DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Edward J. Markey
House of Representatives
Washington, D.C. 20515-2107

DEC 1 1 2006

Dear Mr. Markey:

Thank you for your letter of October 11, 2006, which expresses concern about drugs marketed without Food and Drug Administration (FDA or the Agency) approval. You ask several questions to evaluate the Agency's process for causing the removal of unapproved drugs from the market and ensuring that products on the market are safe and effective. The Agency shares your concern about marketed unapproved drugs and please be assured that we are committed to tackling this problem. We hope the following information addresses your questions.

The recently published guidance, "Marketed Unapproved Drugs --Compliance Policy Guide" (the CPG) (*http://www.fda.gov/cder/guidance/6911fnl.pdf*) outlines Agency enforcement policies, which we believe are well-suited to protecting the public health without imposing undue burdens on consumers or unnecessarily disrupting the market. By first targeting unapproved drugs based on health risk, efficacy, and health fraud factors, the CPG describes FDA's intent to: (1) devote its limited resources to those actions most likely to improve public health; (2) proceed against an individual product or firm, or an entire class of products, as appropriate; and (3) cause the removal of potentially unsafe or ineffective products from the market without awaiting the resolution of lengthy and resource intensive rulemaking processes. Also, the CPG creates incentives for manufacturers of marketed, unapproved drugs to seek approval of their products, a process essential to ensuring that physicians prescribe, and patients take, drug products that are safe, effective, properly manufactured, and accurately labeled.

In addition to a program of enforcement actions guided by the policies articulated in the CPG, FDA is working on a number of other fronts to address the unapproved drugs issue. For example, the Agency understands the importance of providing assistance to firms unfamiliar with the drug approval process to help them secure approval for unapproved drugs they are currently marketing, and is committed to proactive action to facilitate voluntary compliance by these firms. As part of this commitment, the Agency has appointed an unapproved drugs coordinator in the Office of New Drugs. Also, FDA will offer a workshop in January 2007, to educate companies about the drug application and over-the-counter (OTC) monograph processes and provide them with direction on how to bring their products into compliance with approval requirements. The workshop is part of FDA's concerted, multi-pronged

approach to addressing the problem of unapproved drug products in the marketplace. To date, over 300 people have registered for this workshop.

FDA offers the following specific responses to the questions in your letter. Please note our responses focus on the primarily older, unapproved drugs that are the subject of your letter, and not on other types of unapproved drugs, such as compounded or fraudulent drugs. Your questions are repeated below in bold followed by our response.

Question 1: "What process does the FDA have in place to identify unapproved and illegally marketed drugs in U.S.?"

FDA's Drug Registration and Listing System (DRLS) is the primary source for identifying unapproved drugs on the market. All drug establishments, including those selling unapproved drugs, are required to register with FDA each year and to list drug products in commercial distribution. Agency personnel can search DRLS to find listed prescription drug products for which the listing firm did not identify an associated application number.

The Agency is aware that DRLS is neither fully accurate nor complete. Firms do not always list all of their products, provide all required information (such as an application number for a product that is in fact approved), or update listings to reflect reformulation or discontinuation of products. Therefore, when the Agency plans action against a class of unapproved products, staff undertake an intensive process of searching non-FDA data systems (such as IMS or Verispan), review of firm websites, and direct telephone contacts with firms, to confirm that the listed products are still being marketed and to identify similar products that have not been listed with the Agency.

In addition to utilizing DRLS and external data systems, FDA uses its inspection authority to detect unapproved drug products. Drug products of questionable legal status are also referred to FDA through various other means, such as adverse event reports, drug quality reports, recalls, and complaints submitted by consumers, industry, and health care providers. Also, FDA works closely with the Center for Medicare and Medicaid Services (CMS) concerning the reimbursement of prescription drug products through CMS' Medicaid/Medicare programs. These interactions often lead to identification of unapproved drug products applying for reimbursement.

Question 2: "How many of the following enforcement actions has the FDA taken to ensure that companies are not selling, marketing, or making false claims about unapproved and illegal products in each of the past five years?"

Over the past five years, FDA has caused the removal of numerous unapproved drug products from the market. Generally, the Agency has focused its enforcement efforts on classes of unapproved drugs or firms marketing unapproved drugs. Described below are specific enforcement actions taken by the Agency.

a. requesting voluntary compliance:

To promote voluntary compliance with the approval requirements, the Agency developed the CPG on unapproved drugs mentioned above. Although issuance of a guidance document is not itself an enforcement action, the CPG clearly articulates FDA's expectation that manufacturers of products requiring FDA approval submit applications to FDA to show that their products are safe and effective and identifies incentives for voluntary compliance.

To assist firms in bringing unapproved products into compliance with the law, as noted above, on January 9, 2007, the Agency will offer a day-long public workshop aimed at marketers of unapproved products to clarify important aspects of the application process. Title 21, *Federal Regulation* 64284 (November 1, 2006)

Also, FDA is fully prepared to bring enforcement actions when voluntary compliance is not forthcoming.

b. providing notice of action in a Federal Register notice:

In the last five years, the Agency has addressed the following classes of unapproved drugs through issuance of *Federal Register* notices.

