *Federal Register*. The guidance was finalized on September 29, 2006. The guidance describes a comprehensive Quality Systems Model, which, if implemented, will allow manufacturers to support and sustain robust, modern quality systems that are consistent with CGMP regulations. It is intended to serve as a bridge between the 1978 regulations and FDA's current understanding of Quality Systems. The full text of the new guidance is available on

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line at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0443-gdl0002.pdf>.

The new guidance is intended to provide recommendations to the regulated industry on meeting the requirements of the Agency's CGMP regulations via a comprehensive quality systems approach which encourages continuous improvement and risk management in the manufacturing of human and veterinary drugs including human biological products. This guidance is an important development for the manufacturing of pharmaceutical products regulated by FDA. It marks a major recognition in the advancement of pharmaceutical manufacturing science and quality systems. The utilization of this guidance by the pharmaceutical industry is to bring quality to even higher levels than they are today for pharmaceutical products and to help ensure consistent supply of high quality pharmaceuticals to the American public. This guidance is a product of the Pharmaceutical CGMPs for the 21st Century Initiative and is an important element in product actualization under the Agency's critical path initiative (<http://www.fda.gov/oc/initiatives/criticalpath/>).

### **Consent Decree of Permanent Injunction PharmaFab, Inc.**

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On April 24, 2007, a U.S. District Court entered a Consent Decree of Permanent Injunction against PharmaFab, Inc., its subsidiary, PharmaFab LP, and two company officials, Mark Tengler, PharmaFab's president, and its vice president of scientific affairs, Russ McMahan. PharmaFab, Grand Prairie, Texas, is a major contract manufacturer and distributor of more than 100 different prescription and over-the-counter (OTC) drug products, including cough and cold products, ulcer treatments, and postpartum hemorrhage products. These products were not manufactured in compliance with CGMPs and many also lacked required FDA approval. The case was filed in the U.S. District Court for the Northern District of Texas.

The unapproved drugs manufactured by PharmaFab included, but were not limited to:

- De-Congestine Sustained Release Capsules;
- GFN 1200/DM 60/PSE 60 Extended-Release Tablets;
- Rhinacon A Tablets;
- Sudal 12 Chewable Tablets;
- Histex PD 12 Suspension;
- tuss HX CIII; and

- Ergotrate Tablets; and Hyoscyamine Sulfate Time-Release Capsules.

Because these drugs had not undergone FDA approval, their safety and effectiveness had not been established and FDA had not reviewed the adequacy and accuracy of the directions and warnings in their labeling.

According to the complaint filed with the court, PharmaFab did not comply with CGMPs by failing to investigate manufacturing failures and not recording and justifying why it deviated from written manufacturing procedures. Further, the company lacked an effective quality control unit and failed to establish reliable expiration dates for products.

The consent decree requires the defendants to destroy certain illegal drugs and bars them from distributing all drugs until they obtain required FDA approval and fully comply with CGMPs. If they resume distributing drugs, the defendants are required to retain an auditor to conduct inspections of their facilities for a period of five years and to provide reports to FDA analyzing compliance with CGMPs and labeling requirements. The decree also allows FDA to require recall or shutdown in the event of future violations and provides for damages of \$5,000 per day and \$1,000 per violation, up to a maximum of \$5 million per year, if the defendants fail to comply with its terms.

The full text of the consent decree is available online at:

[http://www.fda.gov/cder/drug/unapproved\\_drugs/PharmaFab\\_Decree.pdf](http://www.fda.gov/cder/drug/unapproved_drugs/PharmaFab_Decree.pdf).

### **Warning Letter Issued for Poor CGMPs**

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On March 29, 2007, FDA issued a Warning Letter to the president and CEO of Akorn, Inc., Decatur, Illinois, a pharmaceutical manufacturer. FDA conducted an inspection of Akorn from September 12 through September 29, 2006. During the inspection, FDA investigators documented significant deviations from CGMP regulations for finished pharmaceuticals. These CGMP violations caused the drug products to be adulterated. These violations documented during the inspection include:

- Failure to establish and follow adequate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile;
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- Failure to conduct and document a thorough investigation of any unexplained discrepancy or failure of a drug product batch to meet its specifications or to extend the investigation to other batches that may be associated with the specific failure or discrepancy;
- Failure of the equipment used in the manufacture, processing, packing or holding of drug products to be of appropriate design, of adequate size, and suitably located to facilitate operations for its intended use;
- Failure to establish written procedures for the cleaning and maintenance of equipment used in the manufacturing, processing, packing or holding of drug product;
- Failure to establish separate or defined areas or other control systems as are necessary to prevent contamination or mix-ups during the course of aseptic processing; and
- Failure to establish and follow adequate written procedures applicable to the quality control unit.

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

[http://www.fda.gov/foi/warning\\_letters/s6329c.htm](http://www.fda.gov/foi/warning_letters/s6329c.htm).

### **Warning Letter Issued to Contract Manufacturer for CGMP Problems with Children's Pain Reliever and Allergy Products**

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On April 16, 2007, FDA's New Jersey District Office issued a Warning Letter to Medico Labs' manufacturing facility in Hamilton, New Jersey. The firm manufactures a wide variety of OTC products, including children's pain relievers and children's allergy products. An FDA inspection of the facility from November 2 - 16, 2006, documented significant CGMP problems in drug products manufactured and tested at the site.

