ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

October 12, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
5600 Fisher Lane, Room 1555
Rockville, MD 20857

Dear Dr. von Eschenbach:

As part of the Committee on Energy and Commerce's ongoing investigation into the ability of the Food and Drug Administration (FDA) to protect the American public from excessive risks associated with imported prescription drugs and the ingredients that are used in their manufacture, we recently sent you a request for information concerning FDA's oversight of foreign drug manufacturing facilities (see attached). The purpose of this letter is to outline observations from a recent Committee staff oversight trip to China and India, which was conducted to observe FDA inspections, as well as gather information from industry and regulatory officials in these countries. Information obtained from this investigative trip, in addition to previous and continuing work in this area, has raised a number of matters that warrant your attention.

We wish to emphasize at the outset that, based on Committee staff's observations and discussions with industry officials, the quality of the inspections appears both thorough and professional. As indicated below, however, there are several practical challenges faced by FDA teams that, if addressed, could enhance the agency's ability to conduct its overseas inspections. We understand that Committee staff has briefed you directly on some of the following observations, and we appreciate your prompt attention to these important issues. Nevertheless, we believe that these issues require a formal agency response so that we can better assess the assistance needed for FDA to build a stronger foreign-inspection program. Accordingly, under Rules X and XI of the Rules of the U.S. House of Representatives, we ask that you respond to the following requests by no later than the close of business two weeks from the date of this letter:

1. China and India have become major producers of active pharmaceutical ingredients and finished drug products. According to interviews with key Government and industry officials in both countries, China and India will continue to expand their production capability in these areas. There are already a number of multinational pharmaceutical

companies that have either located facilities in these two countries or plan to do so in the near future. Some of these companies are planning to market products directly within China and India, while others will use these facilities to manufacture and export pharmaceutical products to other countries, including the United States. This will likely pose significant additional workload requirements on FDA in the near future and will further strain an already-stretched FDA foreign inspection program. FDA needs to begin efforts to project what effect this additional workload will have (or is having) on the existing inspection program and determine the level of additional resources that will be needed, including inspectors willing to travel overseas. Please describe how FDA is assessing future workload requirements for its foreign inspection program. In addition, does FDA have any current projections of what the global marketplace in the area of pharmaceuticals will be like in the coming years or decade? If so, please provide any analysis, particularly for China and India.

2. Establishing permanent FDA offices in China and India could greatly facilitate the inspection process, according to certain industry and Government observers who were interviewed by Committee staff. Such an office could assist in coordination of FDA entry and movement within the country and allow for more seamless operations during and between inspections. In addition, these permanent offices could assist in improving collaboration between the United States and other countries by facilitating cross training of regulatory inspectors and standardizing procedures. Please provide your assessment of the value and feasibility of opening permanent offices in China and India.

3. According to Committee staff, senior Indian officials from that country's Government and drug industry have expressed support for having an FDA presence in India. Such presence could serve multiple goals. First, it could provide FDA with the ability to more rapidly inspect Indian firms, as needed, reducing logistical and long-distance travel burdens. Second, it could provide India's key regulatory agencies, which may soon undergo reform to build capability and capacity, with a better understanding of how FDA conducts current good manufacturing practice inspections. Finally, it would facilitate exchanges of information and practices regarding oversight of drug product safety in the growing Indian drug-manufacturing sector. Is FDA or the Department of Health and Human Services (HHS) working with India on any framework that would allow for a permanent presence in that country? If so, please provide details of this work to the Committee. If not, please explain why not, given India's prominence in the area of drug manufacturing and its apparent willingness to have an FDA presence within India.

4. It remains unclear what China's position is on the matter of an FDA office, although Chinese officials emphasized to Committee staff that they seek increased cooperation and collaboration with FDA. We understand that this is the subject of continuing discussions between senior HHS officials and their Chinese counterparts. In a related matter, we understand HHS and FDA are currently working on a Memorandum of Agreement with China regarding the regulation of drug imports. Please provide ongoing

briefings on efforts by FDA and HHS to work with the Chinese on any framework that involves drug inspections.

5. At a minimum, according to Committee staff, a Foreign Service National (FSN) employed by FDA at U.S. embassies in China or India could greatly facilitate travel logistics, independent translation services, and essential background information for FDA inspectors before and during inspections. FSNs dedicated to FDA teams could provide in-country expertise and support to the FDA inspection program until a more formal or elaborate arrangement is made by the United States and certain key host countries. Has FDA considered the use of FSNs in either country to help facilitate its inspection efforts? If so, please describe that effort. If not, is this an area that FDA would contemplate exploring?

6. According to Committee staff, Chinese language translators were provided to FDA teams by the companies being inspected. In general, FDA foreign inspections are technically complex and often confrontational. A translator hired by the company being inspected raises obvious conflicts of interest. It would appear that inspections conducted in certain parts of the world would benefit from translators who work directly for the U.S. Government. The State Department may be able to provide translators to the inspectors to facilitate impartial communications between FDA inspectors and the companies being inspected. Please describe FDA plans to employ U.S.-financed translators for foreign language-related inspections.

