

September 2008

DRUG SAFETY

Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program





Highlights of [GAO-08-970](#), a report to congressional requesters

Why GAO Did This Study

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), oversees the safety and effectiveness of human drugs marketed in the United States, including those manufactured in foreign establishments. FDA inspects foreign establishments in order to ensure that the quality of drugs is not jeopardized by poor manufacturing processes. This report examines (1) the extent to which FDA has accurate data on the number of foreign establishments subject to inspection, (2) the frequency of foreign inspections, and (3) oversight by FDA to ensure that foreign establishments correct serious problems identified during inspections. GAO analyzed information from FDA databases, reviewed inspection reports which identified serious deficiencies, and interviewed FDA officials.

What GAO Recommends

GAO recommends that FDA improve the data that it uses to manage its foreign inspection program, conduct more inspections of foreign establishments, and ensure more timely inspection of foreign establishments where FDA has identified serious deficiencies. HHS agreed that FDA should conduct more foreign inspections but did not comment on the other recommendations. HHS noted that additional inspections are only one component of FDA's strategy to enhance oversight and elaborated on other initiatives, such as database improvements, discussed in this report.

To view the full product, including the scope and methodology, click on [GAO-08-970](#). For more information, contact Marcia Crosse at (202) 512-7114 or crosse@gao.gov.

DRUG SAFETY

Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program

What GAO Found

FDA databases contain inaccurate information on foreign establishments subject to inspection. FDA uses information from a database of establishments registered to market drugs in the United States and a database of establishments that shipped drugs to the United States to compile a list of establishments subject to inspection, but these databases contain divergent estimates—about 3,000 and 6,800, respectively. FDA's registration database contains information about establishments not subject to FDA inspection. Although annual reregistration is required, FDA does not deactivate in its database establishments that do not fulfill this requirement. The agency also does not routinely verify that a registered establishment manufactures a drug for the U.S. market. The accuracy of this information is important in FDA's identification of foreign establishments subject to inspection.

FDA inspects relatively few foreign establishments each year to assess the manufacturing of drugs currently marketed in the United States. FDA inspected 1,479 foreign drug manufacturing establishments from fiscal years 2002 through 2007. Because FDA does not know the number of establishments subject to inspection, the percentage of those inspected cannot be calculated with certainty. However, using a list FDA developed to prioritize foreign establishments for inspection in fiscal year 2007, GAO estimated that FDA may inspect about 8 percent of foreign establishments in a given year. At this rate, it would take the agency more than 13 years to inspect these establishments once. In contrast, FDA estimates that it inspects domestic establishments about once every 2.7 years. Unlike domestic establishments, foreign establishments were generally only inspected if they were named in an application for a new drug. While FDA made progress in fiscal year 2007 in conducting more foreign inspections, GAO estimated it still inspected less than 11 percent of such establishments. As FDA plans additional inspections, it is important that it ensure that foreign and domestic establishments with similar characteristics are inspected at a similar frequency.

FDA's identification of serious deficiencies has led foreign establishments to take corrective actions, but inspections to determine continued compliance are not always timely. FDA identified deficiencies during most foreign inspections, but determining how the agency classified the results of a specific inspection is hindered by inconsistencies in its databases, particularly on the classification of inspections with serious deficiencies. From fiscal years 2002 through 2007, FDA issued 15 warning letters to foreign establishments at which it identified serious deficiencies. FDA generally determined the adequacy of actions taken in response to these letters by reviewing information provided by the establishments. FDA's subsequent inspections to determine establishments' continued compliance were not always timely. Of establishments named in the 15 warning letters, FDA subsequently inspected 4 establishments 2 to 5 years later, generally because these establishments were named in a new drug application. At 3 of these 4 inspections, FDA verified that corrective actions had been taken but identified additional deficiencies.

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Abbreviations

API	active pharmaceutical ingredient
CBP	Customs and Border Protection
CDER	Center for Drug Evaluation and Research
DRLS	Drug Registration and Listing System
D-U-N-S®	Data Universal Numbering System
FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration
GMP	good manufacturing practice regulations
HHS	Department of Health and Human Services
MARCS	Mission Accomplishments and Regulatory Compliance Services
NAI	no action indicated
OAI	official action indicated
OASIS	Operational and Administrative System for Import Support
OCFITS	Office of Compliance Foreign Inspection Tracking System
ORA	Office of Regulatory Affairs
OTC	over-the-counter
SEDS	Shared Establishment Data Service
VAI	voluntary action indicated

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United States Government Accountability Office
Washington, DC 20548

September 22, 2008

The Honorable John D. Dingell
Chairman
The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Bart Stupak
Chairman
The Honorable John Shimkus
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Honorable Charles E. Grassley
Ranking Member
Committee on Finance
United States Senate

The Honorable Ed Whitfield
House of Representatives

The United States is becoming increasingly dependent on drug products and drug ingredients manufactured in foreign countries.¹ Whether drugs are manufactured in foreign or domestic establishments, oversight of the safety and effectiveness of drugs marketed in the United States is the

¹According to GAO analysis of International Trade Centre data, the value of pharmaceutical imports increased 42 percent from 2001 to 2005, adjusted for pharmaceutical inflation. The International Trade Centre is a joint agency of the United Nations Conference on Trade and Development and the World Trade Organization.

responsibility of the Food and Drug Administration (FDA),² an agency within the Department of Health and Human Services (HHS). In fulfilling its responsibility, FDA may inspect foreign establishments whose drugs are imported into the United States. Testing a drug at the border cannot reliably determine safety or quality, and FDA relies on establishment inspections to determine compliance with current good manufacturing practice regulations (GMP)³ and assure that the safety and quality of drugs are not jeopardized by poor manufacturing practices.

Ten years ago, we reported that FDA needed to improve its foreign drug inspection program.⁴ Among other things, we noted that FDA had significant problems managing its foreign inspection data, and we were critical of the small number of inspections FDA conducted at foreign establishments. For example, we found that a database FDA used to track inspections did not always contain correct information about how FDA classified the results of a given foreign establishment inspection.⁵ We also found that the agency did not promptly issue warning letters asking establishments to correct serious GMP deficiencies identified during inspections.⁶

Given the importance of FDA's foreign drug inspection program, you raised questions about the safety of imported drugs and the agency's ability to adequately oversee foreign establishments manufacturing such products. In response, we began work and presented our preliminary findings in a November 2007 hearing before the Subcommittee on

²Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and include components of those articles. 21 U.S.C. § 321(g)(1)(B), (D). FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. 21 C.F.R. § 207.3(a)(8) (2007). In addition, FDA regulations define an establishment as a place of business under one management at one general physical location. 21 C.F.R. § 207.3(a)(7) (2007). Drug firms may have more than one establishment.

³GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210, 211 (2007).

⁴GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, [GAO/HEHS-98-21](#) (Washington, D.C.: Mar. 17, 1998).

⁵FDA classifies inspections based on the seriousness of the deficiencies identified during the inspection.

⁶FDA issues warning letters to those establishments manufacturing drugs for the U.S. market where it has identified violations that may lead the agency to initiate enforcement action if not promptly and adequately corrected.

Oversight and Investigations, House Committee on Energy and Commerce, suggesting that there were serious weaknesses in FDA's foreign drug inspection program similar to those we reported on in 1998.⁷ Following that hearing, questions regarding the safety of drugs manufactured at foreign establishments continued to mount. In January 2008, FDA began an investigation after receiving reports of serious adverse events in people receiving heparin sodium, a commonly used blood thinner. The agency later learned that an active pharmaceutical ingredient (API) found in this drug contained a contaminant and had been manufactured at a Chinese establishment never inspected by FDA.⁸ Since we started our work, FDA began or proposed several initiatives to strengthen its foreign drug inspection program. In April 2008, we testified before this same subcommittee on our preliminary assessment of how these initiatives might address some of the weaknesses we identified in our November 2007 testimony.⁹

In this report, we discuss FDA's foreign drug inspection program, including updates to information presented in our November 2007 and April 2008 testimonies. Specifically, this report examines (1) the extent to which FDA has accurate data on the number of foreign manufacturing establishments subject to inspection, (2) the frequency of foreign inspections, (3) oversight by FDA to ensure that foreign manufacturing establishments correct serious deficiencies identified during inspections and to monitor establishments' continued compliance, and (4) issues unique to conducting foreign inspections.

To address these objectives, we interviewed officials from FDA, including its Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing

⁷GAO, *Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers*, [GAO-08-224T](#) (Washington, D.C.: Nov. 1, 2007).

⁸An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product. See 21 C.F.R. § 210.3(b)(7), (8) (2007). According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients when it receives information indicating potential problems with their manufacture.

⁹GAO, *Drug Safety: Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program*, [GAO-08-701T](#) (Washington, D.C.: Apr. 22, 2008).

the foreign inspection program. To examine the extent to which FDA has accurate data on the number of foreign manufacturing establishments subject to inspection, we obtained information from an FDA database on the number of establishments registered to market their drugs in the United States.¹⁰ We also obtained from FDA's import database data on the number of establishments manufacturing drugs shipped to the United States. We found information about the types of drugs shipped to the United States sufficiently reliable for the purposes of our report. We identified inaccuracies with some parts of FDA's registration and import databases, and we present these data to illustrate the variability in information that FDA's databases provide to agency officials on this topic. To examine the frequency of foreign inspections, we obtained information from another FDA database on the number of inspections conducted by FDA of foreign drug manufacturing establishments. We found counts of inspections sufficiently reliable for the purposes of our report. We also examined methods used by FDA to select establishments for inspection. To examine FDA's response to serious deficiencies identified during inspections of foreign manufacturing establishments, we examined FDA data indicating how the agency classified establishments' compliance with agency requirements. We identified inconsistencies with these data, and we present them to illustrate the variability in information that FDA's databases provide to agency officials on this topic. We also reviewed FDA files on inspections of foreign establishments that occurred from fiscal years 2002 through 2007, during which FDA identified serious deficiencies and subsequently issued warning letters. The files contained information about these establishments, their inspections, and their correspondence with FDA. To examine issues unique to conducting foreign inspections, we obtained information on agency initiatives that may have the potential to improve its program for inspecting foreign establishments. Our work focuses on human drugs regulated by CDER and not on biologics,¹¹ medical devices, veterinary medicines, or other items or products for which FDA conducts inspections. (See app. I for a more detailed

¹⁰Foreign and domestic establishments that manufacture drugs for the U.S. market are required to register annually with FDA. Establishments provide FDA with, among other things, their names and addresses and a listing of the drugs that they manufacture for the U.S. market. 21 U.S.C. §360(b), (i), (j).

¹¹Biologics are materials, such as vaccines, derived from living sources such as humans, animals, and microorganisms. Biologics are generally regulated by FDA's Center for Biologics Evaluation and Research. Biologics regulated by this center are not addressed in this report. However, some biologics are regulated by CDER and inspections related to those products are included in our work.

discussion of the scope and methodology for this report.) We conducted our work from September 2007 through September 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Results in Brief

FDA databases contain inaccurate information on foreign establishments subject to inspection and recent initiatives do not fully address this weakness. FDA uses databases of registered establishments and imported drugs to help it select establishments for inspection, but these databases contain inaccuracies and were not designed for this purpose. FDA's registration database indicates about 3,000 foreign establishments could have been subject to inspection in fiscal year 2007, while its import database contains information indicating that about 6,800 establishments shipped drugs to the United States in that year. FDA's registration database contains information about establishments that are not actually subject to FDA inspection. Although establishments that manufacture drugs for the U.S. market are required to reregister annually, FDA does not enforce this requirement by deactivating in its database establishments that do not fulfill this requirement. Therefore, foreign establishments that are no longer subject to FDA inspection may be included in the database. In addition, the agency does not routinely verify that a registered establishment actually manufactures a drug for the U.S. market. For example, foreign drug manufacturing establishments may register with FDA because, in some foreign markets, registration may appear to convey an "approval" or endorsement by the agency. FDA is making improvements to this database. However, these changes will not ensure that FDA enforces the requirement that establishments update their registration annually or that the agency verifies information provided by establishments. To reduce duplication in its import database, FDA supported a proposal to create a unique identifier for all establishments whose products, including drugs, are imported into the United States that would be used by all federal agencies involved in the oversight of imported products. However, the implementation of this identifier would require action from multiple federal agencies in addition to FDA and the timeline for its implementation is unclear. Finally, initiatives to improve the integration of these databases could be beneficial, but it is too early to know their impact.