The Warning Letter identified the following CGMP problems:

- Failure to establish and follow procedures prescribing a system for reprocessing batches to insure that the reprocessed batches will conform
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- with all established standards, specifications, and characteristics;
- Failure to make written records of investigations into unexplained discrepancies, nor did investigations of unexplained discrepancies extend to other batches of the same drug product or other drug products that may have been associated with the specific failure or discrepancy;
  - Failure to establish a written testing program designed to assess the stability characteristics of drug products;
  - Master production and control records were deficient in that they lacked a justification for the variation in the amount of components used in the preparation of a dosage form;
  - Failure to conducted evaluations at least annually to review records associated with a representative number of batches, whether approved or rejected;
  - Failure to exercise appropriate controls over computers or related systems to assure that changes in analytical methods or other control records were instituted only by authorized personnel;
  - Cleaning validation studies for all products manufactured at this site were not completed;
  - Failure to qualify manufacturing equipment such as the liquid filler, homogenizer and colloidal mill, which were used to manufacture all liquid finished products at the facility.

The Warning Letter also stated that some OTC drug products manufactured by the firm failed to bear required labeling and were misbranded because the labeling failed to fully comply with the OTC drug product labeling regulations in 21 C.F.R. § 201.66 and the tamper evident packaging labeling requirement in 21 CFR 211.132.

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

[http://www.fda.gov/foi/warning\\_letters/s6357c.htm](http://www.fda.gov/foi/warning_letters/s6357c.htm).

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## Internet Warnings

### Warning: FDA Warns of Risks of Buying Accutane on the Internet

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Web Page Warns Consumers that Accutane Can Cause Birth Defects, Miscarriage, Premature Births, and Death in Babies

On March 28, 2007, FDA announced in a Press Release that the agency had created a special web page to warn consumers about the dangers of buying isotretinoin (Accutane) online. Isotretinoin is a drug approved for the treatment of extremely severe recalcitrant acne. Buying this drug over the Internet bypasses important procedures to ensure that patients can take this drug safely. When not used properly, isotretinoin can cause severe side effects, including miscarriages, premature births, birth defects, and death in babies. In addition, serious mental health problems have also been reported with isotretinoin use.

The new web page is configured so that the page will appear when a consumer performs an Internet search using Google or any other search engines for the drug under any of its names. The names include Isotretinoin, sold under the brand name of Accutane and the generic versions called Amnesteem, Claravis, and Sotret.

The web page warns that the drug "should only be taken under the close supervision" of a physician and provides links to helpful information, including ways to check that drugs purchased online come from legitimate pharmacies.

FDA and the manufacturers of isotretinoin have put in place special safeguards to reduce the risks of isotretinoin, including a strict distribution program called iPLEDGE. The aim of the program is to ensure that women using isotretinoin do not become pregnant and that women who are pregnant do not use isotretinoin.

iPLEDGE requires that pharmacies who dispense isotretinoin are registered with iPLEDGE. Additionally, the iPLEDGE program is designed to prevent the sale of isotretinoin over the Internet. The new web page is available online at:

<http://www.fda.gov/buyonline/accutane>.

### FDA Issued Warning Letters to Firms Selling Red Yeast Rice Products

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In August of 2007, FDA issued warning letters to two firms that marketed potentially hazardous red yeast rice products. The products were Red Yeast Rice and Red Yeast Rice/Policosonal Complex, sold by Swanson Healthcare Products, Inc. and

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manufactured by Nature's Value Inc. and Kabco Inc., respectively; and Cholestrix, sold by Sunburst Biorganics. The warning letters stated that the products were unapproved new drugs that were marketed in violation of the Federal Food, Drug, and Cosmetic Act.

All three products were promoted as dietary supplements and sold on web sites. However, FDA testing revealed that they contained lovastatin, the active pharmaceutical ingredient in Mecavor, a prescription drug approved for marketing in the United States as a treatment for high cholesterol.

The red yeast rice products are a threat to health because the possibility exists that lovastatin can cause severe muscle problems leading to kidney impairment. This risk is greater in patients who take higher doses of lovastatin or who take lovastatin and other medicines that increase the risk of muscle adverse reactions. These medicines include the antidepressant nefazodone, certain antibiotics, drugs used to treat fungal infections and HIV infections, and other cholesterol-lowering medications.

On August 9, 2007, FDA issued a press release to warn consumers about the potential dangers posed by red yeast rice products promoted on the Internet for treating high cholesterol. The press release is available at <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01678.html>.

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

[http://www.fda.gov/foi/warning\\_letters/s6455c.htm](http://www.fda.gov/foi/warning_letters/s6455c.htm).

[http://www.fda.gov/foi/warning\\_letters/s6456c.htm](http://www.fda.gov/foi/warning_letters/s6456c.htm).

### **FDA Issued a Warning Letter to a Firm Selling the product "Cocaine"**

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In April 2007, FDA issued a Warning Letter to Redux Beverages, LLC, concerning the firm's marketing of the product "Cocaine" as a dietary supplement on its website. According to information on this website, "Cocaine" was marketed as an alternative to an illicit street drug, and certain ingredients contained therein are intended to prevent, treat, or cure disease conditions. Dietary supplements are products that are intended to supplement the diet. Street drug alternatives, i.e., products that claim to mimic the effects of recreational drugs, are not intended to supplement the diet and, as a result, cannot lawfully be marketed as dietary supplements. In addition, a dietary supplement may not bear claims that it prevents or treats a disease, except for authorized health claims about reducing the risk of a disease. Other disease prevention and treatment claims render the product a drug

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subject to the drug requirements of the Federal Food, Drug, and Cosmetic Act (the Act).