- Carbinoxamine (June 9, 2006). Carbinoxamine is a sedating anti-histamine. Because of safety concerns focused on the use of carbinoxamine-containing products in children under 2 years of age, and after receiving reports of adverse events associated with the use of carbinoxamine in children in this age group, FDA ordered firms to cease making unapproved carbinoxamine products, announcing this enforcement action the same day the final CPG was published.

- Pancreatic enzymes (April 28, 2004). Acting on information of widespread problems affecting the bioavailability of these products that impaired their effectiveness, the Agency declared that firms must market pancreatic enzymes under approved applications to ensure their quality. Because these products are medically necessary (they are used to treat conditions associated with exocrine pancreatic insufficiency, including cystic fibrosis, chronic pancreatitis, pancreatic tumors, and pancreatectomy) the Agency could not order their immediate removal from the market without negative public health consequences. Instead, the Agency notified firms that approved applications must be obtained by 2008.

- Digoxin (June 26, 2002) The Agency resolved lengthy regulatory efforts to address widespread problems affecting the bioavailability and effectiveness of oral digoxin products (tablets and elixir) by announcing that firms must market these products under approved applications. Because these drugs are medically necessary for some cardiac conditions, the Agency had to ensure that an adequate supply of approved product was available before ordering unapproved products off the market. Therefore, the Agency permitted firms making the elixir to continue marketing those products until 2004.

- DESI-drugs: The Agency issued three *Federal Register* notices concluding proceedings under the Drug Efficacy Study Implementation program (DESI), the Agency's retrospective evaluation of the effectiveness of drugs previously approved by FDA for safety alone from 1938 to 1962. When the Agency makes a final determination regarding the efficacy of a class of drugs in a DESI proceeding, all drugs in that class that are not marketed with an approved application are considered unapproved new drugs, and the Agency publishes a *Federal Register* notice ordering firms to obtain approved applications for them. DESI proceedings finalized in the last five years cover the following drugs: Certain Parenteral Multivitamins (April 14, 2005); Isocarboxazid (April 16, 2004); and Trimethobenzamide Hydrochloride Injection and Capsules. (December 24, 2002).

c. issuing an untitled letter:

We are not aware of any untitled letters issued with respect to unapproved new drugs during the past five years.

d. issuing a Warning Letter:

The following warning letters have been issued over the past five years. For letters identified below by firm for which no drug product is named, the letter warned the firm, which was also in violation of current good manufacturing practices or adverse event reporting requirements, that it must cease manufacturing all of its unapproved products.

- Actavis Totowa (August 15, 2006)
- Sheffield Laboratories, Division of Faria Limited LLC (July 24, 2006)
- Concord Laboratories, Inc. (July 11, 2006)
- Neil Laboratories, Inc. (May 31, 2006)
- Scientific Laboratories, Inc. (November 16, 2005)
- C.R. Canfield Co., Inc. (September 24, 2004)
- Humabid made by Carolina Pharmaceuticals, Inc. (March 12, 2004)
- Levothroid (levothyroxine sodium tablets) made by Forest Laboratories, Inc. (August 7, 2003)
- Syntho Pharmaceuticals, Inc. and Intermax Pharmaceuticals, Inc. (March 14, 2003 and May 13, 2003)
- Single-ingredient guaifenesin timed-release drug products (October 11, 2002). Following FDA's approval of Mucinex, the first approved product in this class of drugs, the Agency issued warning letters to the marketers of unapproved versions, ordering them to cease manufacturing these products after a specified "grace period" during which marketing was permitted to ease consumers' transition to the approved products. This action was aimed at providing incentives for firms to obtain approval for unapproved products, a priority made explicit to all firms marketing these products when the Agency subsequently published the draft CPG.

e. seizing products:

We are not aware that the Agency has seized any unapproved drug products in the last five years. Following a seizure enforcement action, a manufacturer may continue to manufacture and market more of the same product. Therefore, an action to obtain an injunction against manufacturing or distributing unapproved drug products, as identified in "f" below, is a more effective means of ensuring that the violative firm will stop marketing unapproved drugs.

f. initiating an injunction:

The following injunction actions have been initiated in the past five years against firms that were manufacturing unapproved drugs and were also in violation of other parts of the Federal Food, Drug, and Cosmetic Act, especially with respect to current Good Manufacturing Practices (cGMP) requirements; the action cited both types of violations.

- Vita-Erb, Ltd. – Order of Permanent Injunction entered on November 14, 2006
- C.R. Canfield Co., Inc. - Consent Decree of Permanent Injunction entered on September 18, 2006
- Syntho Pharmaceuticals, Inc. and Intermax Pharmaceuticals, Inc. - Consent Decree of Permanent Injunction entered on August 10, 2006
- Pharmakon Laboratory, Inc. - Order of Permanent Injunction entered on July 25, 2005
- Propharma, Inc. - Consent Decree of Permanent Injunction entered on November 19, 2004

g. taking other regulatory actions:

Agency regulatory actions against unapproved products are described in items "a" to "f" above. As described below, the Agency is developing eDRLS, a new system for listing marketed products that, when fully implemented, will enable firms to electronically list products directly into the eDRLS database and provide much more accurate and complete information regarding drugs marketed without approval. While developing such a system is not itself an enforcement action, the data in the system would significantly enhance FDA's ability to ensure that unapproved products are not marketed in violation of the law.