FDA inspects few foreign establishments, relative to domestic establishments, each year to assess the manufacturing of drugs currently marketed in the United States. FDA inspected 1,479 foreign drug manufacturing establishments from fiscal years 2002 through 2007. Although FDA does not know how many foreign establishments are actually subject to inspection, using the list of 3,249 establishments from which FDA prioritized establishments for inspection in fiscal year 2007, we found that the agency may inspect about 8 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment on this list once, assuming that no additional establishments are subject to inspection. In comparison, the agency estimates that it inspects domestic establishments manufacturing drugs about once every 2.7 years. From fiscal years 2002 through 2007, FDA selected few foreign establishments for inspections to conduct surveillance of drugs currently marketed in the United States. FDA generally only inspects foreign establishments if they are named in an application for new drug approval. In comparison, most of the domestic establishments inspected by FDA are selected for surveillance purposes to examine the manufacture of drugs currently marketed in the United States. While FDA made progress in fiscal year 2007 in conducting more foreign inspections, it still inspected relatively few establishments. The agency has proposed plans for conducting many more foreign inspections in fiscal year 2009, but these plans will require the agency to dedicate substantially more resources to such inspections than in the past.

FDA's identification of serious deficiencies has led foreign establishments to take corrective actions, but subsequent inspections to determine continued compliance are not always timely. FDA identified deficiencies during most of its inspections of foreign establishments, but determining the number of such inspections during which the agency identified serious deficiencies is hindered by classification inconsistencies in FDA's databases. As a result, consistent information may not be readily accessible to FDA staff responsible for the oversight of those establishments manufacturing drugs marketed in the United States. In response to serious deficiencies that FDA identified at establishments inspected from fiscal years 2002 through 2007, the agency issued 15 warning letters requesting corrective actions; the agency generally did not restrict importation of drugs manufactured by these establishments. FDA had previously identified deficiencies that required corrective actions at establishments named in most of these letters, but had not issued a warning letter at that time. According to FDA files, corrective actions were taken by establishments that received warning letters. As of July 2008, FDA had deemed adequate the corrective actions of establishments named

in 11 of the 15 warning letters; corrective actions taken by establishments referenced in the other 4 warning letters had not yet been accepted by FDA. Most often, FDA deemed an establishment's corrective actions adequate by reviewing documentation and other information provided by the establishment. Subsequent inspections by FDA to determine establishments' continued compliance were not always timely. Since deeming their corrective actions adequate, FDA subsequently inspected 4 of these 11 establishments. In 1 case, FDA met its recommendation to inspect the establishment within 2 years by conducting a surveillance inspection. In the other 3 cases, the establishments were inspected about 4 to 5 years after the inspection that resulted in the warning letter, although it had been recommended that they be inspected within 1 year. These 3 inspections were not conducted as part of routine surveillance, but rather because the establishment was named in an application for a new drug. Although FDA verified at 3 of the 4 subsequent inspections that the establishments had taken the promised corrective actions, the agency also identified additional deficiencies that required corrective actions. However, these additional deficiencies did not result in the issuance of a warning letter.

Human resource and logistical challenges unique to foreign inspections influence the manner in which FDA conducts those inspections. For example, FDA does not have a dedicated staff to conduct foreign inspections and relies on those inspecting domestic establishments to volunteer. In addition, while FDA may conduct unannounced GMP inspections of domestic establishments, it does not arrive unannounced at foreign establishments. It also lacks the flexibility to easily extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country. Finally, language barriers can make foreign inspections more difficult to conduct than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator. FDA is pursuing initiatives that could address some of these challenges. For example, the agency plans to establish an office in China and has proposed overseas offices in other locations, but the impact that these offices will have on overcoming these challenges is unknown.

Initiatives proposed by FDA could help address weaknesses in the agency's oversight of foreign establishments manufacturing drugs for the U.S. market, but additional actions are needed. Improving the accuracy of its databases could allow the agency to make better informed selections of

foreign establishments for inspection. FDA's plans for additional inspections could provide it with an opportunity to conduct the inspections that are vital to its oversight of establishments manufacturing drugs that are currently marketed in the United States. Although the agency identifies deficiencies at foreign establishments at least as often as domestic establishments, foreign establishments are unlikely to be selected in order to inspect the manufacturing of drugs currently marketed in the United States. Therefore, it is important that the agency reassess its priorities to ensure that foreign and domestic establishments with similar characteristics are inspected at a similar frequency. Further, the continued identification of deficiencies at foreign establishments that previously received warning letters points to the need for FDA to promptly conduct subsequent inspections of establishments with a history of serious deficiencies so problems do not go undetected for extended periods. Therefore, we recommend that FDA take the following five actions: (1) enforce the requirement that establishments manufacturing drugs for the U.S. market update their registration annually, (2) establish mechanisms for verifying information provided by the establishment at the time of registration, (3) ensure that information on the classification of inspections with serious deficiencies is accurate in all FDA databases, (4) conduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics, and (5) conduct timely inspections of foreign establishments that have received warning letters to determine continued compliance.

HHS commented on one of our recommendations and agreed that FDA should conduct more inspections of foreign establishments. It did not comment on the other four recommendations we made. HHS noted that conducting additional inspections is only one component of FDA's overall strategy to enhance oversight of imported drugs. It also elaborated on some of the other FDA initiatives—such as database improvements and establishing foreign offices—that were discussed in our report.

Background

FDA is responsible for overseeing the safety and effectiveness of human drugs marketed in the United States, whether they are manufactured in foreign or domestic establishments. As part of its efforts to ensure the safety and quality of imported drugs, FDA may inspect foreign establishments whose drugs are imported into the United States. The purpose of these inspections is to ensure that foreign establishments meet

the same manufacturing standards for quality, purity, potency, safety, and efficacy as required of domestic establishments.

Requirements governing FDA's inspection of foreign and domestic establishments differ. Specifically, FDA is required to inspect every 2 years those domestic establishments that manufacture drugs marketed in the United States,¹² but there is no comparable requirement for inspecting foreign establishments. However, drugs manufactured by foreign establishments that are offered for import may not enter the United States if FDA determines—through the inspection of an establishment, a physical examination of drugs offered for import, or otherwise—that there is sufficient evidence of a violation of applicable laws or regulations.

Within FDA, CDER sets standards and evaluates the safety and effectiveness of prescription and over-the-counter (OTC) drugs. Among other things, CDER requests that ORA inspect both foreign and domestic establishments to ensure that drugs are produced in conformance with federal statutes and regulations, including current GMPs. CDER requests that ORA conduct inspections of establishments that produce drugs in finished-dosage form as well as APIs used in finished drug products. These inspections are performed by investigators and, as needed, laboratory analysts.¹³ ORA conducts two primary types of drug manufacturing establishment inspections:

- Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States.¹⁴ These inspections occur following FDA's receipt of a new drug application or an abbreviated new drug application and focus on the

¹²21 U.S.C. § 360(h).

¹³ORA investigators lead inspections. Investigators are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing. In some instances, staff from CDER may participate in inspections.

¹⁴When FDA receives an application for drug approval, officials review the inspection history of each establishment listed on the application. According to FDA officials, if an establishment listed on the application has received a satisfactory GMP inspection in the previous 2 years and the agency has no new concerns, FDA will consider this inspection sufficient and will not perform a preapproval inspection of this establishment.

manufacture of a specific drug.¹⁵ Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications to determine that the establishment is following commitments made in the application. FDA also determines that the establishment manufacturing the finished drug product, as well as each manufacturer of an API used in the finished product, manufactures, processes, packs, and labels the drug adequately to preserve its identity, strength, quality, and purity.

- GMP inspections focus on an establishment's systemwide controls for ensuring that the processes it uses to manufacture drugs marketed in the United States produce drugs that are of high quality. Systems examined during these inspections include those related to materials, quality control, production, facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drugs. For the purpose of surveillance, FDA conducts GMP inspections of establishments manufacturing drugs currently marketed in the United States to determine establishments' ongoing compliance with laws and regulations. FDA conducts for-cause GMP inspections when it receives information indicating problems in the manufacture of approved drugs, as well as when it follows up on establishments that were not in compliance with GMPs during previous inspections.

FDA may conduct an inspection that combines both preapproval and GMP components during a single visit to an establishment. As the results of a GMP inspection can often be generalized to all drugs manufactured at a particular establishment, FDA can use the results of the combined inspection to make decisions in the future if the establishment is listed in another application.

¹⁵FDA must approve an application for a new drug before it can be marketed in the United States. FDA reviews scientific and clinical data contained in these applications as part of its process in considering them for approval to be marketed. Approval for a generic drug is sought through an abbreviated new drug application, which generally does not require preclinical and clinical data but which must demonstrate that the generic drug performs in the same manner as the new drug on which the generic is based. While new OTC drugs may reach the market through FDA's review of a new drug or abbreviated new drug application, the majority of OTC drugs are marketed today through a different process, which has established the marketing conditions for various categories of OTC drugs with particular active ingredients. Drugs marketed through this different process may be marketed without FDA preapproval and establishments that manufacture such drugs may not receive a preapproval inspection.

FDA uses a risk-based process to select some domestic and foreign establishments for GMP inspections to conduct surveillance of drugs currently marketed in the United States. According to an FDA report,¹⁶ the agency developed the process after recognizing that it did not have the resources to meet the requirement for inspecting domestic establishments every 2 years. The process uses a risk-based model to identify those establishments that, based on characteristics of the establishment and of the drug being manufactured, have the greatest public health risk potential should they experience a manufacturing defect. Through this process, CDER annually prepares a prioritized list of domestic establishments and a separate, prioritized list of foreign establishments. FDA began applying this risk-based process to domestic establishments in fiscal year 2006 and expanded it to foreign establishments in fiscal year 2007.¹⁷

FDA's process for determining whether a foreign establishment complies with GMPs involves both CDER and ORA. During an inspection, ORA staff report observations of significant objectionable conditions and practices that do not conform to GMPs on the list-of-observations form, commonly referred to as an FDA Form 483. They provide this Form 483 to the establishment, along with a briefing on the inspection's results, on the last day of the inspection. ORA staff discuss the observations on the Form 483 with the establishment's management to ensure that they are aware of any deficiencies that were observed during the inspection and suggest that the establishment respond to FDA in writing concerning all actions taken as a result of the observations.

Once ORA staff complete the inspection, they prepare an establishment inspection report to document their inspection findings. Inspection reports describe the manufacturing operations observed during the inspection and any conditions that may violate federal statutes and regulations. Based on its inspection findings, ORA recommends whether the establishment is acceptable to supply drug products or drug ingredients to the United States.

¹⁶Department of Health and Human Services, U.S. Food and Drug Administration, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model" (September 2004), http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm (accessed June 26, 2008).

¹⁷For more information about this process, see [GAO-08-224T](#).

ORA makes a recommendation regarding the classification of the inspection. All inspection reports and classification recommendations related to inspections of foreign establishments are forwarded to CDER. CDER reviews the ORA recommendation and determines the final classification and whether regulatory action is necessary.

- A classification of no action indicated (NAI) means that insignificant or no deficiencies were identified during the inspection.
- A classification of voluntary action indicated (VAI) means that deficiencies were identified during the inspection, but the agency is not prepared to take regulatory action. Therefore, any corrective actions are left to the establishment to take voluntarily.
- A classification of official action indicated (OAI) means that serious deficiencies were found that warrant regulatory action.

Inspections classified as OAI may result in regulatory action, such as the issuance of a warning letter. FDA issues warning letters to those foreign establishments manufacturing drugs for the U.S. market that are in violation of the law or implementing regulations and may be subject to enforcement action if the violations are not promptly and adequately corrected.¹⁸ In addition, warning letters notify the establishment that FDA may refuse entry of the establishment's drugs at the border and will recommend disapproval of any new drug applications listing the establishment until sufficient corrections are made. It is FDA policy to consider many factors in determining whether to issue a warning letter. For example, the agency is to consider corrective actions taken or promised by the establishment since the inspection, and it may decide to not issue a letter if an establishment's corrective actions are adequate and the violations that would have supported the letter have been corrected. Warning letters are issued after the review and approval of FDA's Office of Chief Counsel. FDA policy states that the agency will strive to issue warning letters within 4 months of the last day of the inspection.