The street drug alternative claims and the claims to prevent, treat, or cure disease conditions cause “Cocaine” to be a drug, as defined by section 201(g)(1) of the Act, 21 U.S.C. § 321(g)(1). Additionally, this product is a new drug, as defined by section 201(p) of the Act, 21 U.S.C. § 321(p), because there is no evidence that it is generally recognized as safe and effective for its labeled uses. Pursuant to section 505(a) of the Act, 21 U.S.C. § 355(a), this product does not have an approved application and its introduction and delivery into interstate commerce violates section 301(d) of the Act, 21 U.S.C. § 331(d). Furthermore, “Cocaine” was a misbranded drug under section 502(f)(1) of the Act, 21 U.S.C. § 352(f)(1) because its labeling lacks adequate directions for its intended use.

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

[http://www.fda.gov/foi/warning\\_letters/b6312d.htm](http://www.fda.gov/foi/warning_letters/b6312d.htm).

## **Over-the-Counter Products**

### **FDA Sends Warning Letter to DuPont about Unsubstantiated Claims with Two of Its Topical Antimicrobials**

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On May 7, 2007, FDA sent a Warning Letter to E.I. duPont de Nemours and Company (DuPont), Wilmington, Delaware, for unsubstantiated claims regarding two OTC topical antimicrobial drug products: “DuPont RelyOn Antiseptic Spray” and “DuPont RelyOn Antiseptic Hand Wipes.”

The Agency stated that the products’ claims and directions for use caused it to be an unapproved “new” drug under the Federal Food, Drug, and Cosmetic Act. The Warning Letter further advised that the package labeling and the Internet websites for these products covered topical antimicrobial uses in preventing serious diseases caused by pathogenic microorganisms for which “DuPont RelyOn Antiseptic Spray” and “DuPont RelyOn Antiseptic Hand Wipes” were not generally recognized as safe and effective. These uses include effectiveness in preventing diseases caused by Hepatitis A, B, and C, HIV-1 (AIDS virus), methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococcus faecalis (VRE), Herpes simplex-Type 2, Escherichia coli (E.Coli)-strain 0157, Mycobacterium bovis (BCG, TB surrogate), Salmonella choleraesuis, Respiratory syncytial virus (RSV), Rotavirus

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(SA-11-Group A), Influenza type A-2 virus (Hong Kong), Tricophyton mentagrophytes (Athletes foot fungus), Cytomegalovirus (CMV), and Adenovirus-Type2. The Agency also noted that these uses were not covered by existing OTC drug monographs or any ongoing rulemakings under FDA's OTC Drug Review.

Under the OTC drug monograph system, FDA allows OTC drugs to be marketed without first obtaining Agency approval in certain circumstances. These drugs must be covered by the OTC Drug Review and comply with applicable standards regarding any final monographs that specify conditions for the drugs' labeling and formulation. OTC drugs that do not have FDA approval and do not meet these requirements are considered unapproved drugs that are unlawfully marketed.

OTC antiseptic cleansers and OTC first aid antiseptics are being evaluated under FDA's OTC Drug Review. Tentative final monographs (TFMs) for these products were published in the Federal Register of June 17, 1994, (59 FR 31402) and July 22, 1991 (56 FR 336444). Although the active ingredient in "DuPont Rely On Antiseptic Spray" and "DuPont Rely On Antiseptic Hand Wipes" (i.e., isopropyl alcohol) is covered by these ongoing rulemakings and for certain topical antimicrobial uses, it is not covered for the uses cited in the Warning Letter. Based on their formulations and labeling, these products are also subject to the final monograph for OTC antifungal drug products, but failed to meet that monograph.

FDA allows companies to market their products (which would otherwise be unapproved new drugs) under proposed monographs, as long as the companies comply with the conditions in those proposed monographs. In this case, however, the antimicrobial claims cited in the Warning Letter are not allowed under the proposed monograph and the antifungal claims are not permitted by the final monograph for OTC antifungal drug products. Since the Rely-On products fall outside the provisions of the proposed and final monographs, they are regarded as unapproved new drugs.

FDA regards compliance with its NDA approval and 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.

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

[http://www.fda.gov/foi/warning\\_letters/s6379c.htm](http://www.fda.gov/foi/warning_letters/s6379c.htm).

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## FDA Warns Procter & Gamble about Unlawful Marketing of Hand Sanitizer for School Children

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On September 14, 2007, FDA issued a Warning Letter to Procter & Gamble for making unlawful claims about its Vicks Early Defense Foaming Hand Sanitizer (Early Defense) product.

The Agency stated that the product's claims and directions for use caused it to be an unapproved "new" drug under the Federal Food, Drug, and Cosmetic Act. The Warning Letter cited Procter & Gamble's promotion of Early Defense for use by schoolchildren "...to prevent colds and to provide antimicrobial activity for up to three hours." Although FDA is not aware of significant health risks associated with Early Defense, the Agency is concerned because this product has not been proven safe and effective for these claims.