7. The current schedule of FDA inspections can require FDA teams to travel for three continuous weeks in order to conduct three inspections. Senior inspectors told Committee staff that this is a particularly demanding schedule that can compromise the quality of the inspections. In the United States, when problems are identified in a particular firm, FDA inspectors can remain additional days to complete their work. In the overseas arena, inspections are usually bundled together as a single trip—which may involve multiple countries. Given the complex travel logistics, FDA inspectors have no extra time to spend on a particular inspection. Has FDA done a cost-benefit analysis of these tightly scheduled, multi-firm, multi-country, multi-week trips? Would FDA be better served changing the structure of foreign inspection trips in order to reduce trip duration and to allow more time and flexibility on particular inspections if problems are found?

8. Committee staff observed that FDA inspectors did not receive briefings on the regulatory and political climate of the countries they entered. Briefings provided either directly by FDA or by the State Department could assist FDA inspectors to maneuver more easily within foreign countries. Moreover, it is our understanding that inspectors do not specialize in a particular country or region of the world, but instead may travel to any country where a firm is subject to an FDA inspection. Please describe whether you believe country-specific briefings would assist FDA inspection teams in conducting their work and, if so, how you plan to incorporate this into your foreign inspection program.

Moreover, please describe whether there would be an advantage for FDA inspectors to specialize in certain countries or regions.

9. Committee staff observed that FDA inspectors did not receive health briefings regarding disease risks in the countries they were entering, or what precautions should be taken to prevent potentially contracting diseases while in those countries. Diseases such as malaria and dengue are prevalent in many countries and pose significant health risks to FDA inspectors. Standardized health briefings would greatly enhance the ability of FDA teams to avoid illness and maintain the integrity of the foreign inspection program. In addition, it appears that FDA inspectors were not fully aware that the U.S. Embassy staff could assist with travel and health-related issues to FDA employees on official Government business. Please describe how FDA inspectors are briefed regarding disease threats in specific countries and what precautions FDA formally provides inspectors about guarding their health before they begin a foreign assignment. Also, please describe what contingency options are provided to FDA inspectors regarding travel and other extraordinary circumstances before they begin an assignment.

Thank you for your prompt attention to this matter. If you have any questions related to this request, please contact us or have your staff contact Christopher Knauer or Paul Jung of the Committee Majority staff at (202) 226-2424 or Peter Spencer of the Committee Minority staff at (202) 225-3641.

Sincerely,

John D. Dingell
Chairman

Joe Barton
Ranking Member

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Ed Whitfield
Ranking Member
Subcommittee on Oversight and Investigations

Attachment

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

October 2, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-0001

Dear Dr. von Eschenbach:

Under Rules X and XI of the Rules of the U.S. House of Representatives, the Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations are investigating the ability of the Food and Drug Administration (FDA) to protect the American public from excessive risks associated with imported prescription drugs and the ingredients that are used in their manufacture. As part of this investigation, Committee staff recently accompanied FDA staff on several foreign inspections in both China and India, which are major manufacturers and exporters of pharmaceutical products. We appreciate the cooperation we received from your agency to ensure that our staff could observe these inspections as well as your staff's assistance with our overall investigation.

The Committee examined the FDA's foreign drug inspection program nearly 10 years ago and identified a number of deficiencies. Unfortunately, many of these deficiencies appear to continue to plague the program today, and in some cases appear to be worse. For example, databases and computer systems used by FDA to track drug firms exporting to the U.S. still seem incapable of providing meaningful, real-time data regarding which firms are actively shipping products to the U.S. and when they were last inspected. Moreover, the amount of time between surveillance inspections appears inconsistent and, in some cases inspections are quite overdue. Finally, constraints on general resources appear to be having a direct effect on a several aspects of the program. This includes the ability to hire and use language interpreters so that FDA staff are not forced to use an interpreter provided by the drug firm being inspected; the length of time they can stay at a particular firm for an inspection; and the ability to do rapid follow-up inspections once problems are identified.

Given the limitation on these resources and the effect it is having on the program, coupled with the increasing growth in overseas drug manufacturers seeking to export products to U.S. markets, the Committee remains concerned about the overall capability of the FDA's foreign drug inspection program and its ability to keep up with a changing global marketplace. As the U.S. increasingly relies upon drug products from foreign manufacturers, it is critical that FDA have a robust capability to oversee foreign drug manufacturing facilities, which will clearly require significant re-tooling of this program. We believe your office should give this matter increased and immediate attention.