In addition to a warning letter, FDA may take other regulatory actions if it identifies serious deficiencies during the inspection of a foreign establishment. For example, FDA may issue an import alert, which

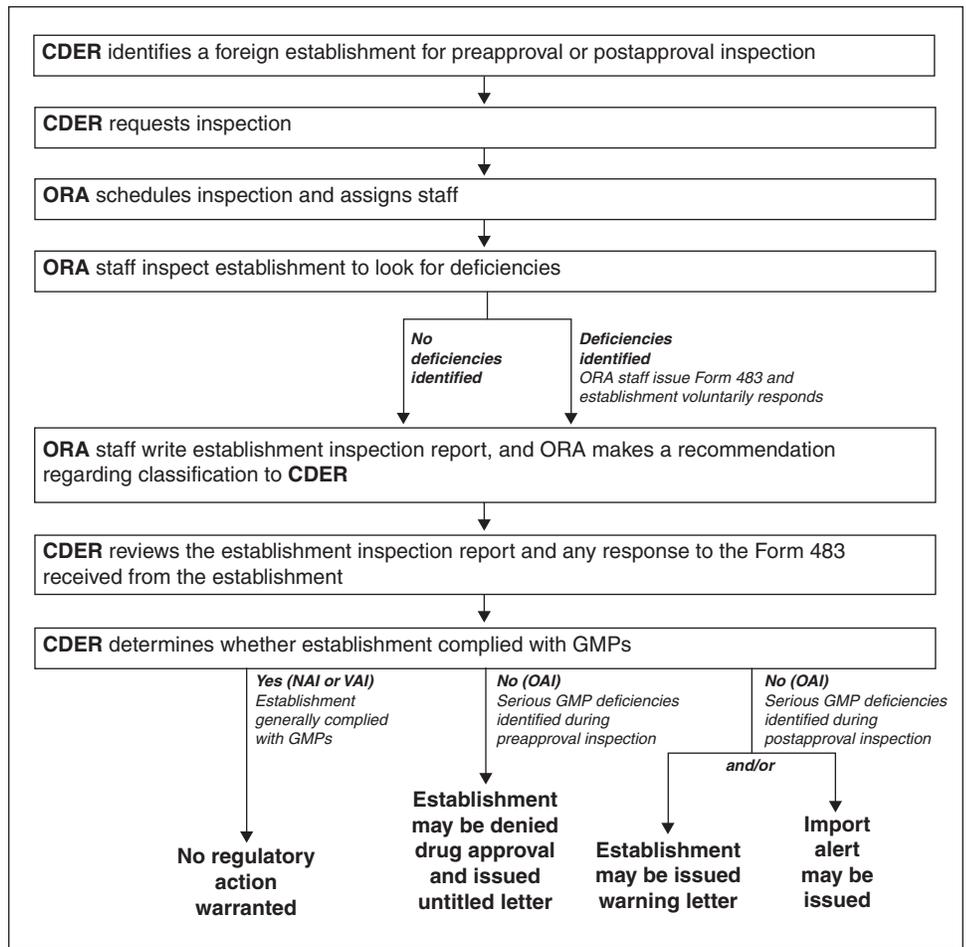
¹⁸FDA issues untitled letters to violative foreign establishments that were inspected as part of the agency's review of an application and intend to market a drug in the United States but do not yet do so.

instructs FDA staff that they may detain drugs manufactured by the violative establishment that have been offered for entry into the United States.¹⁹ In addition, FDA may conduct regulatory meetings with the violative establishment. Regulatory meetings may be held in conjunction with the issuance of a warning letter to emphasize the significance of the deficiencies or for the purpose of obtaining prompt voluntary compliance in those instances in which the deficiencies do not warrant the issuance of a warning letter.

FDA uses multiple sources of information to determine whether the actions taken by an establishment to correct violations are adequate. FDA may, for example, review documentation describing completed or proposed corrective actions; hold meetings with representatives of the establishment to discuss corrective actions; agree to consider reports of inspections conducted by private consultants; obtain inspection reports from foreign regulatory bodies; and reinspect the establishment itself, though it is not required to do so. As part of this process, agency staff may also make a recommendation for when the establishment should next receive a surveillance inspection. See figure 1 for a description of this process.

¹⁹An import alert can apply to specific drugs or all drugs manufactured by an establishment.

Figure 1: FDA's Process for Managing Inspections of Foreign Establishments



Source: GAO.

FDA uses multiple databases to manage its foreign drug inspection program.

- The Drug Registration and Listing System (DRLS) contains information on foreign and domestic drug establishments that have registered with FDA to market their drugs in the United States. These establishments provide information, including company name and address and the drugs they manufacture for commercial distribution in the United States, on paper forms, which are entered into DRLS by FDA staff.

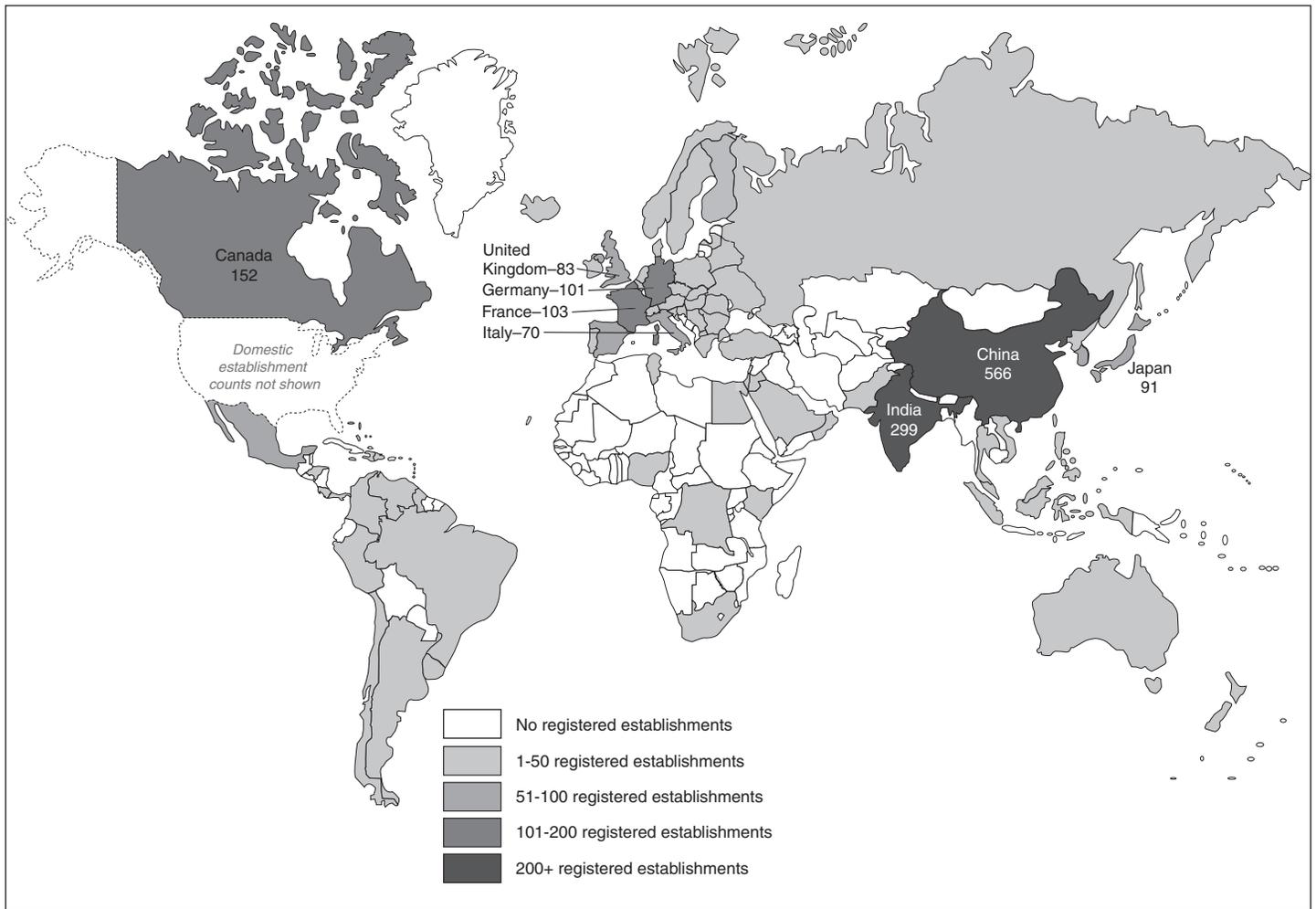
-
- The Operational and Administrative System for Import Support (OASIS) contains information on drugs and other FDA-regulated products offered for entry into the United States, including information on the establishment that manufactured the drug. The information in OASIS is automatically generated from data managed by Customs and Border Protection (CBP). The data are originally entered by customs brokers based on the information available from the importer.²⁰ CBP specifies an algorithm by which customs brokers generate a manufacturer identification number from information about an establishment's name and address.
 - The Field Accomplishments and Compliance Tracking System (FACTS) contains information on foreign and domestic establishments inspected by ORA, the type of inspection conducted, and the outcome of those inspections. Investigators and laboratory analysts enter information into FACTS following completion of an inspection.
 - The Office of Compliance Foreign Inspection Tracking System (OCFITS) contains information that CDER uses to track its review of foreign inspection reports submitted by ORA staff, such as information on the type of inspection conducted, CDER actions taken in connection with its review of inspection reports, and the outcome of those inspections. Information in OCFITS is entered by CDER staff.

According to DRLS, in fiscal year 2007, foreign countries that had the largest number of registered establishments were China, India, Canada, France, Germany, Japan, the United Kingdom, and Italy (see fig. 2).²¹ These countries are also listed in OASIS as having the largest number of establishments offering drugs for import into the United States. Specifically, according to OASIS, China had more establishments manufacturing drugs that were offered for import into the United States than any other foreign country. According to OASIS, in fiscal year 2007, a wide variety of prescription and OTC drugs manufactured in China were offered for import into the United States, including pain killers, antibiotics, blood thinners, and hormones.

²⁰ Customs brokers are private individuals, partnerships, associations, or corporations that are licensed, regulated, and empowered by CBP to assist in meeting federal requirements governing imports and exports.

²¹ The counts include foreign establishments that were registered to manufacture human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishment specifically manufacturing human drugs.

Figure 2: Foreign Establishments Registered to Manufacture Drugs for the U.S. Market by Country, Fiscal Year 2007



Source: Copyright © Corel Corp. All rights reserved (map); GAO analysis of FDA data.

Note: The counts include foreign establishments that were registered to manufacture human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishment specifically manufacturing human drugs.

FDA Lacks Accurate Information to Effectively Manage the Foreign Drug Inspection Program

FDA does not know how many foreign establishments are subject to inspection, and the agency's recently announced initiatives do not fully address this weakness. The databases that FDA uses to select establishments for inspection do not contain accurate information on the number of establishments manufacturing drugs for the U.S. market. Instead of maintaining a list of establishments subject to inspection, FDA relies on information from databases that contain inaccuracies and that were not designed for this purpose. Furthermore, officials indicated that these databases cannot be electronically integrated or readily interact with one another to compare data, so some comparisons are done manually for each individual establishment. FDA has supported initiatives that could provide it with more accurate information about foreign establishments subject to inspection, but it is too early to tell if these efforts will provide the agency with an accurate count.

FDA's Drug Registration Database Contains Inaccuracies and Planned Changes Will Not Ensure the Availability of Accurate Information on Foreign Establishments

DRLS provides FDA with some information that the agency uses to select establishments for inspection, but contains inaccuracies and does not provide a complete count of establishments subject to inspection. DRLS, established in 1991, is intended to list the registered establishments that manufacture drugs for the U.S. market. Requirements for the registration of foreign establishments were implemented in 2002.²² FDA expected that requiring foreign establishments to register would provide it with a comprehensive list of establishments that manufacture drugs for the U.S. market. In fiscal year 2007, approximately 3,000 foreign establishments that reported manufacturing human drugs, biologics, or veterinary drugs were registered with FDA; FDA was unable to determine from this database the number of registered establishments specifically manufacturing human drugs.

FDA officials told us that the count of registered foreign establishments in DRLS does not reflect the actual number whose drugs are being imported into the United States for several reasons. First, although foreign establishments are required to renew their registration information annually, FDA does not enforce this requirement by deactivating the registration of establishments that do not fulfill this requirement. Agency officials told us that some foreign establishments may not report to FDA if

²²See Pub. L. No. 105-115, §§ 417; 111 Stat. 2296, 2379 (1997). FDA issued implementing regulations in 2001 (21 C.F.R. § 207.40), which were effective February 11, 2002. 66 *Fed. Reg.* 59138 (Nov. 27, 2001).

they stop manufacturing drugs for the U.S. market or go out of business, although establishments are required to do so. Thus, these establishments may still be listed in DRLS as actively registered establishments. Second, foreign establishments may register with FDA whether or not they actually manufacture drugs for the U.S. market. FDA officials told us that this is made more likely by the fact that FDA does not charge foreign establishments a fee to register. FDA officials pointed out that some foreign establishments register because, in foreign markets, registration may erroneously convey an “approval” or endorsement by FDA. FDA officials told us that the agency does not routinely verify the information provided by establishments to ensure that it is accurate.²³ Nor does FDA confirm that the establishment actually manufactures drugs for the U.S. market. FDA does not know how many foreign establishments are erroneously registered. In addition, DRLS does not provide the agency with a complete count of establishments subject to inspection because foreign establishments that manufacture APIs are not required to register if their products are not directly imported into the United States.²⁴

Planned changes to DRLS could help FDA improve this database but will not provide an accurate count. In July 2008, FDA initiated a pilot of a voluntary electronic registration and listing system for establishments that manufacture drugs;²⁵ the agency plans to accept only electronic registration beginning June 2009. The new system allows drug manufacturing establishments to submit registration and listing information electronically, rather than submitting it on paper forms. FDA hopes that electronic registration will result in efficiencies allowing the agency to shift resources from data entry to assuring the quality of the databases. Through this new system, FDA also plans to require establishments to update their registration information every 6 months, rather than annually, as is currently required. In addition, FDA has asked establishments to voluntarily submit a unique identification number—a

²³If the agency learns of an error, it asks the establishment to submit corrected information.