There is a proposed OTC monograph that covers triclosan, the active ingredient in Early Defense. FDA allows companies to market their products (which would otherwise be unapproved new drugs) under proposed monographs, as long as the companies comply with the conditions in the proposed monograph. In this case, the product's claims that it "prevents colds and provides up to three hours of antimicrobial activity" are not allowed under the proposed monograph. Under the proposed monograph, when antimicrobial products use triclosan as their active ingredient, their labeling must direct consumers to rinse with water after use, and Early Defense does not. Early Defense falls outside the proposed monograph and is considered an unapproved new drug because it lacks these directions and makes these impermissible claims.

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

[http://www.fda.gov/foi/warning\\_letters/s6508c.htm](http://www.fda.gov/foi/warning_letters/s6508c.htm).

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## Nationwide Recall of Acetaminophen Caplets

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Small Metal Fragments Found in  
500 mg Caplets of Acetaminophen

On November 9, 2006, FDA alerted the public to a voluntary recall being conducted by Perrigo Company (Perrigo) of Allegan, Michigan, for 383 lots of acetaminophen 500mg caplets manufactured and distributed under various store-



brands. This recall was initiated as a result of small metal fragments found in a small number of these caplets. Approximately 11 million bottles containing varying quantities of acetaminophen 500mg caplets were affected by this recall.

For a list of batches affected, please see:

[www.fda.gov/oc/po/firmrecalls/perrigo/perrigobatchlist.html](http://www.fda.gov/oc/po/firmrecalls/perrigo/perrigobatchlist.html).

Consumers can determine if they are in possession of the recalled acetaminophen by locating the batch number printed on the container label. A list of stores that carry store-brands, potentially affected by this recall, is located on FDA's website at: [www.fda.gov/oc/po/firmrecalls/perrigo/perrigocustlist.html](http://www.fda.gov/oc/po/firmrecalls/perrigo/perrigocustlist.html).

Based on information available, the FDA believes the probability of serious adverse health consequences is remote; however, if a consumer were to swallow an affected caplet, it could result in minor stomach discomfort and/or possible cuts to the mouth or throat. Consumers should consult with their physician if they suspect they've been harmed by use of this product.

FDA investigated the cause of the metal particles found in the acetaminophen 500 mg caplets. Perrigo originally informed FDA of this problem after discovering through its own regulatory quality control procedures that their tableting equipment was wearing down prematurely. The investigations revealed the presence of the metal fragments in caplets of acetaminophen, 500 mg Perrigo reported to FDA that 70 million caplets were passed through a metal detector; resulting in the discovery of approximately 200 caplets containing metal fragments ranging in size from "microdots" to portions of wire 8 mm in length.

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

<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01507.html>.

### **FDA Advises Manufacturers to Test Glycerin for Possible Contamination**

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On May 4, 2007, FDA issued a warning to pharmaceutical manufacturers, suppliers, drug repackers, and health professionals who compound medications to be especially vigilant in assuring that glycerin, a sweetener commonly used worldwide in liquid OTC and prescription drug products, was not contaminated with DEG.

DEG is a known poison used in antifreeze and as a solvent. On May 4, 2007, FDA

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issued Guidance to Industry recommending methods of testing glycerin and other controls to identify any contamination with DEG before use in the manufacture or preparation of pharmaceutical products.

At that time, FDA had no reason to believe that the U.S. supply of glycerin was contaminated with DEG, though the agency was cognizant of reports from other countries over the past several years in which DEG-contaminated glycerin had caused human deaths. FDA emphasized the importance of testing glycerin for DEG due to the serious nature of this potentially fatal problem in combination with the global nature of the pharmaceutical supply chain and problems that continue to occur with this kind of contamination in some parts of the global supply of glycerin.

### **Historical Background**

The most recent incident occurred in Panama in September 2006 that involved DEG-contaminated glycerin used in cough syrup where dozens were hospitalized with serious injuries and more than 40 deaths. In late 1995 and early 1996, at least 80 children died in Haiti due to DEG-contaminated glycerin used in the manufacture of acetaminophen syrup. Between 1990 and 1998, similar incidents of DEG poisoning were reported to have occurred in Argentina, Bangladesh, India, and Nigeria and resulted in hundreds of deaths. In 1937, more than 100 people died in the United States after ingesting DEG-contaminated Elixir Sulfanilamide, a drug used to treat infections. This incident led to the enactment of the Federal Food, Drug, and Cosmetic Act, which is the nation's primary statute on the regulation of drugs.

To read the full text of FDA's Warning, go to:

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01628.html>.

For a copy of the Guidance for Industry, go to:

<http://www.fda.gov/cder/guidance/7654fnl.htm>.

## **Incompatible Dosage Delivery Devices**

### **Adams Recalls Children's Mucinex Liquid Products with Confusing Dosage Cup**

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Responding to reports that consumers were administering tablespoon rather than

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the correct teaspoon dosages of Children's Mucinex, FDA negotiated a recall of these products with Adams Laboratories, Inc. (Adams). The dosage cup packaged with these products included both teaspoon and tablespoon calibrations, while the labeled dosage directions specified dosages in teaspoons only. On April 2, 2007, Adams initiated a recall of all affected lots and began packaging these products with new dosage cups bearing only teaspoon markings.