To date, Committee staff has attempted to both obtain basic data on FDA's foreign drug inspection program and its present workload obligations. This has included several meetings and conference calls with FDA officials responsible for managing this program. Perhaps because of the limitations and configurations of current FDA databases that provide information on drug imports, FDA has apparently experienced considerable difficulty in providing basic information to the Committee. These limitations include the inability to provide: (1) number of firms currently exporting to the U.S.; (2) when they were last inspected; (3) where they are located, and (4) projections of new firms seeking to export drug products to the United States. On August 23, 2007, Committee staff conducted a conference call with members of your staff to obtain a basic outline of data regarding FDA inspections of foreign drug product manufacturers. From that discussion, Committee staff understood your employees to represent the following information regarding FDA's present knowledge about foreign drug manufacturers that ship product to the U.S. (and other related inspection activities). Based on this, we request that your office confirm whether the following information is accurate, and that you supply additional information as requested:

1. As of August 23, 2007, there were 2,967 pharmaceutical product-manufacturing firms registered with the U.S. that are likely shipping to the U.S. and would be subject to: (a) pre-approval inspection; and (b) ongoing surveillance inspections.

2. Of these nearly 3,000 firms, they break down as follows: (a) 183 are making both dosage/active pharmaceutical ingredients (API) products; (b) 1,146 are making API only; (c) 1,036 are making dosage only; and (d) 600 firms are making products "unknown to the FDA." Please provide a description of what is meant by "unknown to FDA."

3. FDA has conducted approximately 1,379 foreign inspections since Fiscal Year 2002—1,196 were both pre-approval and current good manufacturing practice (CGMP) inspections, 107 were pre-approval inspections only, and 76 were CGMP inspections only.

4. Each year, FDA defines and identifies through its risk model approximately 100 "high risk" firms for CGMP surveillance inspection, but can only undertake about 25 such inspections annually due to resource constraints. Please provide the risk scores for the top 150 firms assessed by FDA's risk model for 2006 inspections.

5. FDA does not know the exact number of firms that currently manufacture and export over-the-counter (OTC) products to the U.S. or whether those firms have been inspected.

6. FDA databases do not provide full accounts of what is entering the U.S. at any given time and what is the present inspection workload. FDA is, however, working to update and "coordinate" these databases.

7. FDA is currently unable to easily distinguish between firms which are "registered" to ship to the U.S. and firms which are actually "shipping" to the United States.

Finally, we request additional information on the following questions:

1. Please provide a comprehensive list of all foreign companies that manufacture drug products, including OTC drugs, prescription drugs, and APIs, and the specific products each firm exports to the United States.

2. For each firm on this list, please provide: (a) where the company is located; (b) how long the firm has been exporting to the U.S.; and (c) when FDA last inspected the firm. Also, please identify which firms have undergone a New Drug Application or Abbreviated New Drug Application inspection (referred hereafter as a "pre-approval" inspection). Please further identify which of these firms have received a CGMP inspection and with what frequency.

3. Please provide a detailed description of the risk management model FDA currently uses to determine which foreign inspections to undertake.

4. How many foreign firms manufacture drug products for export to the U.S. but have never received an FDA inspection of any kind?

5. Pursuant to 21 USC 360(h), it is required that every *domestic* "establishment engaged in the manufacture, propagation, compounding, or processing of a drug" be inspected by the FDA at least once every two years. Does FDA inspect domestic firms once every two years? If not, which firms subject to the requirement are not inspected once every two years? If a subset of firms is identified in this category, please explain why they are not subject to an inspection once every two years.

6. What are the average differences in the frequency of inspections between foreign and domestic firms? Are there any difficulties for FDA in obtaining these data?

7. What statutory or regulatory requirements exist for FDA to inspect foreign drug manufacturing firms at a particular frequency?

8. In its 1998 report entitled "FDA: Improvements Needed in the Foreign Drug Inspection Program," the Government Accountability Office (GAO) found that FDA lacked a comprehensive, automated system for managing its foreign inspection program. At the

time, GAO observed that 15 different computer systems—very few of which were integrated—were used to manage FDA's foreign drug inspection program. Almost 10 years later, FDA officials have told staff that they still have considerable difficulty with the computer databases used to track and manage foreign inspections for those firms exporting drug products to the United States. What are the current limitations on FDA's ability to track drug exports sent to the U.S., and what limitations do the present systems have on managing foreign inspections? What action is FDA taking to strengthen this information technology?

9. Please provide a detailed description of the personnel structure for foreign inspections. How do foreign inspectors fit within FDA's Division of Field Investigations (DFI)? Who performs foreign inspections, and how many of these inspectors are there? How are inspections assigned? What are the requirements for inspectors to prepare for foreign inspections? Do they specialize in certain regions of the world?

10. Does FDA assess and work with foreign inspectorates to maximize the effectiveness of its foreign inspection program? Describe how FDA's DFI works with the Department of State to ensure an adequate level of in-country knowledge and support (e.g., for translations and logistics) for foreign inspections?

We appreciate your attention to this matter and look forward to working with you to address this important public health matter. We are requesting that you provide answers to these questions on a rolling basis, but no later than three weeks from the date of this letter. If you have any questions about this request, please contact us or have your staff contact Chris Knauer or Joanne Royce with the Committee Majority staff at (202) 226-2424 or Peter Spencer with the Committee Minority staff at (202) 225-3641.

Sincerely,

John D. Dingell
Chairman

Joe Barton
Ranking Member

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Ed Whitfield
Ranking Member
Subcommittee on Oversight and Investigations