Question 3: "How much did the FDA spend on such enforcement actions against unapproved products for each of the past five years?"

It is not possible to accurately report the amount of time and resources that were spent on the numerous enforcement actions. Each enforcement action against an unapproved drug product is a coordinated effort by many offices within FDA, including the Center for Drug Evaluation and Research's (CDER) Office of Compliance; FDA Office of Chief Counsel; FDA Office of Regulatory Affairs; CDER Office of Surveillance and Epidemiology; CDER Office of New Drugs; FDA Office of Public Affairs; CDER Office of Regulatory Policy; and CDER Office of the Center Director. Since each of these offices operates on a separate budget and resource expenditure are often not tracked by program area, the Agency does not

have a central mechanism to track and report the total amount of time and resources spent by each office on enforcement actions related to a particular category of products.

Question 4: "Please provide a list of all of the unapproved drugs that are currently on the market. For each product, please identify:

a. The name of the unapproved product;
b. the company that manufactures the product;
c. whether the FDA believes the product is being marketed illegally;
d. when the FDA first became aware of the product;
e. whether the product is subject to an ongoing Drug Efficacy Study Implementation proceeding or ongoing Over-The-Counter (OTC) drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which an effective final monograph is not yet in place)or subject to the 1962 Grandfather clause or the 1938 grandfather clause;
f. whether the company registered the product with the FDA, and
g. what actions the FDA has taken to ensure their safety and effectiveness.

Because of the limitations of the current DRLS system, the Agency does not maintain a list of all unapproved drug products with the information as requested. Any such list generated from the DRLS database would contain numerous inaccuracies as to any particular product, although the DRLS data are useful in the aggregate for guiding enforcement actions in the unapproved drugs area.

FDA has proposed revision of Title 21, Code of Federal Regulations, Part 207 (21 FR 51276, August 29, 2006) to mandate electronic submission of drug registration, listing, and labeling information, and require mandatory certification of the accuracy of listed information in June and December of each year. FDA is working on an electronic drug facility registration and drug product listing system to implement this process. The development of accurate, complete, and up-to-date drug product information through electronic DRLS will enable us to more fully identify marketed unapproved drugs and take appropriate enforcement action. Firms will be required to provide an accurate new drug application/abbreviated new drug application number to FDA when they list and can be required to provide a legal justification for marketing an unapproved drug. FDA intends to use this to further scrutinize firms' claims that their products are legally marketed.

Question 5: "How would a consumer know if the product that he/she is taking has been approved by the FDA or is unapproved?"

As mentioned above, the Agency is working to implement and develop the eDRLS database, which will provide accurate and complete information to consumers about those drugs which are unapproved. In the meantime, to find out if a drug is approved, consumers can go to http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (Drugs@FDA) and type in the active ingredient or name of the drug. The names of the approved companies for a drug will be listed. If the manufacturer of a consumer's drug is not listed, the drug may be unapproved or

there may be a data error. The drug also may be an approved drug, but distributed under the name of another company. Consumers are advised to check with the drug's manufacturer.

In addition, when FDA finalized the CPG on marketed unapproved drugs, it launched an unapproved drug website that is accessible from the CDER home page, *http://www.fda.gov/cder/drug/unapproved_drugs/default.htm*. The website delineates unapproved drug policies, provides notices and access to important documents, addresses consumer questions, and outlines recent enforcement actions.

Question 6: "If lack of resources limits the FDA's ability to take action against unapproved illegal products, what additional resources does the FDA need in order to identify unapproved drugs on the market and to ensure that products on the market are safe and effective?"

The administration will request whatever resources it deems appropriate for this program. However, the removal of unapproved drug products from the market is an important public health issue, and the Agency's unapproved drugs program is part of the Agency's ongoing drug safety initiative.

Regardless of the level of resources available, the Agency is committed to sustained, ongoing action to ensure that all drugs marketed in the U.S. meet legal standards for safety, effectiveness, manufacturing, and labeling. The CPG discusses the approach the Agency intends to use to efficiently and rationally bring such drugs into the approval process, and its priorities will guide the order of our enforcement actions against unapproved drugs. Any enforcement action, whether against a class of unapproved products or a firm marketing such drugs, is labor intensive, involving personnel from a number of offices in FDA and CDER headquarters and in the field. The speed at which these products can be removed, though, is in part dependent on the availability of staff to take the enforcement action.

While the Agency uses its limited budget resources to address many public health priorities, we assure you that we will continue to use available resources aggressively to address concerns about marketed unapproved drugs.

Thank you again for your concerns about this important issue. If you have any further questions, please let us know.

Sincerely,

David W. Boyer
Assistant Commissioner
for Legislation