### **Wyeth Recalls Cough and Cold Medicines with Faulty Dosage Cup**

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As part of its continuing surveillance of the marketplace for incompatible dosage delivery devices packaged with finished pharmaceuticals, FDA discovered that Wyeth Consumer Healthcare was producing children's cough and cold medicines accompanied by faulty dosing cups. The dosing cups failed to show a half-teaspoon mark that is necessary to help measure a dose for children aged two to six. FDA held discussions with Wyeth Consumer Healthcare regarding this issue. As a result, on October 29, 2007, the firm voluntarily recalled and replaced seven cold and cough products such as Robitussin Cough and Cold medicines and Children's Dimetapp Cold & Chest Congestion.

## **Pharmacy Compounding**

### **Pharmacy Receives Warning Letter for Poor CGMPs**

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On September 28, 2007, FDA's New Orleans District issued a Warning Letter to the President and CEO of Med-South Pharmacy, Inc., d/b/a Partners In Care, located in Orange Beach, Alabama. FDA issued the Warning Letter following an inspection of this facility. On December 20-21, 2006, an FDA investigator conducted an investigation at a facility located in Pelham, Alabama. The investigation was initiated in response to reports of injuries relating to betamethasone acetate/betamethasone sodium phosphate multi-dose injectable drug product made by Med-South Pharmacy. Additionally, on February 21-23 and March 2, 2007, a follow-up inspection was conducted at this firm. During both inspections, FDA investigators documented serious violations of the Federal Food, Drug, and Cosmetic Act (the Act).

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The Warning Letter stated that FDA found that the firm had received at least 70 complaints associated with use of injectable betamethasone acetate/betamethasone sodium phosphate 6mg/mL injectable suspension made by the company. Complaints included redness, large swollen areas, bruising at the injection site, rash, fever, and cellulitis with some patients requiring intravenous antibiotics. The company recalled two lots of the product on December 22, 2006. It was later revealed that the firm had implemented a new formulation and an incorrect amount of benzalkonium chloride had been added to the product as a preservative.

The Warning Letter stated FDA's concern about public health risks associated with the large-scale production of injectable drugs that are copies or essentially copies of FDA-approved commercially available products and manufactured rather than "compounded" by firms not meeting drug manufacturing laws and regulations.

- The Warning Letter also noted that the pharmacy's operation exceeded the scope of traditional pharmacy practice. The firm had sales representatives who obtained physician orders for the injectable drugs and produced large volumes of at least 12 commercially available drugs.
- To view the full text of the Warning Letter, go to [http://www.fda.gov/foi/warning\\_letters/s6529c.htm](http://www.fda.gov/foi/warning_letters/s6529c.htm).

### **FDA Issues Warning Letters to Five Firms Compounding Topical Anesthetic Creams**

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On December 4, 2006, FDA issued Warning Letters to five firms: Triangle Compounding Pharmacy, University Pharmacy, Custom Scripts Pharmacy, Hal's Compounding Pharmacy and New England Compounding Center, advising these firms to stop compounding and distributing standardized versions of topical anesthetic creams which are marketed for general distribution rather than responding to the unique medical needs of individual patients.

FDA is concerned about the serious public health risks related to compounded topical anesthetic creams. Exposure to high concentrations of local anesthetics, like those in compounded topical anesthetic creams, can cause grave reactions including seizures and irregular heartbeats. Two deaths have been connected to compounded topical anesthetic creams made by Triangle Compounding Pharmacy and University Pharmacy, two of the five pharmacies that received the

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Warning Letters. Similar topical anesthetic creams are compounded by the other firms and these Warning Letters serve as a general warning to firms that produce standardized versions of these creams.

Compounded topical anesthetic creams are often used to lessen pain in procedures such as laser hair removal, tattoos, and skin treatments. They may be dispensed by clinics and spas that provide these procedures or by pharmacies and doctors' offices.

These creams contain high doses of local anesthetics including lidocaine, tetracaine, benzocaine, and prilocaine. When different anesthetics are combined into one product, each anesthetic's potential for harm is increased. This potential harm may also increase if the product is left on the body for long periods of time or applied to broad areas of the body, particularly if an area is then covered by a bandage, plastic, or other dressing. The risk of harm is even greater in small children, patients with pre-existing heart disease, and patients with severe liver disease.

There are FDA-approved topical anesthetic products which are commercially available and properly labeled and are regularly used in health-care settings. However, some pharmacies create their own standardized versions of these products, often including combinations of ingredients and ingredients at higher strengths than found in FDA-approved products and often lacking appropriate warnings or directions for use.

The five firms warned by FDA stated that they produce their topical anesthetic creams as part of the practice of pharmacy compounding. Traditional pharmacy compounding typically involves pharmacies preparing drugs that are not commercially available, such as a unique medicine for a patient who is allergic to an ingredient in a FDA-approved drug. This kind of compounding follows a physician's decision that his or her patient has a special medical need that cannot be met by FDA-approved drugs.

FDA normally permits such traditional pharmacy compounding and FDA's action did not target this practice. By contrast, FDA's concern was that the five firms receiving Warning Letters were behaving like drug manufacturers, not traditional compounding pharmacies, because they produced standardized versions of topical anesthetic creams for general distribution.

