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DRUG SAFETY

Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

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Highlights of [GAO-08-224T](#), a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

Many drugs marketed in the United States are manufactured in foreign countries and the value of such products entering the country is increasing. The Food and Drug Administration (FDA) is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments. Foreign establishments that market their drugs in the United States must register with FDA and FDA inspects foreign establishments to ensure that they meet the same standards that are required of domestic ones. GAO reported 9 years ago that FDA needed to improve its foreign drug inspection program ([GAO/HEHS-98-21](#)). Questions remain as to whether FDA has improved its management of the foreign drug inspection program.

This statement discusses preliminary information on (1) the extent to which FDA has accurate data to manage the foreign drug inspection program, (2) the frequency of foreign inspections and factors influencing the selection of establishments to inspect, and (3) issues unique to conducting foreign inspections. To address these issues GAO interviewed FDA officials; reviewed pertinent statutes, regulations, and guidance; and analyzed information from FDA databases. Because of the preliminary nature of our work, we are not making recommendations at this time.

To view the full product, including the scope and methodology, click on [GAO-08-224T](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

DRUG SAFETY

Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers

What GAO Found

FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its databases. FDA does not know how many foreign establishments are subject to inspection. Instead, FDA relies on databases that were not designed for this purpose. Further, these databases contain inaccuracies that FDA cannot easily reconcile. One database indicates there were about 3,000 foreign establishments registered to market drugs in the United States in fiscal year 2007, while another indicates that about 6,800 foreign establishments actually imported drugs in that year. FDA recognizes these flaws. Further, because the databases cannot exchange information, any comparisons of the data are performed manually, on a case-by-case basis. FDA officials told GAO that they have not generated an accurate count of foreign establishments whose drugs are imported into the United States.

FDA inspects relatively few foreign establishments. Data from FDA suggest that the agency may inspect about 7 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that no additional establishments require inspection. However, FDA cannot provide an exact number of foreign establishments that have never been inspected. Most of the foreign inspections performed are conducted as part of a review associated with processing an application to market a new drug, rather than inspections for monitoring the quality of marketed drugs. Although FDA uses a risk-based process to develop a prioritized list of foreign establishments for inspections to monitor the quality of marketed drugs, few are completed in a given year. This prioritized list was used to select foreign establishments for inspection in fiscal year 2007. According to FDA, about 30 such inspections were completed in that year and at least 50 are targeted for inspection in fiscal year 2008.

The foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections to monitor the quality of a marketed drug, FDA does not arrive unannounced at a foreign establishment. 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 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.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you examine the Food and Drug Administration's (FDA) inspections of foreign drug manufacturers whose products are imported into the United States. In 1998, we reported that FDA needed to improve its foreign drug inspection program.¹ Among other things, we noted that FDA had serious problems managing its foreign inspection data and that it lacked a comprehensive automated system for tracking this important information. We were also critical of the number of inspections FDA conducted at foreign manufacturers. At that time, FDA reported on our growing dependence on imported pharmaceutical products, noting that as much as 80 percent of the bulk drug substances² used by manufacturers in the United States to produce prescription drugs was imported and that the number of finished drug products manufactured abroad for the U.S. market was increasing. Today, we are still dependent on foreign establishments³ manufacturing drugs for the U.S. market as the value of pharmaceutical products coming into the United States from abroad continues to increase.⁴

Given the importance of FDA's foreign drug inspection program, you expressed concern about FDA's ability to oversee foreign establishments manufacturing drugs and asked whether FDA has improved its management of the foreign drug inspection program since our previous report was issued. My testimony today will summarize preliminary findings from our ongoing work to update our 1998 report. My remarks will focus on (1) the extent to which FDA has accurate data to manage its foreign drug inspection program, (2) the frequency of foreign inspections and factors influencing the selection of establishments to inspect, and (3) issues unique to conducting foreign inspections.

¹GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, [GAO/HEHS-98-21](#) (Washington, D.C.: Mar. 17, 1998).

²A bulk drug substance is any substance that is represented for use in a drug that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished drug product. 21 C.F.R. § 207.3(a)(4)(2007).

³FDA 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.

⁴According 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.