²⁴For example, an establishment in China may export an API to Germany. The German establishment may use the API in its production of a drug that is imported into the United States. Although the German establishment would be required to notify FDA of its arrangement with the Chinese establishment, and the Chinese establishment would be subject to inspection by FDA, the Chinese establishment is not required to register.

²⁵This voluntary program was established through release of draft FDA guidance in July 2008. See “Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing” at <http://www.fda.gov/cder/guidance/index.htm> (accessed July 30, 2008).

Dun and Bradstreet Data Universal Numbering System (D-U-N-S®) Number—as part of their registration.²⁶ An official said the agency plans to make this a requirement after it implements electronic registration in June 2009. This identification number could provide FDA with confidence regarding certain information about the establishment, such as its name and location. However, it will not prevent foreign establishments that do not manufacture drugs for the U.S. market from registering. As a result, the registration database will continue to contain inaccuracies when FDA selects establishments for inspection.²⁷

FDA has also proposed, but not yet implemented, initiatives that could help improve the accuracy of information FDA maintains on registered establishments. FDA proposed a program to contract with an external organization to help manage and improve DRLS, which it describes in its proposal as fragmented and unreliable. As part of the contract, FDA states that the contractor would “establish reasonable credibility” of some of the information provided by establishments. However, as of June 2008, the agency had not yet solicited proposals for this program. In addition, the agency has proposed the Foreign Vendor Registration Verification Program. Through this program, FDA plans to contract with an external organization to conduct on-site verification of the registration data and product listing information of foreign establishments shipping drugs and other FDA-regulated products to the United States. FDA has solicited

²⁶The D-U-N-S® Number is a unique nine-digit sequence recognized as the federal government’s universal standard for identifying and keeping track of business entities. Submitting the site-specific number for an entity would provide, by reference to the number, certain business information for that entity that is otherwise required for drug establishment registration. For example, a D-U-N-S® Number could be used to identify trade names used by the entity; addresses; additional ownership information, such as the name of each partner or the name of each corporate officer and director; and the state of incorporation.

²⁷In fiscal year 2008, another FDA center implemented changes affecting the registration of medical device manufacturing establishments, an activity for which we previously identified problems similar to those found in DRLS. See *Medical Devices: FDA Faces Challenges in Conducting Inspections of Foreign Manufacturing Establishments*, [GAO-08-780T](#) (Washington, D.C.: May 14, 2008). Officials indicated that the Center for Devices and Radiological Health began deactivating the registrations of those establishments that fail to complete the annual registration process. In addition, it implemented an electronic registration system and began charging an annual user fee, \$1,706 in fiscal year 2008, per registration for certain medical device establishments. (CDER does not have authority to charge such a fee to drug establishments.) Officials found that, combined, these changes resulted in the elimination of establishments from the database. They anticipated that this would provide FDA with a smaller, more accurate database of medical device establishments.

proposals for this contract but is still developing the specifics of the program. For example, the agency has not yet formalized the criteria it would use to determine which establishments would be visited for verification purposes or determined how many establishments it would verify annually. As of July 2008, FDA had not yet awarded this contract. Given the early stages of these proposals, it is too soon to determine whether they will improve the accuracy of the data FDA maintains on foreign drug establishments.

FDA's Import Database Contains Inaccurate Data on Establishments Offering Drugs for Import into the United States

OASIS, which FDA also uses to help it select establishments for inspection, provides an inaccurate count of foreign establishments manufacturing drugs offered for import into the United States. According to OASIS, 6,760 foreign establishments manufactured drugs that were offered for import into the United States in fiscal year 2007. However, this count is inaccurate as a result of unreliable manufacturer identification numbers generated by customs brokers when a drug is offered for import.²⁸ FDA officials told us that these errors result in the creation of multiple records for a single establishment, which results in inflated counts of establishments offering drugs for import into the U.S. market. FDA officials acknowledged this problem but were unable to provide us with an estimate of the extent of these errors. In addition, the agency does not have a process for systematically identifying and correcting these errors. To mitigate this problem, the officials told us that FDA has provided training to brokers as a way to improve accuracy.

FDA has supported a proposal with the potential to address weaknesses in OASIS, but FDA does not control the implementation of this proposed change. FDA, in conjunction with other federal agencies, is pursuing the creation of a governmentwide unique establishment identifier that could minimize duplication. Agencies currently rely on the creation and entry of an identifier at the time of import. Under this new proposal, establishments offering products, including drugs, for import into the United States would obtain a unique establishment identifier through a commercial service that would verify certain information about the

²⁸The algorithm currently used by customs brokers to assign the manufacturer identification number does not provide for a number that is reliably reproduced or inherently unique.

establishment.²⁹ This unique identifier would then be stored within the proposed Shared Establishment Data Service (SEDS)³⁰ and submitted as part of import entry data when required by FDA or other government agencies. The unique identifier could thus eliminate the problems that have resulted in multiple identifiers associated with an individual establishment. The implementation of SEDS is dependent on action from multiple federal agencies, including the integration of the concept into a CBP import and export system that is under development and scheduled for implementation in 2010.³¹ In addition, once implemented by CBP, FDA and other participating federal agencies would be responsible for bearing the cost of integrating SEDS with their own operations and systems. FDA officials are not aware of a specific time line for the implementation of SEDS.

FDA's Databases Are Not Currently Electronically Integrated, which Could Help Reconcile Data Inaccuracies

The databases FDA uses to select establishments for inspection are not electronically integrated, and their integration could help reconcile data inaccuracies. To create a list of foreign establishments subject to inspection, the agency relies on information from databases that were not designed for that purpose and contain divergent estimates—about 3,000 and 6,760 from DRLS and OASIS, respectively. FDA officials told us that these databases are not electronically integrated and do not readily

²⁹If an establishment did not already have an identification number, it would request an identification number and data about the establishment would be verified through a commercial service. This commercial service would provide federal agencies with researched and validated records on domestic and foreign establishments.

³⁰The SEDS proposal was developed by the Federal Health Architecture Food Safety Work Group, which is comprised of representatives from FDA, the Environmental Protection Agency, and the departments of Agriculture, Commerce, Defense, and Homeland Security. These agencies are involved in the oversight of products imported into the United States. In addition, developing an implementation plan for SEDS was recommended by the Interagency Working Group on Import Safety in 2007. In July 2007, the Interagency Working Group on Import Safety was established to conduct a comprehensive review of current import safety practices and determine where improvements could be made. Interagency Working Group on Import Safety, *Action Plan for Import Safety: A Roadmap for Continual Improvement* (November 2007) (www.importsafety.gov/report/actionplan.pdf, accessed May 6, 2008).

³¹In October 2007, we reported on CBP's implementation of its import and export system, known as the Automated Commercial Environment. We found that CBP has made progress but warned that further efforts were needed to avoid major program schedule delays and cost overruns. See *Information Technology: Improvements for Acquisition of Customs Trade Processing System Continue, but Further Efforts Needed to Avoid More Cost and Schedule Shortfalls*, GAO-08-46 (Washington, D.C.: Oct. 25, 2007).

interact with one another to help reconcile the data. FDA indicated that any electronic comparison of the data in these databases is complex and the agency conducts some comparisons manually for each individual establishment. For example, for fiscal year 2007, FDA used DRLS and other data to develop a list of 3,249 foreign establishments ranked by their risk level in order to select establishments for surveillance inspection. However, due to inaccuracies in DRLS, FDA must also check OASIS to determine which of these establishments actually had imported drugs into the United States and were subject to inspection. FDA officials indicated that they had to manually compare establishments on this list with establishments in OASIS. Because these databases are not electronically integrated, DRLS and OASIS are not conducive to routine analysis to compare the data and identify errors.

FDA is in the process of improving the integration of some of its current data systems, which could make it easier for the agency to establish an accurate count of foreign drug manufacturing establishments subject to inspection. The agency's Mission Accomplishments and Regulatory Compliance Services (MARCS) is intended to help FDA electronically integrate data from multiple systems. It is specifically designed to give individual users a more complete picture of establishments but could also help the agency compare information in multiple databases to obtain an accurate count of establishments subject to inspection. For example, an FDA official indicated that MARCS in combination with planned improvements to the agency's registration database will allow FDA to electronically integrate FDA's drug registration and import data. FDA officials estimate that MARCS, which is being implemented in stages, could be fully implemented by 2011 or 2012. An FDA official told us that the agency may be able to electronically integrate its registration and import data by the end of fiscal year 2009, but this implementation has previously faced delays. FDA officials told us that implementation has been slow because the agency has been forced to shift resources away from MARCS and toward the maintenance of current systems that are still heavily used, such as FACTS and OASIS. It is too early to tell whether the implementation of MARCS will improve FDA's management of its inspection program.

FDA Inspects Relatively Few Foreign Establishments to Assess the Manufacture of Drugs Currently Marketed in the United States

FDA inspects few foreign establishments, relative to domestic establishments, each year to assess the manufacture of drugs currently marketed in the United States. The percentage of such foreign establishments that have been inspected cannot be calculated with certainty because FDA does not know how many foreign establishments manufacture drugs for the U.S. market and are thus actually subject to inspection. Of the foreign establishments that FDA inspected, few were selected to conduct surveillance of drugs currently marketed in the United States. Instead, most foreign establishments are selected for inspection as part of the agency's review process associated with applications for approving a new drug.

FDA Inspects Few Foreign Establishments Each Year, Relative to Its Inspection of Domestic Establishments

In each year we examined, FDA inspected fewer foreign establishments manufacturing drugs for the U.S. market than it inspected domestically. However, its lack of an accurate count of foreign establishments subject to inspection makes it difficult to exactly determine the relative size of that portion. Based on our review of data on inspections, FDA conducted an average of 247 foreign establishment inspections per year from fiscal years 2002 through 2007.³² Comparing this average number of inspections with FDA's count of 3,249 foreign establishments that it used to prioritize its fiscal year 2007 surveillance inspections suggests that the agency inspects about 8 percent of foreign establishments in a given year.³³ At this rate it would take FDA more than 13 years to inspect this group of establishments once, assuming that no additional establishments are subject to inspection. In contrast, from fiscal years 2002 through 2007 FDA conducted about 1,528 inspections of domestic establishments each year. FDA officials estimated that there were about 3,000 domestic establishments manufacturing drugs in fiscal year 2007. They told us that the agency inspects these domestic establishments about once every 2.7 years.

³²Our analysis includes all foreign and domestic inspections that were identified in FDA's FACTS database as being either related to the drug application approval process or GMP. It does not include a small number of other inspections, such as inspections conducted to determine whether drug manufacturers are submitting to FDA, as required, complete and accurate data on adverse drug experiences associated with marketed drugs.

³³In preparing this list, FDA drew on information from DRLS. It also obtained information from previous inspections to help it identify establishments that are subject to inspection but are not required to register—such as the manufacturer of an API whose product is not directly imported into the United States. However, as a result of the inaccuracies in its data, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

FDA's data indicate that some foreign establishments have never received an inspection, but the exact number of such establishments is unclear. Of the list of 3,249 foreign establishments, there were 2,133 foreign establishments for which the agency could not identify a previous inspection. Agency officials told us that this count included registered establishments whose drugs are being imported into the United States that have never been inspected, as well as establishments whose drugs were never imported into the United States or those who have stopped importing drugs into the United States without notifying FDA. FDA was unable to provide us with counts of how many establishments fall into each of these subcategories. Of the remaining 1,116 establishments on FDA's list, 242 had received at least one inspection, but had not received a GMP inspection since at least fiscal year 2000.³⁴ The remaining 874 establishments had received at least one GMP inspection since fiscal year 2000. Of these 874 establishments, 326 had last been inspected in fiscal years 2005 or 2006, 292 were last inspected in fiscal years 2003 or 2004, and the remaining 256 received their last inspection in fiscal years 2000 through 2002.

FDA recently increased the number of foreign establishments it inspects, most of which are concentrated in a small number of countries. From fiscal years 2002 through 2007, the number of foreign establishment inspections FDA conducted varied from year to year, but increased overall from 220 in fiscal year 2002 to 332 in fiscal year 2007. During this period, FDA inspected establishments in a total of 51 countries. More than three quarters of the 1,479 foreign inspections the agency conducted during this period were of establishments in 10 countries, as shown in table 1. Because some establishments were inspected more than once during this time period, FDA actually inspected 1,119 unique establishments. For example, of the 94 inspections that FDA conducted of Chinese establishments, it inspected 80 unique establishments. The proportion of establishments inspected in each of these 10 countries varied. The country with the lowest proportion of establishments inspected was China, for which FDA inspected 80 of its estimated 714 establishments. In contrast, the agency inspected 43 of the estimated 61 establishments in Ireland.