The full text of the Warning Letters can be viewed by click on the link(s) below:

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Warning Letter to Triangle Compounding Pharmacy (Cary, NC)  
[http://www.fda.gov/foi/warning\\_letters/archive/g6144d.htm](http://www.fda.gov/foi/warning_letters/archive/g6144d.htm).

Warning Letter to University Pharmacy (Salt Lake City, UT)  
[http://www.fda.gov/foi/warning\\_letters/archive/g6143d.htm](http://www.fda.gov/foi/warning_letters/archive/g6143d.htm).

Warning Letter to Hal's Compounding Pharmacy, Inc. (San Diego, CA)  
[http://www.fda.gov/foi/warning\\_letters/archive/g6146d.htm](http://www.fda.gov/foi/warning_letters/archive/g6146d.htm).

Warning Letter to New England Compounding Center (Framingham, MA)  
[http://www.fda.gov/foi/warning\\_letters/archive/g6147d.htm](http://www.fda.gov/foi/warning_letters/archive/g6147d.htm).

### **FDA Warns ComputeRx/Broncho-Dose, Ltd. To Stop Mass-Producing Unapproved Inhalation Drugs**

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In March 2007, FDA warned ComputeRx/Broncho-Dose, Ltd. to stop its manufacturing and nationwide distribution of thousands of doses of compounded, unapproved inhalation drugs. Inhalation drugs are typically used to treat diseases including asthma, emphysema, bronchitis, and cystic fibrosis. These are potentially life-threatening conditions for which numerous FDA-approved drugs are available.

The firm claimed it produces inhalation drugs as part of the practice of pharmacy compounding. However, traditional pharmacy compounding typically involves drugs that are not commercially available, such as a unique medicine for a patient who is allergic to an ingredient in an FDA-approved drug. This kind of compounding follows a physician's decision that his or her patient has a special medical need that cannot be met by FDA-approved drugs. FDA normally permits traditional pharmacy compounding and did not target this practice.

The Warning Letter noted that ComputeRx/Broncho-Dose, Ltd.'s compounded inhalation drugs were being distributed to patients in multiple states and that, in compounding mass amounts of inhalation drugs, the firm went well beyond traditional compounding. The Warning Letter also noted that FDA had significant concerns about the quality of the firm's compounded inhalation drugs. During an inspection on December 1, 2005, FDA collected a sample of budesonide inhalation solution. This sample was tested for potency and was found to be subpotent. On June 6, 2006, the firm conducted a recall of product as a result of FDA's analysis. During a June 2006 inspection, FDA collected another sample of budesonide inhalation solution, tested it for potency, and found it to be subpotent.

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To view the full text of the Warning Letter, go to:  
[http://www.fda.gov/foi/warning\\_letters/b6309d.htm](http://www.fda.gov/foi/warning_letters/b6309d.htm).

### **FDA Issues Warning to Firm Compounding Domperidone, Progesterone, and Testosterone Products**

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On December 1, 2006, FDA's Cincinnati District Office issued a Warning Letter to the Owner of Spoonamore Drug Co., Inc., located in Louisville, Kentucky. FDA conducted an inspection of this firm on November 17 - December 9, 2005. This inspection revealed that the firm compounded human prescription drugs including domperidone capsules, progesterone capsules, testosterone 5% gel, and nicotine lollipops.

The Warning Letter stated that FDA's position is that the Federal Food, Drug, and Cosmetic Act (the Act) establishes Agency jurisdiction over "new drugs", including compounded drugs. FDA's view is that compounded drugs are "new drugs" and are not "generally recognized, among experts as safe and effective." The Warning Letter noted FDA's policy that, because these are "new drugs" under the Act, compounded drugs may not be introduced into interstate commerce without FDA approval. The Warning Letter further advised the firm of FDA's concerns regarding the compounding of the following drug products:

#### **Compounded Domperidone Drug Products**

FDA advised the pharmacy that it does not sanction the use of this drug in pharmacy compounding and would not exercise enforcement discretion with respect to products that contain domperidone. FDA expressed concern 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. This product has been withdrawn from marketing in several countries.

#### **Compounded Progesterone Capsules**

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FDA advised the pharmacy that this product is essentially a copy of an FDA-approved progesterone mg capsule product. The firm claimed that its compounded product is not a copy of a commercially available drug because it lacks peanut oil to which some patients are allergic. However, FDA's Warning Letter noted that the firm was not able to document a single instance of a patient taking this product for this reason.

### **Compounded Testosterone 5% Gel Products**

FDA advised the firm that this product was a copy or essentially a copy of an FDA-approved product. FDA advised that the firm's product claim differed from its FDA-approved competitors because it delivered an equivalent level of testosterone in a smaller dosage size. The availability of a different dosage size was not a meaningful difference because the amount of testosterone was the same in both products.

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

[http://www.fda.gov/foi/warning\\_letters/archive/g6154d.htm](http://www.fda.gov/foi/warning_letters/archive/g6154d.htm).

## **Marketing of Unapproved Drugs**

In FY 2006, FDA published a Compliance Policy Guide (CPG) outlining its risk-based priorities for taking enforcement action against marketed unapproved drugs. This CPG was issued in final form on June 8, 2006, and is entitled "Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs." Section 440.100 is designed to ensure that all drugs marketed in the United States, prescription and OTC, have been shown to be safe and effective and are properly manufactured and accurately labeled. The CPG heralded the Agency's renewed emphasis on this issue and sent a clear signal to industry that FDA expects all marketed drugs to have required FDA approval, and that the Agency will take action to make that happen.