To address these issues, we interviewed officials from FDA's Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing the foreign drug inspection program. We 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 practices (GMP).⁵ These documents included FDA's Compliance Program Guidance Manuals, its Guide to Inspections of Foreign Pharmaceutical Manufacturers, and its Investigations Operations Manual 2007. We also obtained information from FDA databases on establishments whose drugs have been imported into the United States. Specifically, we obtained data from the Drug Registration and Listing System (DRLS), the Field Accomplishments and Compliance Tracking System (FACTS), and the Operational and Administrative System for Import Support (OASIS). 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 from FACTS. We found the data in the FACTS database reliable for our purposes. We also found that DRLS was reliable, 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. In addition, we found that OASIS is likely to over-estimate the number of foreign establishments whose drugs have been imported into the United States, due to uncorrected errors in the data. 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. Our ongoing work is focused on human drugs regulated by CDER and not on biologics,⁶ medical devices, veterinary medicines, or other items or products for which FDA conducts inspections. We received technical comments on a draft of this statement from FDA, which we incorporated as appropriate.

⁵GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality products. See 21 C.F.R. pts. 210, 211 (2007).

⁶Biologics are materials, such as vaccines, derived from living sources such as humans, animals, and microorganisms. Some biologics are regulated by CDER and inspections related to those products are included in our work.

Our work is being performed in accordance with generally accepted government auditing standards.

In summary, our preliminary results indicate that more than 9 years after we issued our last report on this topic, FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its data systems. FDA does not know how many foreign establishments are subject to inspection. FDA relies on information from several databases that were not designed for this purpose. One of these databases contains information on foreign establishments that have registered to market drugs in the United States, while another contains information on drugs imported into the United States. One database indicates about 3,000 foreign establishments could have been subject to inspection in fiscal year 2007, while another indicates that about 6,800 foreign establishments could have been subject to inspection in that year. Despite the divergent estimates of foreign establishments subject to inspection generated by these two databases, FDA does not verify the data within each database. For example, the agency does not routinely confirm that a registered establishment actually manufactures a drug for the U.S. market. However, FDA used these data to generate a list of 3,249 establishments from which it prioritized establishments for inspection.

Because FDA is not certain how many foreign establishments are actually subject to inspection, the percentage of foreign establishments that have been inspected cannot be calculated with certainty. We found that FDA inspects relatively few foreign establishments. Using the list of 3,249 establishments from which FDA prioritized establishments for inspection, we found that the agency may inspect about 7 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. FDA cannot provide the exact number of foreign establishments that have never been inspected. Most of the foreign inspections are conducted as part of processing a new drug application (NDA) or an abbreviated new drug application (ANDA),⁷ rather than as GMP surveillance inspections, which are used to monitor the quality of marketed drugs. Although FDA used a risk-based process to develop a prioritized list of foreign establishments

⁷FDA must approve an NDA in order for a new drug product to be marketed in the United States; approval for a generic drug is sought through an ANDA. FDA also reviews scientific and clinical data contained in these applications, as part of its process in considering them for approval to be marketed.

for GMP surveillance inspections in fiscal year 2007, few such inspections are completed in a given year. According to FDA, about 30 such inspections were completed in fiscal year 2007 and at least 50 are targeted for inspection in fiscal year 2008. Further, the data on which this risk-based process depends limits its effectiveness.

Finally, the very nature of the foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA does not have a dedicated staff to conduct foreign inspections and relies on those inspecting domestic establishments to volunteer. While FDA may conduct unannounced GMP surveillance 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.

Because of the preliminary nature of our work, we are not making recommendations at this time.

Background

FDA is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments.⁸ Foreign establishments that market their drugs in the United States must register with FDA. As part of its efforts to ensure the safety and quality of imported drugs, FDA is responsible for inspecting foreign establishments whose products 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 foreign and domestic inspections differ. Specifically, FDA is required to inspect registered domestic establishments

⁸FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. See 21 C.F.R. § 207.3(a)(8) (2007).

that have been previously approved to market their drugs in the United States every 2 years,⁹ but there is no comparable requirement for inspecting foreign establishments. FDA does not have authority to require foreign establishments to allow the agency to inspect their facilities. However, FDA has the authority to conduct physical inspections of the imported product or prevent its entry at the border.