³⁴According to FDA officials, some of these establishments may have received an inspection for another type of product, such as a veterinary drug.

Table 1: Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the U.S. Market, by Country for the 10 Most Frequently Inspected Countries, Fiscal Years 2002 through 2007

Country	Number of inspections							Number of unique establishments inspected	Estimated number of establishments ^a
	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	Total		
India	11	19	38	33	34	64	199	152	410
Germany	24	15	35	25	19	25	143	95	199
Italy	17	30	26	21	18	28	140	98	150
Canada	29	12	17	23	23	20	124	88	288
United Kingdom	17	21	15	18	15	16	102	84	169
China	11	9	17	21	17	19	94	80	714
France	14	15	13	12	16	24	94	71	162
Japan	11	13	14	21	13	22	94	82	196
Switzerland	12	12	11	17	9	17	78	50	83
Ireland	11	5	11	14	3	14	58	43	61
All other countries	63	38	63	61	45	83	353	276	817
Total	220	189	260	266	212	332	1,479	1,119	3,249

Source: GAO analysis of FDA data.

^aThis count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections.

While FDA has recently made progress in conducting more foreign inspections, it still inspects relatively few such establishments. FDA conducted more foreign establishment inspections in fiscal year 2007 than it had in each of the 5 previous fiscal years. However, the agency still inspected less than 11 percent of the foreign establishments on the prioritized list that it used to plan its fiscal year 2007 surveillance inspections.

In order to inspect foreign establishments biennially, as is required for domestic establishments, FDA would have to dedicate substantially more resources than it has dedicated to such inspections in the past. In fiscal year 2007, FDA dedicated about \$10 million to inspections of foreign establishments. FDA estimates that, based on the time spent conducting inspections of foreign drug manufacturing establishments in fiscal year 2007, the average cost of such an inspection ranged from approximately

\$41,000 to \$44,000.³⁵ If these estimates are applied to the 3,249 foreign drug establishments on the list FDA used to plan its fiscal year 2007 surveillance inspections, it could cost the agency \$67 million to \$71 million each year to inspect each of those establishments biennially. Using FDA's estimates for the cost of each inspection also suggests that it could cost the agency \$15 million to \$16 million each year to biennially inspect the estimated 714 drug manufacturing establishments in China, the country estimated to have the largest number of establishments. According to FDA budget documents, the agency estimates that it will dedicate a total of about \$11 million in fiscal year 2008 to foreign drug inspections.

Significant changes were recently made to the fiscal year 2009 budget request for FDA. The President's original budget request to the Congress called for \$2.4 billion in fiscal year 2009 for FDA, including \$13 million to conduct all inspections of foreign drug establishments. However, in June 2008, the President submitted an amendment requesting an additional \$275 million for fiscal year 2009, an approximately 11 percent increase over the original request. According to the submission, some of these additional funds were requested to allow FDA to conduct an additional 143 inspections of foreign drug establishments and 75 inspections of domestic drug establishments.³⁶

FDA is pursuing initiatives with drug regulators in foreign countries that are intended to help the agency improve its inspectional coverage. FDA has announced an initiative with the regulatory body of the European Union to pilot joint inspections of establishments that manufacture finished drug products in either the United States or the European Union and supply both of these markets. FDA indicated that these joint inspections could help it leverage resources by allowing the agency to utilize staff from the E.U. regulatory body when forming joint inspection teams. According to FDA, the joint inspections will help the agency and the E.U. regulatory body build confidence in each other's inspections,

³⁵According to FDA, the cost of conducting foreign inspections varies, depending on the time spent at an establishment, the number of FDA staff conducting the inspection, the costs associated with traveling to the country in which the establishment is located, and whether the type of inspection was a preapproval or GMP surveillance inspection.

³⁶The submission requested funds for FDA to conduct a total of 2,100 inspections in addition to those the agency already planned to conduct. Of the 2,100 inspections, 1,050 would be of foreign establishments manufacturing food, drugs, and other medical products and 1,050 would be of domestic establishments manufacturing food, drugs, and other medical products.

which could allow FDA to review an inspection report completed by E.U. regulators instead of conducting its own inspection. As of July 2008, no joint inspections had been scheduled under this program, but they were in preliminary discussions with one establishment to conduct a joint inspection. In addition, FDA has announced an initiative with the regulatory bodies of the European Union and Australia to share their plans for and results of inspections of API manufacturing establishments in these and other countries. For example, FDA could receive the results of inspections conducted by these regulatory bodies and then determine if regulatory action or a follow-up inspection is necessary. FDA contends that prospectively sharing information about inspection plans will allow these regulatory bodies to more efficiently use their resources by minimizing the overlap in their plans. FDA and the other regulatory bodies held initial discussions in July 2008 and plan to further discuss the program in September 2008. While both initiatives are intended to improve FDA's knowledge of foreign establishments, both were recently announced and their impact will depend on the extent to which FDA effectively utilizes the information that it receives from the other regulatory bodies.

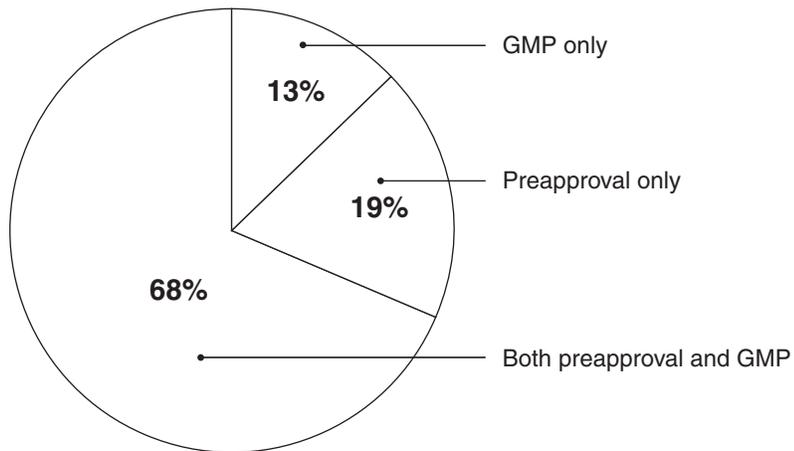
FDA Selects Few Foreign Establishments to Inspect the Manufacturing of Drugs Currently Marketed in the United States, in Contrast to Its Inspections of Domestic Establishments

FDA selected few foreign establishments for inspection in order to examine the manufacturing of drugs currently marketed in the United States. We reported in 1998 that 20 percent of the agency's foreign inspections were for the purpose of routine surveillance.³⁷ For fiscal years 2002 through 2007, we found that about 13 percent of foreign inspections were GMP inspections conducted to examine the manufacturing of drugs currently marketed in the United States, rather than to inspect an establishment listed in a new drug application. (See fig. 3.) In comparison, for fiscal years 2002 through 2007, about 85 percent of FDA's inspections of domestic establishments were GMP inspections conducted to examine the manufacturing of drugs currently marketed in the United States. FDA conducts a similar number of preapproval inspections in domestic and foreign establishments each year, but many more domestic GMP inspections. Agency officials said that preapproval inspections are driven by specific goals for the timely review of new drug applications, which

³⁷ [GAO/HEHS-98-21](#), 23.

may necessitate the inspection of establishments referenced in those applications.³⁸

Figure 3: FDA Foreign Establishment Inspections by Type of Inspection, Fiscal Years 2002 through 2007



Source: GAO analysis of FDA data.

FDA often included a systemwide GMP inspection when it visited a foreign establishment for a preapproval inspection. From fiscal years 2002 through 2007, the majority of FDA's foreign inspections combined a preapproval inspection with a broader GMP inspection. According to FDA officials, because foreign establishments are inspected infrequently, it is expedient for the agency to conduct preapproval inspections and GMP inspections during the same visit to a foreign establishment.³⁹

³⁸When FDA receives a new drug application, CDER officials review the inspection history of each establishment listed on the application. According to FDA officials, if an establishment listed on the application has received a satisfactory GMP inspection in the previous 2 years and the agency has no new concerns, FDA will consider this inspection sufficient for the review of the application and will not perform a preapproval inspection of this establishment. Otherwise, the agency may inspect the establishment as part of the application review process.

³⁹Because a GMP inspection examines the major manufacturing systems at an establishment, the results of such an inspection can often be generalized to all drugs manufactured at a particular establishment. FDA can thus use the results of the combined inspection to make decisions in the future if that establishment is listed in another new drug application.

Relatively few foreign establishments identified through CDER's risk-based process are selected for the agency to conduct surveillance of drugs currently marketed in the United States. In fiscal year 2007, after using this process to rank the 3,249 establishments by their potential risk level, CDER forwarded to ORA a list of 104 foreign establishments that it considered to be a high priority for inspection and requested that ORA complete surveillance inspections of 25 of them. FDA officials indicated that 29 such inspections were actually completed in fiscal year 2007. In fiscal year 2008, CDER submitted a list of 110 foreign establishments to ORA, with a target of at least 50 inspections.

FDA's Identification of Serious Deficiencies Has Led Establishments to Take Corrective Actions, but Subsequent Inspections Were Not Always Timely

Though FDA oversight resulted in foreign establishments taking actions to address serious deficiencies identified during inspections, FDA's subsequent inspections of these establishments were not always timely. FDA identified deficiencies during most of its inspections of foreign establishments. However, determining the number of inspections during which FDA identified serious deficiencies is hindered by inconsistent data on inspection classifications. FDA issued 15 warning letters to foreign drug establishments found to be out of compliance with GMPs. To determine the adequacy of an establishment's corrective actions, FDA often relied on information provided by the establishment, rather than information obtained from another FDA inspection. Although FDA verified these corrective actions during subsequent inspections, FDA inspections to determine establishments' continued compliance were not always timely and identified additional deficiencies.

FDA Identified Deficiencies during Most of Its Inspections of Foreign Establishments, but FDA's Databases Contain Inconsistent Information about Inspection Classifications

FDA identified deficiencies during most of its inspections of foreign establishments. Based on our review of classification data in FACTS, FDA identified deficiencies necessitating a classification of VAI or the more serious OAI in about 62 percent of foreign inspections conducted from fiscal years 2002 through 2006,⁴⁰ compared to about 51 percent of inspections of domestic establishments. However, we determined that FDA's data did not provide reliable information about the number of foreign inspections with serious deficiencies classified specifically as OAI.

⁴⁰We present data from fiscal years 2002 through 2006 because, at the time we received these data, some inspections conducted in fiscal year 2007 may not have received their final classification.

Determining the number of inspections during which FDA identified serious deficiencies is hindered by inconsistencies in databases used by FDA to track inspections. FDA uses two databases to track information about foreign inspections—FACTS, which is accessible to ORA staff and staff in CDER and other FDA centers, and OCFITS, which is only accessible to CDER staff who review foreign inspection reports. In comparing inspection classification information for foreign inspections conducted from fiscal years 2002 through 2006, we found that of the inspections that could be identified in both databases,⁴¹ 92 percent were consistently classified. However, for inspections that identified serious deficiencies, this rate was much lower. Of inspections classified as OAI in FACTS, 53 percent were identified in OCFITS as receiving the less serious classification of VAI. CDER officials told us that the final inspection classification should be the same in both FACTS and OCFITS.

FDA officials suggested that inconsistencies between FACTS and OCFITS may result when changes in inspection classifications are not appropriately updated by FDA staff during the review process. Following an inspection of a foreign establishment, ORA staff enter classification recommendations into FACTS. However, CDER makes the final classification decision, which may be either more or less serious than ORA's recommendation. CDER officials enter this final classification into OCFITS and, according to FDA policy, should also update this information in FACTS. However, FDA officials indicated that CDER staff may not always update FACTS.⁴² FACTS is the database used by ORA investigators and staff in other FDA centers to check establishments' compliance history. When FACTS is not always updated consistent information on foreign establishments may not be readily accessible to FDA staff

⁴¹We were unable to match all inspection information in the two databases. For fiscal years 2002 through 2006, we identified 1,147 inspections in FACTS and 1,128 inspections in OCFITS. Of these, we were able to reliably determine that 1,060 inspections in each database were indeed the same inspections.