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

On June 8, 2006, FDA took its first action under this CPG, announcing that FDA was taking enforcement action to stop the manufacture of unapproved carbinoxamine-containing products because of safety concerns focused on the use in children under two years of age. Carbinoxamine is a sedating antihistamine.

Since then, in furtherance of this initiative to remove unapproved drugs from the market, the Agency has taken enforcement action against five additional different drug classes, beginning in with hydrocodone, for which the Agency has received reports of medication errors associated with formulation changes and reports of confusion over the similarity of the names of unapproved products to approved drug products.

On September 28, 2007, FDA announced its intention to take enforcement action against companies marketing unapproved prescription drug products containing hydrocodone, a narcotic widely used to treat pain and suppress coughs. Most of the hydrocodone cough suppressants on the market lack FDA approval. At the time of the action, there were seven cough suppressant products containing hydrocodone that were approved by FDA, including both tablet and syrup dosage forms. There were also a number of antitussive products, both prescription and OTC, that do not contain hydrocodone.

Hydrocodone is one of the strongest medications available to treat pain or to suppress cough. The drug has been an extremely popular drug of abuse and can lead to serious illness, injury, or death, if improperly used. Hydrocodone overdose can result in breathing problems or cardiac arrest and its use may impair motor skills and judgment.

FDA had received reports of medication errors associated with formulation changes in unapproved hydrocodone products, as well as reports of confusion over the similarity of the names of unapproved products to approved drug products. FDA was particularly concerned about improper pediatric labeling of unapproved hydrocodone cough suppressants (also known as antitussives) and the risk of medication error involving the unapproved products.

Since then the Agency has taken action against the following four classes of drugs:

1. Quinine sulfate drug products, for which the Agency received 665 reports of adverse events, including 93 deaths;
2. Ergotamine-containing drug products, for which companies omitted from the labeling critical warnings regarding the potential for serious, possibly fatal interactions with certain other drugs;
3. Trimethobenzamide hydrochloride suppositories, which lacked evidence of effectiveness;

4. Guaifenesin extended release combination drug products, which directly competed with an approved drug.

The following enforcement activities highlight FDA's efforts which focus on the above initiatives.

### **Initiative No. 1**

#### **FDA Orders Unapproved Quinine Drugs from the Market**

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On December 11, 2006, FDA ordered firms to stop marketing unapproved drug products containing quinine, a drug used to treat malaria, citing serious safety concerns, including deaths, associated with quinine products. In 2006, there were multiple unapproved products containing quinine on the market and only one quinine product approved by the FDA, marketed under the name of Qualaquin.

An important drug for treating some cases of the life-threatening disease of malaria, quinine nevertheless poses many safety risks. It is associated with a variety of serious adverse events, some of them potentially fatal, including cardiac arrhythmias, hypersensitivity reactions, thrombocytopenia (a decrease in blood platelets that can cause hemorrhage or clotting problems) and other serious hematological events, permanent visual and hearing disturbances, hypoglycemia, renal failure, and generalized anaphylaxis. Additionally, quinine interacts with many other drugs and its use is contraindicated in many conditions. Unlike the labeling for the approved product, the labeling for the unapproved quinine products did not provide the most up-to-date information physicians need to use quinine drugs as safely and effectively as possible, which could contribute to inappropriate prescribing and unnecessary serious adverse events. Further, quinine is known to have a very narrow margin of safety between doses that are therapeutic in the treatment of malaria and doses that are toxic, making proper manufacture and dosing recommendations essential.

As part of its action, FDA also cautioned consumers about off-label use of quinine to treat leg cramps. Quinine is approved for treatment of malaria, but it is also commonly prescribed to treat leg cramps and similar conditions. Because malaria is life-threatening, the risks associated with quinine use are justified for that condition. But because of the drug's risks, FDA believes it should not be used to prevent or treat leg cramps.

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To read FDA's Press Release, go to:

<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01521.html>.

The full text of the Federal Register Notice announcing FDA's intentions is available online at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/06-9713.htm>.

## Initiative No. 2

### FDA Issues Warning Letters to Twenty Firms Marketing Unapproved Ergotamine For Migraines

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Critical Warnings Regarding the  
Potential for Serious, Possibly Fatal,  
Interactions with Other Drugs  
Omitted from Labeling

On February 26, 2007, FDA issued Warning Letters to 20 firms – 8 manufacturers and 12 distributors – advising the companies to cease marketing unapproved drug products containing ergotamine tartrate and

warning them that they are subject to further enforcement action if they do not stop manufacturing and distributing these products. Ergotamine tartrate products are used to treat vascular headaches, including migraines.

In addition to marketing these products without FDA approval, most of the companies receiving Warning Letters had omitted from the labeling critical warnings regarding the potential for serious, possibly fatal, interactions with certain other drugs. Based on recent scientific information, the five marketed, approved versions of ergotamine-containing products have updated labeling to include a box warning (the strongest agency warning) against using such products when also taking potent CYP 3A4 inhibitors, including some antifungal agents, protease inhibitors, and certain antibiotics. CYP 3A4 is a metabolic enzyme that helps the body eliminate drugs or other chemicals. Serious and life-threatening ischemia (a restriction in blood supply), including death and gangrene, have resulted when such products are used together. Most unapproved versions of the drug do not carry these warnings.

For additional information, including copies of the Warning Letters (which identify the firms involved and the names of their products), go to:

[http://www.fda.gov/cder/drug/unapproved\\_drugs/ergotamine\\_WL.htm](http://www.fda.gov/cder/drug/unapproved_drugs/ergotamine_WL.htm).

**Initiative No. 3****FDA Issues *Federal Register* Notice:  
Marketing Trimethobenzamide Hydrochloride Suppositories is Unlawful**

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On April 9, 2007, FDA issued a Federal Register Notice declaring that the marketing of unapproved trimethobenzamide hydrochloride suppository products is unlawful and subject to FDA regulatory action. Suppository drug products containing trimethobenzamide hydrochloride are used to treat nausea and vomiting in adults and children. These products have been marketed under various names, including Tigan, Tebamide, T-Gen, Trimazide, and Trimethobenz.

FDA took this action because trimethobenzamide hydrochloride suppositories lack substantial evidence of effectiveness. The Notice advised that firms should be aware that FDA intends to take enforcement action without further notice against any firm that manufactures or ships in interstate commerce any unapproved product covered by this Notice after May 9, 2007.

The action concluded the proceeding covering products containing trimethobenzamide under the Drug Efficacy Study Implementation program (DESI). FDA undertook this program following passage of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, which required that drugs be shown to be effective, as well as safe. FDA evaluated the evidence of effectiveness for thousands of drug products previously approved for safety only, including those products marketed under the name of Tigan containing trimethobenzamide. Because DESI findings apply to any unapproved products that are identical, related, or similar to DESI-reviewed drugs, conclusion of this proceeding makes the marketing of any unapproved trimethobenzamide hydrochloride suppository products unlawful.

To read the full text of the Federal Register Notice go to:  
<http://www.fda.gov/OHRMS/DOCKETS/98fr/E7-6593.htm>.

**Initiative No. 4****Unapproved Timed-Release Guaifenesin Products**

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On May 25, 2007, FDA announced that it would take action against companies that market unapproved guaifenesin products in timed-release dosage form. Guaifenesin

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is a substance commonly used in medicines to relieve cough and cold symptoms by stimulating the removal of mucous from the lungs. It is used in both prescription and OTC medicines.

The unapproved products included timed-release forms of products that contain only guaifenesin and those that contain guaifenesin combined with other active ingredients. These products may be prescription or OTC medicines. At the time, about 20 firms were making timed-release products containing guaifenesin that had not undergone FDA review and were marketed without FDA approval. There are many legally marketed OTC products containing guaifenesin in immediate release form. Immediate release guaifenesin products will remain on the market.

Timed-release products release the active ingredients over an extended period of time, reducing the number of doses needed per day. Other words synonymous with timed-release are extended-release, long-acting, or sustained-release. For products in timed-release form, FDA approval is also essential to make 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.

In addition, one company, Adams Respiratory Therapeutics, has obtained FDA approval for timed-release products containing guaifenesin. The approved timed-released products include the following OTC drugs:

- Humibid
- Mucinex
- Mucinex-D
- Mucinex-DM

For more information on timed-release drug products containing guaifenesin:  
[http://www.fda.gov/cder/drug/unapproved\\_drugs/enforcement.htm#guaifenesin](http://www.fda.gov/cder/drug/unapproved_drugs/enforcement.htm#guaifenesin).

### **FDA Issues Health Risk Alert for 'True Man' and 'Energy Max' Products**

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On May 10, 2007, FDA issued a Health Risk Alert advising consumers not to purchase or use "True Man" or "Energy Max" products promoted and sold as dietary supplements throughout the U.S. Both products -- touted as sexual

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enhancement products and as treatments for erectile dysfunction (ED) -- are illegal drug products that contain potentially harmful, undeclared ingredients.

FDA advised that consumers should discontinue use of True Man and Energy Max and consult their health care professional about approved treatments for ED. FDA has not approved True Man and Energy Max; therefore, the safety and effectiveness of these products are unknown. Both products are often advertised as "all natural" alternatives to approved ED drugs in advertisements appearing in newspapers, retail stores, and on the Internet.

Steven Galson, M.D., MPH, former Director of the FDA's Center for Drug Evaluation and Research, stated, "These products threaten the health of the people using them because they contain undeclared chemicals that are similar to the active ingredients used in FDA-approved prescription drug products. The risk is even more serious because consumers may not know that these ingredients can interact with medications and dangerously lower their blood pressure."

The undeclared analog ingredients in True Man and Energy Max may interact with nitrates found in some prescription drugs such as nitroglycerin and may lower blood pressure to dangerous levels. Men with diabetes, high blood pressure, high cholesterol or heart disease often take nitrates.

FDA's chemical analysis revealed that Energy Max contains a thione analog of sildenafil, a substance with a structure similar to sildenafil, the active ingredient in Viagra, an FDA-approved drug for ED. Substances like these are called analogs because they have a structure similar to another drug and may cause similar side effects and drug interactions.

True Man contained a thione analog of sildenafil or piperadino vardenafil, an analog of vardenafil, the active ingredient in Levitra, another FDA-approved prescription drug for ED. Neither the thione analog of sildenafil nor piperadino vardenafil are components of approved drug products.

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

<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01633.html>.