⁴²We identified a similar weakness in our 1998 report. We reported that a 1988 FDA evaluation of its foreign inspection program found that an inspection tracking database that served as a precursor to FACTS contained incomplete information for 37 percent of foreign inspections conducted between fiscal years 1982 and 1987. The evaluation attributed this error to CDER staff not updating the inspection tracking database after reviewing and classifying inspection reports. In addition, our review of data on inspections conducted between January 1, 1994, and May 15, 1996, found that these data were missing or incorrect in 15 percent of inspections. Similar to FDA's 1988 findings, we attributed some of these errors to staff not updating the database after reviewing and classifying inspection reports. [GAO/HEHS-98-21](#).

responsible for the oversight of foreign establishments manufacturing drugs marketed in the United States.⁴³

FDA Issued Warning Letters to Establishments, Most of which Had Previous Deficiencies

FDA issued warning letters to establishments at which it identified serious deficiencies. Of the 1,479 inspections of foreign drug establishments that FDA conducted from fiscal years 2002 through 2007,⁴⁴ the agency issued a warning letter following 15 inspections in which serious deficiencies were identified (see table 2).⁴⁵ The rate of warning letters issued to foreign establishments was similar to that for domestic establishments.⁴⁶ Foreign establishments that received warning letters were located in 10 countries. For establishments listed in 4 of the 15 warning letters, in addition to issuing a warning letter, FDA also issued import alerts authorizing detention of the establishments' drugs if they were offered for import into the United States. When issuing the other 11 warning letters, FDA did not restrict importation of the establishments' drugs, but notified the establishments that failure to correct the identified deficiencies could result in the agency denying entry of their drugs when they were offered for import into the United States.

⁴³Although we have concerns about the consistency with which CDER staff update final classification information in FACTS, we use FACTS, rather than OCFITS, as our source for this information. FDA inspections of both domestic and foreign establishments are tracked in FACTS, while only foreign inspections are tracked in OCFITS. Thus, for purposes of comparison, we report both domestic and foreign inspection counts from FACTS. For consistency, we used that same count of inspections to conduct our analysis of classification information. As we report, our analysis of FACTS data suggested that about 62 percent of foreign inspections conducted from fiscal year 2002 through 2006 were classified as VAI or OAI. Similarly, about 61 percent of foreign inspections in OCFITS were classified as VAI or OAI, though classifications of individual inspections differed between the two databases.

⁴⁴FDA only issues warning letters to those foreign establishments manufacturing drugs for the U.S. market at which it has identified violations that could lead to enforcement action. If the violative foreign establishment is not yet manufacturing any drugs for the U.S. market, but intends to, the agency may issue an untitled letter. Because our analysis may have included inspections of establishments named in a new drug application that did not yet manufacture a drug for the U.S. market, in some instances the identification of serious deficiencies could have resulted in an untitled letter and not a warning letter.

⁴⁵One warning letter related to the inspection of two establishments as drug production was being moved from one establishment to the other. As FDA referred to both inspections in its warning letter, we count this as a single inspection.

⁴⁶We base this statement on a comparison of inspections conducted and warning letters issued from fiscal years 2004 through 2007. The number of domestic warning letters issued prior to fiscal year 2004 was not readily available.

Table 2: Warning Letters Issued by FDA to Foreign Establishments in Response to Inspections Conducted from Fiscal Years 2002 through 2007

Date inspection ended	Date warning letter issued	Location of establishment	Import alert issued	Time from inspection to warning letter issuance
Fiscal year 2002				
April 16, 2002	November 21, 2002	Australia	No	7 months, 5 days
Fiscal year 2003				
September 10, 2003	January 15, 2004	Czech Republic	No	4 months, 5 days
Fiscal year 2004				
October 29, 2003	January 5, 2004	Taiwan, Republic of China	No	2 months, 7 days
October 31, 2003	February 10, 2004	China	Yes	3 months, 10 days
May 13, 2004	August 3, 2004	Switzerland	No	2 months, 21 days
Fiscal year 2005				
October 15, 2004	February 15, 2005	Canada	Yes	4 months
March 24, 2005	July 21, 2005	Italy	No	3 months, 27 days
April 8, 2005	August 16, 2005	Switzerland	No	4 months, 8 days
Fiscal year 2006				
November 11, 2005	February 21, 2006	India	No	3 months, 10 days
February 8, 2006	April 28, 2006	Croatia	No	2 months, 20 days
February 25, 2006	June 15, 2006	India	No	3 months, 21 days
September 13, 2006	February 23, 2007	Canada	No	5 months, 10 days
Fiscal year 2007				
April 25, 2007 ^a	September 6, 2007	China	Yes ^b	4 months, 12 days
August 30, 2007	October 31, 2007	China	Yes	2 months, 1 day
August 2, 2007	January 14, 2008	Japan	No	5 months, 12 days

Source: GAO review of FDA warning letters.

^aThis warning letter related to inspections of two establishments as drug production was being moved from one establishment to the other. As FDA referred to both establishments in its warning letter, we count the end date of the inspection of the second establishment as the relevant end date.

^bThe import alert only applied to drugs manufactured at the establishment from which production was being moved.

During the inspections that resulted in these 15 warning letters, FDA identified various deficiencies. Identified deficiencies included those related to: laboratory controls, such as lack of an adequate impurity

profile;⁴⁷ documentation and records, such as records that did not include complete and accurate information relating to the production of each batch of drug produced; and facilities and equipment, such as an “unknown soft, yet flaking, black residue” inside a piece of equipment.

FDA generally met its internal goal for the timely issuance of warning letters, and establishments usually began responding to deficiencies identified on the Form 483 prior to receiving the warning letter. FDA issued 9 of the 15 warning letters within 4 months of completing its inspection—as is FDA’s policy—and issued 3 other letters in just over 4 months. While FDA was reviewing the results of the inspection and drafting the warning letters, inspected establishments generally responded in writing to deficiencies identified on the Form 483, which establishments receive on the last day of an inspection. In all but one instance, the establishments responded in writing to Form 483 observations within 5 weeks following the completion of the inspection.⁴⁸ These written responses included information on the establishments’ proposed, completed, or soon to be implemented corrective actions taken to address deficiencies identified during the FDA inspection. In more than half of the cases, FDA noted that more comprehensive corrective actions were needed than those outlined in the establishments’ responses or that the responses lacked sufficient details, explanation, or documentation. The agency proceeded to issue the warning letters after finding the establishments did not provide sufficient written responses to the deficiencies identified during the inspection.

Most of the foreign drug establishments to which FDA issued the 15 warning letters had previously been found by the agency to be out of compliance with GMPs. FDA had previously inspected establishments named in 12 of the 15 warning letters.⁴⁹ These previous inspections had

⁴⁷An impurity profile describes the identified and unidentified impurities present in an API. GMP guidance notes that impurity profiles should be compared with historical data at appropriate intervals to detect changes in the API.

⁴⁸One establishment did not respond to the identified deficiencies until 6 months after the FDA inspection. FDA did not receive a response from the establishment until after it issued the warning letter.

⁴⁹In the case of three establishments that received warning letters but that FDA had not previously inspected, the establishments manufactured OTC drugs. FDA does not generally conduct preapproval inspections for establishments manufacturing OTC drugs because the majority of OTC drugs may be marketed without FDA preapproval. FDA generally considers establishments manufacturing OTC drugs to have a lower inspection priority.

been conducted 1 to 7 years prior to the inspection that resulted in the issuance of the warning letter, with 9 of the 12 previous inspections occurring within 4 years of the warning letter inspection. FDA identified deficiencies in almost all of the 12 previous inspections, classifying 10 as VAI and 1 as OAI, but did not issue any warning letters.⁵⁰ For 7 of these inspections, the deficiencies FDA identified at these establishments were again identified during the inspection that led to the issuance of a warning letter.

FDA often identified the warning letter deficiencies, which relate to the manufacture of a currently marketed drug, when it inspected the establishment as part of its review of a new drug application. In 7 of the 15 cases, FDA selected the establishment for inspection as part of its review of a drug application. In 3 cases, FDA conducted the inspection for surveillance purposes. In 3 other cases, FDA conducted the inspections following the receipt of information from an informant, such as allegations of insanitary conditions. In the 2 remaining cases, FDA conducted the inspection to follow up on a previous inspection performed by FDA or a foreign government that identified deficiencies.

FDA Oversight Has Led Establishments to Take Corrective Actions, but Subsequent Inspections to Determine Continued Compliance Are Not always Timely

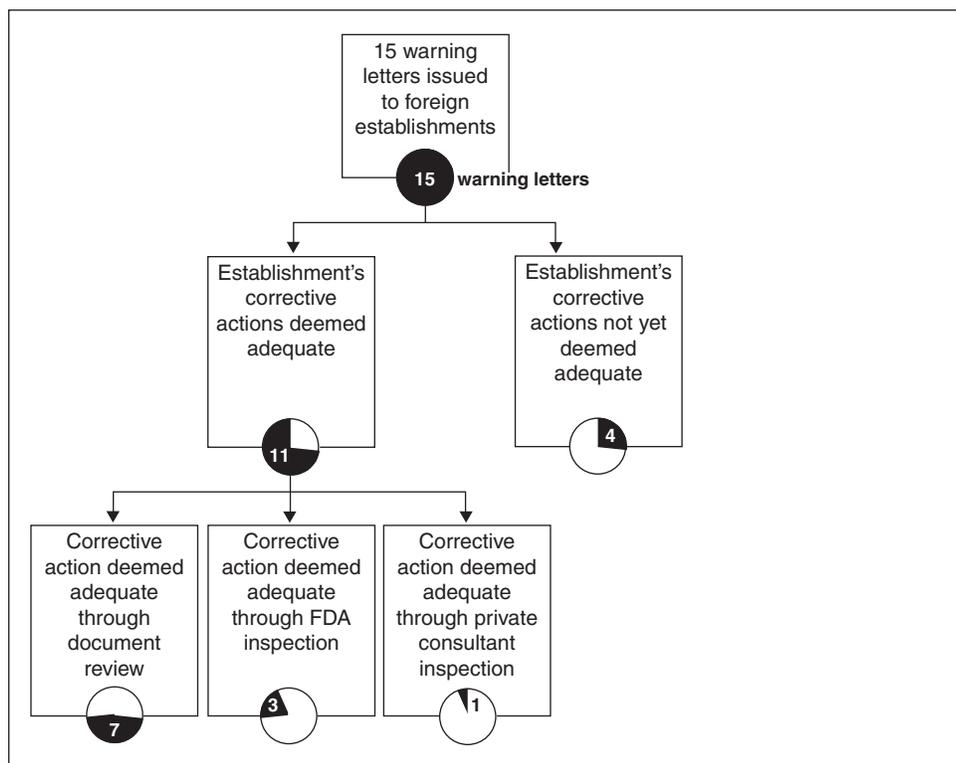
FDA oversight resulted in establishments taking actions to correct serious deficiencies, but the agency has not always conducted timely subsequent inspections to determine whether establishments continued to comply with agency requirements. FDA often relied on information provided by the establishment, rather than obtained from an FDA inspection, to determine the adequacy of an establishment's corrective actions. As of July 2008, FDA had determined that the corrective actions taken by establishments referenced in 11 of the 15 warning letters were adequate.⁵¹ (See fig. 4.) For 7 of these 11 establishments, FDA relied on information provided by the establishment to make this determination. For example, establishments provided FDA with an outline of corrective actions to be taken. In some of these cases, FDA also met with officials from the establishments or held telephone conferences to discuss the corrective

⁵⁰None of the inspections that directly preceded the warning letter inspection resulted in a warning letter. However, FDA indicated that two of the establishments in our review had received a previous warning letter since fiscal year 1995, the year from which FDA could reliably determine warning letter issuance.

⁵¹As of July 2008, the corrective actions of establishments referenced in the other four warning letters had not been accepted by FDA.

actions. This process often involved multiple communications between FDA and the establishment. FDA typically notified these establishments that their corrective actions were adequate within 4 months of issuing the warning letter. In this notification, the agency generally stated that it would verify the corrective actions taken at the time of the next inspection.

Figure 4: FDA's Methods for Determining the Adequacy of Corrective Actions for 15 Warning Letters Issued Following Foreign Inspections Conducted from Fiscal Years 2002 through 2007



Source: GAO analysis of FDA documents.

FDA conducted an inspection or used the results of an inspection conducted by a private consultant to determine the adequacy of the establishments' corrective actions for the other four establishments it deemed adequate. FDA inspected three of these establishments between 8 and 21 months after the issuance of the warning letter. Based on these inspections and other documentation, FDA determined that the deficiencies that led to the warning letter had been corrected. In two of

those three inspections, FDA also found additional deficiencies that led to a classification of VAI. For one establishment, instead of waiting for FDA to conduct an inspection to determine the adequacy of its corrective actions, FDA agreed that the establishment could arrange for an inspection by a private consultant. The consultant found that the establishment had made the corrective actions requested by FDA. The agency stated that it would verify the corrective actions during its next inspection.

FDA inspections to determine establishments' continued compliance were not always timely. As of June 2008, FDA had subsequently inspected 4 of the 11 establishments it determined had taken adequate corrective actions in response to the warning letters. For 3 establishments, FDA had previously determined the adequacy of their corrective actions by reviewing information provided by the establishment. Although CDER staff had recommended that they be inspected within 1 year, these 3 establishments were inspected about 4 to 5 years after the inspection that resulted in the warning letter. However, FDA officials told us that dates recommended by CDER staff for subsequent inspections are only regarded as suggestions and scheduling inspections must be considered in light of other priorities. They noted that the selection of foreign establishments for inspection is driven by the drug approval process. We found that, in these 3 cases, FDA next selected the establishment for inspection as part of processing an application for a new drug, rather than for the purpose of surveillance. For the fourth establishment, FDA had previously determined the adequacy of the establishment's corrective actions by reviewing an audit report from a private consultant's inspection. CDER staff had recommended that this establishment be inspected within 2 years and the agency met this recommendation by conducting a surveillance inspection.

FDA verified corrective actions during three of these four inspections subsequent to deeming the establishments' corrective actions adequate, but it also identified additional deficiencies. The agency found that the three establishments had taken the corrective actions indicated in their response to the warning letters. However, FDA found other deficiencies requiring correction at those establishments. FDA classified all four of these inspections as VAI and none resulted in the issuance of a warning letter.

Challenges Unique to Foreign Inspections Influence the Manner in which FDA Conducts Such Inspections

Inspections of foreign drug establishments pose unique challenges to FDA—in both human resources and logistics—that influence the manner in which such inspections are conducted. For example, FDA does not have a dedicated staff devoted to conducting foreign inspections and relies on staff to volunteer. In addition, unlike domestic surveillance inspections, foreign surveillance inspections are announced in advance and inspections cannot be easily extended due to travel itineraries that involve more than one establishment. Other factors, such as language barriers, can also add complexity to the challenge of completing foreign establishment inspections. FDA has recently announced proposals to address some of the challenges unique to conducting foreign inspections, but it is unclear if these proposals will address all of these challenges.

Inspections of Foreign Drug Establishments Pose Unique Challenges to FDA

Human resource and logistical challenges unique to foreign inspections influence the manner in which FDA conducts those inspections. According to FDA officials, the agency does not have a dedicated staff to conduct foreign inspections. Instead FDA relies on investigators and laboratory analysts to volunteer to conduct foreign inspections. Officials explained that the same investigators and laboratory analysts are responsible for conducting both foreign and domestic inspections. These staff members must meet certain criteria in terms of their experience and training in order to conduct inspections of foreign establishments. For example, they are required to take certain training courses and must have at least 3 years of experience conducting domestic inspections before they are considered qualified to conduct a foreign inspection. FDA reported that in fiscal year 2007 it had approximately 335 employees who were qualified to conduct foreign inspections of drug manufacturing establishments. Approximately 250 of these employees were investigators and 85 were laboratory analysts.⁵²

FDA officials told us that it is difficult to recruit investigators and laboratory analysts to voluntarily travel to certain countries and FDA does not mandate that they do so. However, officials noted that the agency

⁵²These counts do not represent the number of individuals who actually conduct foreign inspections in a given year. Not all investigators and laboratory analysts who are qualified to conduct a foreign inspection do so in a given year, while other qualified investigators and laboratory analysts may perform multiple inspections during the same period. While an investigator and laboratory analyst team may participate in foreign inspections, FDA officials stated that in certain circumstances, such as inspections that do not involve the review of laboratory facilities, only an investigator is sent.

provides various incentives to recruit employees for foreign inspection assignments. For example, employees receive a \$300 bonus for each 3-week foreign inspection trip completed, when their inspection reports are submitted within established time frames. FDA indicated that if the agency could not find an individual to volunteer for a foreign inspection trip, it would mandate that travel. However, FDA has not typically sent investigators and laboratory analysts to countries for which the Department of State has issued a travel warning.⁵³ We found that 49 foreign establishments registered as manufacturers of drugs for the U.S. market were located in 10 countries that had travel warnings posted as of October 2007.⁵⁴ However, FDA officials told us that they have conducted inspections in countries with travel warnings. They also provided us with one example in which an establishment in a country with a travel warning hired security through the Department of State to protect the inspection team.

FDA also faces several logistical challenges in conducting inspections of foreign drug manufacturing establishments. FDA guidance states that inspections of foreign establishments are to be approached in the same manner as domestic inspections. However, the guidance notes that logistics pose a significant challenge to the inspection team abroad. For example, FDA is unable to conduct unannounced inspections of foreign drug establishments, as it does with domestic establishments. FDA policy states that the agency, with few exceptions, initiates inspections of establishments without prior notification to the specific establishment or its management so that the inspection team can observe the establishment under conditions that represent normal day-to-day activities. However, prior notification is routinely provided to foreign establishments. FDA officials noted that the time and expense associated with foreign travel require them to ensure that managers of the foreign establishments are available and that the production line being inspected is operational during the inspection. In addition, FDA often needs the permission of the foreign government prior to the inspection. FDA officials explained that in some cases investigators and laboratory analysts may need to obtain a visa or letters of invitation to enter the country in which the establishment is located. Furthermore, FDA does not have the same flexibility to extend

⁵³Travel warnings are issued when the Department of State recommends that Americans avoid travel to a certain country.

⁵⁴These 10 countries were Colombia, the Democratic Republic of the Congo, Haiti, Indonesia, Israel, Kenya, Nigeria, Pakistan, the Philippines, and Saudi Arabia.

the length of foreign inspection trips if problems are encountered as it does with domestic inspections because of the need to maintain the inspection schedule, which FDA officials told us typically involves inspections of multiple establishments in the same country. In our review of FDA inspection reports, we identified instances in which FDA was unable to fully complete inspections of foreign establishments in the allotted time. For example, in one instance, the FDA staff had a commitment to travel to another city to inspect another establishment. In this instance, an unexpected cancellation during that same trip allowed FDA staff to return to the establishment at a later date to complete the inspection.

FDA officials also told us that language barriers can make foreign inspections more difficult to complete than domestic inspections. The agency does not generally provide translators in foreign countries, nor does it require that foreign establishments provide independent interpreters. Instead, FDA staff may have to rely on an English-speaking employee of the foreign establishment being inspected, who may not be a translator by training, rather than rely on an independent translator. In our review of FDA inspection reports, we identified instances in which the translational support provided by an establishment created challenges. For example, an FDA investigator noted that during one inspection it was difficult to get an interpreter provided by the establishment to translate employee statements verbatim. FDA officials told us that while the presence of a translator is helpful, it is not necessary. They also pointed out that for inspections related to the review of a drug application, the establishment is required to submit its documentation in English.

Unclear if Recent FDA Proposals Will Address All Challenges Unique to Foreign Inspections

FDA has recently announced proposals to address some of the challenges unique to conducting foreign inspections, but the extent to which these proposals will improve FDA's program is unclear. FDA is exploring the creation of a cadre of investigators who would be dedicated to conducting foreign inspections.⁵⁵ FDA officials indicated that the agency plans to begin a pilot of the foreign cadre in early fiscal year 2009. As of July 2008, FDA had not yet begun recruiting investigators to participate in the foreign cadre, but officials expected the pilot group to consist of 15 investigators specializing in the inspection of drug establishments. An FDA official told

⁵⁵See Food and Drug Administration, *Revitalizing ORA: Protecting the Public Health Together In a Changing World* (Rockville, Md.: January 2008).

us, however, that it may recruit investigators specializing in other FDA-regulated products, such as food or medical devices, if it is unable to recruit 15 drug investigators. The official also stated that the foreign cadre will be composed of investigators who have experience conducting foreign inspections. FDA has indicated that it would take approximately 4 years before a newly hired investigator would be able to complete independent inspections of foreign drug manufacturing establishments. According to FDA, the full size of the foreign cadre will be determined in fiscal year 2010, taking lessons learned from the fiscal year 2009 pilot and resources into consideration.

FDA also recently announced plans to establish a permanent foreign presence overseas, although little information about these plans is available. Through an initiative known as “Beyond our Borders,” FDA intends to establish foreign offices to improve cooperation and information exchange with foreign regulatory bodies, improve procedures for expanded inspections, allow it to inspect facilities quickly in an emergency, and facilitate work with private and government agencies to assure standards for quality. FDA’s proposed foreign offices are intended to expand the agency’s capacity for regulating, among other things, drugs, medical devices, and food. The extent to which the activities conducted by foreign offices are relevant to FDA’s foreign drug inspection program is uncertain. Initially, FDA plans to establish a foreign office in China with three locations—Beijing, Shanghai, and Guangzhou—composed of a total of eight FDA employees and five Chinese nationals. The Beijing office, which the agency expects will be partially staffed by the end of 2008, will be responsible for coordination between FDA and the Chinese regulatory agencies. FDA staff located in Shanghai and Guangzhou, who the agency announced it will hire in 2009, will be focused on conducting inspections and working with Chinese inspectors to provide training as necessary. FDA has noted that the Chinese nationals will primarily provide support to FDA staff including translation and interpretation. The agency also plans to begin staffing offices in Central America, Europe, and India by the end of 2008 and in the Middle East in 2009. While the establishment of both a foreign inspection cadre and offices overseas has the potential for improving FDA’s oversight of foreign establishments and providing the agency with better data on foreign establishments, it is too early to tell whether these steps will be effective or will increase the number of foreign drug inspections.

Agreements with foreign governments, such as one recently reached with China’s State Food and Drug Administration as part of Beyond our Borders, may help the agency address certain logistical issues unique to

conducting inspections of foreign establishments.⁵⁶ We have noted that one challenge facing FDA involved the need for its staff to obtain a visa or letter of invitation to enter a foreign country to conduct an inspection. However, FDA officials told us that the agency's agreement with China recently helped FDA expedite this process when it learned of the adverse events associated with a Chinese heparin manufacturing establishment. According to these officials, the agreement with China greatly facilitated FDA's inspection of this establishment by helping the agency send investigators much more quickly than was previously possible.

Conclusions

Americans depend on FDA to ensure the safety and effectiveness of drugs marketed in the United States. More than 10 years ago we reported that FDA needed to make improvements in its foreign drug inspection program. Our current work indicates that flaws we identified at that time persist. The recent incident involving contaminated heparin sodium also underscores the need for FDA to obtain more information about foreign drug establishments, conduct more inspections overseas, and improve its overall management of this critical program. FDA recently announced initiatives that represent important steps for the agency and, if fully implemented, could address some of the concerns we identified in 1998 and reiterated in recent testimonies. However, given the growth in foreign drug manufacturing for the U.S. market and the large gaps in FDA's foreign drug inspection program, significant challenges—such as improving its data systems and increasing the rate of inspection—remain.

FDA's oversight of its foreign inspection program is hampered by inaccurate and inconsistent data on foreign establishments. An important component of selecting establishments for inspection is an accurate list of establishments subject to inspection, which currently is not readily available to the agency. To reduce the creation of duplicate counts in its import database, FDA supports the establishment of a unique governmentwide identifier for foreign establishments. Such an identifier has the potential to improve the accuracy of the data that FDA maintains on foreign drug manufacturing establishments, and FDA's continued exploration of this option is an important step to improving the accuracy of its data. However, the establishment and utilization of a unique governmentwide identifier would be dependent on the actions of multiple

⁵⁶For additional information about FDA's agreements with foreign regulatory bodies, see [GAO-08-701T](#).

agencies and would not provide an immediate solution to correcting the inaccuracies in FDA's databases. In addition, the agency's plan to institute electronic registration may provide FDA with a more efficient way to maintain information on each establishment, but it is unlikely to make a meaningful improvement in FDA's registration database by preventing erroneous registration and providing an accurate count of establishments subject to inspection. Enforcing the requirement that establishments update their registration annually, or biannually, as planned, is an important step towards keeping this database up to date. However, it is also important that FDA verify the information provided by establishments at the time of registration to ensure that establishments are appropriately registered. In addition, inconsistencies in databases that FDA uses to track inspections of foreign drug manufacturing establishments provide it with unreliable data on those establishments for which it identified serious manufacturing deficiencies. As a result, the different FDA staff responsible for oversight of these foreign establishments may not have ready access to accurate information on their compliance history when carrying out regulatory responsibilities.

Conducting additional surveillance inspections of foreign establishments manufacturing drugs currently marketed in the United States is vital, but FDA's selection of foreign establishments for inspection has instead been driven by the need to inspect establishments named in an application for a new drug. While these preapproval inspections are an important component of FDA oversight, without additional surveillance inspections FDA has little opportunity to monitor the ongoing compliance of establishments manufacturing drugs currently marketed in the United States. In addition, FDA has not utilized its risk-based process to select foreign establishments for inspection to the extent it has for selecting domestic establishments. However, both FDA's inspection classifications and issuance of warning letters indicate that deficiencies, including serious GMP deficiencies, are found in foreign establishments at least as often as in domestic ones. Therefore, it is important that FDA inspect foreign and domestic establishments with similar characteristics at comparable frequencies. A reassessment of FDA's inspection priorities could help the agency to ensure that it is frequently inspecting those establishments, foreign or domestic, that pose the greatest potential risk to public health should they experience a manufacturing defect.

Although foreign establishments have been responsive to FDA warning letters, the agency's subsequent inspections have often identified additional deficiencies. This points to the need for FDA to promptly inspect establishments with a history of serious deficiencies so problems do not go undetected for extended periods. FDA's plans to establish overseas offices and a cadre of investigators dedicated to foreign inspections are promising and have the potential to address many of the challenges unique to conducting foreign inspections. However, it is too early to tell whether these steps will be effective in improving the agency's foreign drug inspection program.

Recommendations for Executive Actions

To address weaknesses in FDA's oversight of foreign establishments manufacturing drugs for the U.S. market, we recommend that the Commissioner of FDA take the following five actions:

- Enforce the requirement that establishments manufacturing drugs for the U.S. market update their registration annually.
- Establish mechanisms for verifying information provided by the establishment at the time of registration.
- Ensure that information on the classification of inspections with serious deficiencies is accurate in all FDA databases.
- Conduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics.
- Conduct timely inspections of foreign establishments that have received warning letters to determine continued compliance.

Agency Comments and Our Evaluation

HHS reviewed a draft of this report and provided comments, which are reprinted in appendix II. HHS also provided technical comments, which we incorporated as appropriate. HHS commented on one of our recommendations and agreed that FDA should conduct more inspections of foreign establishments. It did not comment on the other four recommendations we made. HHS also stated that our report raises some important issues regarding FDA's foreign drug inspection program and noted that FDA has made efforts to improve this program.

HHS agreed that additional inspections are needed to strengthen its foreign drug inspection program. The agency did not provide a specific plan or timeframe for conducting additional foreign inspections. HHS noted that these inspections represent only one component of its overall strategy to enhance oversight of imported drugs. HHS also said that conducting foreign inspections based on the same criteria as domestic inspections is problematic because of challenges associated with foreign inspections. As we noted in our draft report, we recognize that inspections of foreign establishments pose unique challenges to FDA. Nevertheless, foreign and domestic establishments with characteristics that pose similar potential risks to public health need to be inspected at comparable frequencies. As we noted, FDA finds serious GMP deficiencies in foreign establishments at least as often as in domestic ones. Therefore, we believe that it is important for the agency to use its resources, in coordination with its other initiatives, to prioritize for inspection those establishments, whether they are located in the United States or a foreign country, that have the greatest potential to negatively impact public health.

HHS also elaborated on some of the initiatives to improve FDA's foreign drug inspection program that were discussed in our report—such as initiatives to improve FDA databases, establish foreign offices, and collaborate with foreign governments. In particular, HHS noted that as FDA implements electronic registration, it also plans to require establishments to update their registration at 6-month intervals, which is more frequent than is currently required. We have revised our report to reflect this proposed change. While requiring establishments to update their registration more often could enhance the accuracy of FDA's registration information, we remain concerned about the agency's enforcement of this provision. There is already a requirement for establishments to update this information annually, but FDA has not enforced it. FDA's proposal to direct establishments to update their registration information at more frequent intervals will only be meaningful if the agency takes steps to actively enforce this requirement.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days after its issue date. At that time, we will send copies of this report to the Commissioner of FDA and appropriate congressional committees. We will also make copies available to others on request. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix III.

A handwritten signature in black ink that reads "Marcia Crosse". The signature is written in a cursive style with a long horizontal line extending to the right.

Marcia Crosse
Director, Health Care

Appendix I: Scope and Methodology

To address our reporting objectives, we interviewed officials from several components of the Food and Drug Administration (FDA), including the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA). We also reviewed pertinent statutes and regulations as well as agency documents that provide guidance on conducting inspections and provide the basis for FDA's assessment of an establishment's compliance with current good manufacturing practice regulations (GMP). These documents included FDA's *Compliance Program Guidance Manuals; Guide to Inspection of Foreign Pharmaceutical Manufacturers; Investigations Operations Manual 2008; Regulatory Procedures Manual, March 2008; and Field Management Directives*. To obtain perspectives from relevant stakeholders, we also interviewed officials from the Generic Pharmaceutical Association, Pharmaceutical Research and Manufacturers of America, and Synthetic Organic Chemical Manufacturers Association.

To examine the extent to which FDA has accurate data on the number of foreign manufacturing establishments subject to inspection, we obtained information from FDA databases on establishments whose drugs have been imported into the United States. Specifically, we obtained data from CDER's Drug Registration and Listing System (DRLS) and ORA's Operational and Administrative System for Import Support (OASIS).

- From DRLS, we obtained counts of establishments registered with FDA in fiscal year 2007 to market drugs in the United States. We assessed the reliability of these data by (1) reviewing existing information about the data and the databases that produced them and (2) interviewing agency officials knowledgeable about the data. We found that DRLS was reliable for our purposes, to the extent that it accurately reflects information provided by foreign establishments that register to market drugs in the United States. However, we determined that these data do not necessarily reflect all foreign establishments whose drugs are imported into the United States.
- From OASIS, we obtained counts of establishments that offered drugs for import into the United States in fiscal year 2007. We also obtained fiscal year 2007 data from OASIS to determine the types of drugs manufactured in China and offered for import into the United States. We assessed the reliability of these data by (1) reviewing existing information about the data and the databases that produced them, (2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of data elements. We found that while OASIS is likely to overestimate the number of foreign establishments involved in the

manufacture of those drugs because of uncorrected errors in the data, it provides sufficiently reliable information about the types of drugs offered for import into the United States.

Therefore, we present information from both DRLS and OASIS to illustrate the variability in information that FDA's databases provide to agency officials on this topic. This represents the best information available and is what FDA relies on to manage its foreign drug inspection activities. We examined FDA's plans to improve these and other databases. We also obtained information from the Center for Devices and Radiological Health to learn about changes to one of its databases that address problems similar to CDER's problems with DRLS.

To examine the frequency of foreign inspections and factors influencing the selection of such establishments for inspection, we obtained data on foreign and domestic inspections from ORA's Field Accomplishments and Compliance Tracking System (FACTS). Our analysis includes all foreign and domestic inspections that were identified in FACTS as being either related to the drug application approval process or GMP. Our November 2007 testimony included the number of inspections from FACTS as of September 26, 2007.¹ Therefore, we obtained FACTS data that contained information on fiscal year 2007 inspections conducted or entered into this database since September 26, 2007, to update the data presented in our November 2007 testimony. We assessed the reliability of these data by (1) reviewing existing information about the data and the databases that produced them, (2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of data elements. We found these data from the FACTS database reliable for our purposes. In addition, we examined methods used by FDA to help it select foreign and domestic establishments for inspection, including its risk-based site selection process.

To examine FDA's response to serious deficiencies identified during inspections of foreign manufacturing establishments and FDA's monitoring of establishments' corrective actions and continued compliance, we examined data in two sources, FACTS and CDER's Office of Compliance Foreign Inspection Tracking System, which each contain information on how the agency classified establishments' compliance with agency requirements. We assessed the reliability of these data by

¹[GAO-08-224T](#), 15.

interviewing agency officials knowledgeable about the data and performing electronic testing to compare the data from each of these databases. We found that these databases sometimes presented inconsistent information about the final classification of foreign inspections. Therefore, we present data from these databases on inspection classification to illustrate the variability in information that FDA's databases provide to agency officials on this topic. We also reviewed case files provided by FDA that relate to inspections of foreign establishments conducted from fiscal years 2002 through 2007, during which FDA identified serious deficiencies and subsequently issued warning letters. The case files contained information about these establishments, their inspections, and their correspondence with FDA.

To examine issues unique to conducting foreign inspections, we reviewed FDA practices and policies related to the conduct of foreign inspections and interviewed FDA officials about these topics. We also obtained information about recent or proposed FDA initiatives that may have the potential to improve the agency's foreign drug inspection programs.

We conducted the work for this report from September 2007 through September 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Appendix II: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

SEP 02 2008

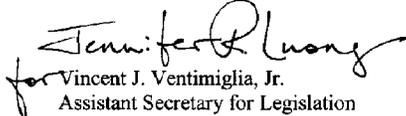
Marcia Crosse
Director, Health Care
441 G Street NW
U.S. Government Accountability Office
Washington, D.C. 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program" (GAO 08-970).

The Department appreciates the opportunity to comment on this draft before its publication.

Sincerely,


for Vincent J. Ventimiglia, Jr.
Assistant Secretary for Legislation

Attachment

COMMENTS OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "DRUG SAFETY: BETTER DATA MANAGEMENT AND MORE INSPECTIONS ARE NEEDED TO STRENGTHEN FDA'S FOREIGN DRUG INSPECTION PROGRAM" (GAO 08-970)

The Food and Drug Administration (FDA) appreciates the opportunity to review and comment on the Government Accountability Office's (GAO) draft report. GAO has raised some important issues regarding FDA's foreign drug inspection program. FDA strives continually to advance its public health mission, and this includes significant efforts to improve the foreign drug inspection program. As stated in the report's title, GAO is recommending that more inspections are needed to strengthen this program. Although FDA recognizes the need for additional risk-based targeted foreign inspections, this is only one component of FDA's overall strategy to enhance oversight of imported drugs. The overall approach is multi-faceted and includes conducting risk-based targeted inspections of foreign firms, working collaboratively with the importing community and state and local governments, reaching out to foreign producers, exporters and governments, improving information technology (IT), and expanding FDA's foreign presence. FDA believes that strategic use of resources for this multi-faceted approach to foreign firms, as opposed to simply increasing numbers of inspections, will provide the greatest public health protection. With our Import Safety Action Plan, FDA is adopting a strategy that shifts the primary emphasis for import safety from intervention to a risk-based "prevention with verification" model. GAO acknowledges that there are unique challenges to foreign inspections not present in the domestic arena. Therefore, the conclusion that FDA should endeavor to conduct foreign inspections based on the same criteria as domestic inspections is also problematic because of the differences in regulatory methodology and resources.

FDA has many initiatives underway focused on improving the foreign drug inspection program. The FDA "Beyond Our Borders" initiative is a multi-pronged approach to promote and verify compliance of imported food, cosmetics, and medical products with FDA requirements. Key components of this initiative are establishing an FDA presence in China, India, Latin America, Europe and the Middle East; increased FDA inspections; greater laboratory capacity; greater sharing and use of foreign regulatory authority inspection reports and other information; use of third party certification; and increased capacity building with countries that have less developed regulatory systems to ensure product safety. FDA plans to establish offices in several countries around the world, starting with China and India. On July 25, 2008, seven new positions within FDA's China Office were announced in addition to the previously selected country director. Consumer safety officer positions in India were also recently announced. These positions demonstrate FDA's efforts toward a more global approach to our regulatory responsibilities. FDA also plans to establish a foreign inspection cadre, which will consist of highly qualified consumer safety officers with relevant skills and experience to conduct foreign inspections. The supervisory position in the Division of Field Investigations for the cadre has also been announced.

FDA also has several plans to enhance its IT systems in ways that will enable the Agency to better utilize risk-based information from the entire life-cycle of imported products. These projects will improve databases, enhance interoperability of systems within the Agency and among other regulatory agencies, and provide better analytical function to assess and control risk. The following are specific examples of ongoing IT projects:

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- One of many activities proceeding under the auspices of the Bioinformatics Board and in particular the Product Quality Business Review Board is the Harmonized Inventory project, which is bringing together many databases to have a common identifier for each establishment, a problem most acute for foreign establishments.
- The Center for Drug Evaluation and Research (CDER) is working vigorously to establish electronic Drug Registration and Listing (eDRLS) which will, among other things, require firms to update their registration electronically every 6 months to be active. Overall, these efforts will modernize our databases to prevent outdated, inaccurate, and duplicative information.
- CDER has recently published a draft guidance on eDRLS which is piloting its use prior to the actual regulatory implementation date. One of the features of this pilot will be to have establishments enter their Dun and Bradstreet number (DUNS) to serve as a recognized identifier to avoid duplications and error. The link to this draft guidance is provided here -- <http://www.fda.gov/cder/guidance/OC2008145.htm>.

All of these activities will improve FDA's ability to ensure the safety and efficacy of human drugs, regardless of where they are manufactured.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

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Acknowledgments

In addition to the contact named above, Geraldine Redican-Bigott, Assistant Director; Katherine Clark; Andrew Fitch; William Hadley; Cathleen Hamann; Julian Klazkin; Daniel Ries; and Monique B. Williams made key contributions to this report.

Related GAO Products

Medical Devices: FDA Faces Challenges in Conducting Inspections of Foreign Manufacturing Establishments. [GAO-08-780T](#). Washington, D.C.: May 14, 2008.

Drug Safety: Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program. [GAO-08-701T](#). Washington, D.C.: April 22, 2008.

Medical Devices: Challenges for FDA in Conducting Manufacturer Inspections. [GAO-08-428T](#). Washington, D.C.: January 29, 2008.

Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers. [GAO-08-224T](#). Washington, D.C.: November 1, 2007.

Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program. [GAO/HEHS-98-21](#). Washington, D.C.: March 17, 1998.

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