Within FDA, CDER sets standards for and evaluates the safety and effectiveness of prescription drugs and over-the-counter 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 finished drug products. CDER also requests inspections of those that produce bulk drug substances, including the active pharmaceutical ingredients (API)¹⁰ used in finished drug products. These inspections are performed by investigators and laboratory analysts.¹¹ ORA conducts two primary types of inspections¹²:

- Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States. These inspections occur following FDA's receipt of an NDA or ANDA and focus on the manufacture of a specific drug product. Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications and ensures that the manufacturer of the finished drug product, as well as each manufacturer supplying a bulk drug substance used in the finished

⁹21 U.S.C. § 360(h).

¹⁰An 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. According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis. 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.

¹¹ORA investigators lead inspections. They are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing.

¹²FDA may also conduct other postapproval inspections, such as to address adverse events associated with a particular drug. In addition, FDA conducts for-cause inspections when it receives information indicating problems in the manufacture of approved drug products, as well as when it follows up on manufacturers that were not in compliance with GMPs during previous inspections.

product, manufactures, processes, and packs the drug adequately to preserve its identity, strength, quality, and purity.

- Postapproval GMP surveillance inspections are conducted to ensure compliance with applicable laws and regulations pertaining to the manufacturing processes used by domestic and foreign establishments in the manufacture of finished drug products marketed in the United States and bulk drug substances used in the manufacture of those products. These inspections focus on a manufacturer's systemwide controls for ensuring that drug products are high in quality. Systems examined during these inspections include those related to quality control, production, and packaging and labeling. These systems may be involved in the manufacture of multiple drug products.

FDA allocates funds to ORA to carry out preapproval and postapproval inspections of foreign and domestic establishments. ORA develops an annual work plan and a budget that estimates human resources available to conduct activities related to foreign inspections. ORA also develops estimates for inspections of domestic establishments. Typically, ORA investigators and laboratory analysts travel abroad for about 3 weeks at a time, during which they inspect approximately three establishments. Each establishment inspection typically lasts a week, with 1 day of each week set aside for documenting the inspection or for extending the inspection, if necessary.

CDER uses a risk-based process to select some domestic and foreign establishments for postapproval GMP surveillance inspections. According to an FDA report,¹³ 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.¹⁴ The process uses a risk model to identify those establishments that, based on characteristics of the establishment and of the product being manufactured, have the greatest public health risk potential should they experience a manufacturing defect. (See table 1 for a description of the risk-based site selection model

¹³Department 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 Oct. 21, 2007).

¹⁴Previously, FDA used other less formal risk-based systems to prioritize its inspections. For example, we noted in our 1998 report that FDA had used a risk-based site selection system, in which it classified establishments according to risk tiers. See [GAO/HEHS-98-21](#).

used by FDA in fiscal year 2007.) For example, FDA considers the risk to public health from poor quality over-the-counter drugs to be lower than for prescription drugs, and consequently establishments manufacturing only over-the-counter drugs receive a lower score on this factor than other manufacturers. Through this process, CDER annually prepares a prioritized list of domestic establishments and a separate, prioritized list of foreign establishments. CDER began applying this risk-based process to domestic establishments in fiscal year 2006 and expanded it to foreign establishments in fiscal year 2007.

Table 1: Summary of Factors in FDA’s Risk-Based Site-Selection Model in Fiscal Year 2007

Category of factor	Description	Example(s)
Product	Factors pertaining to the intrinsic properties of drug products such that quality deficiencies could potentially and adversely affect public health	FDA considers establishments manufacturing prescription drugs, as opposed to only over-the-counter drugs, to be higher risk
Process	Factors pertaining to aspects of drug manufacturing operations that may predict potential difficulties with process control or vulnerability to various forms of contamination	FDA considers establishments manufacturing small-volume drugs administered intravenously to be higher risk than those manufacturing prompt release tablets, because of the greater risk of contamination associated with the manufacture of small-volume intravenous products
Facility	Factors relating to characteristics of a manufacturing site believed to be predictive of potential quality risks	FDA considers establishments that have not had a recent GMP inspection to be higher risk than those that have received a recent GMP inspection

Source: GAO analysis of FDA’s risk model.

FDA relies on multiple databases to manage the foreign drug inspection program. FDA assigns unique numeric identifiers to establishments, known as the FDA establishment identifier (FEI) number. An FEI number could be assigned at the time of registration, importation, or inspection.

- DRLS contains information on foreign and domestic drug establishments that have registered with FDA. Establishments that market their drugs in the United States must register with FDA. These establishments provide information, such as company name and address and the drug products they manufacture for commercial distribution in the United States, on paper forms that are entered into DRLS by FDA.

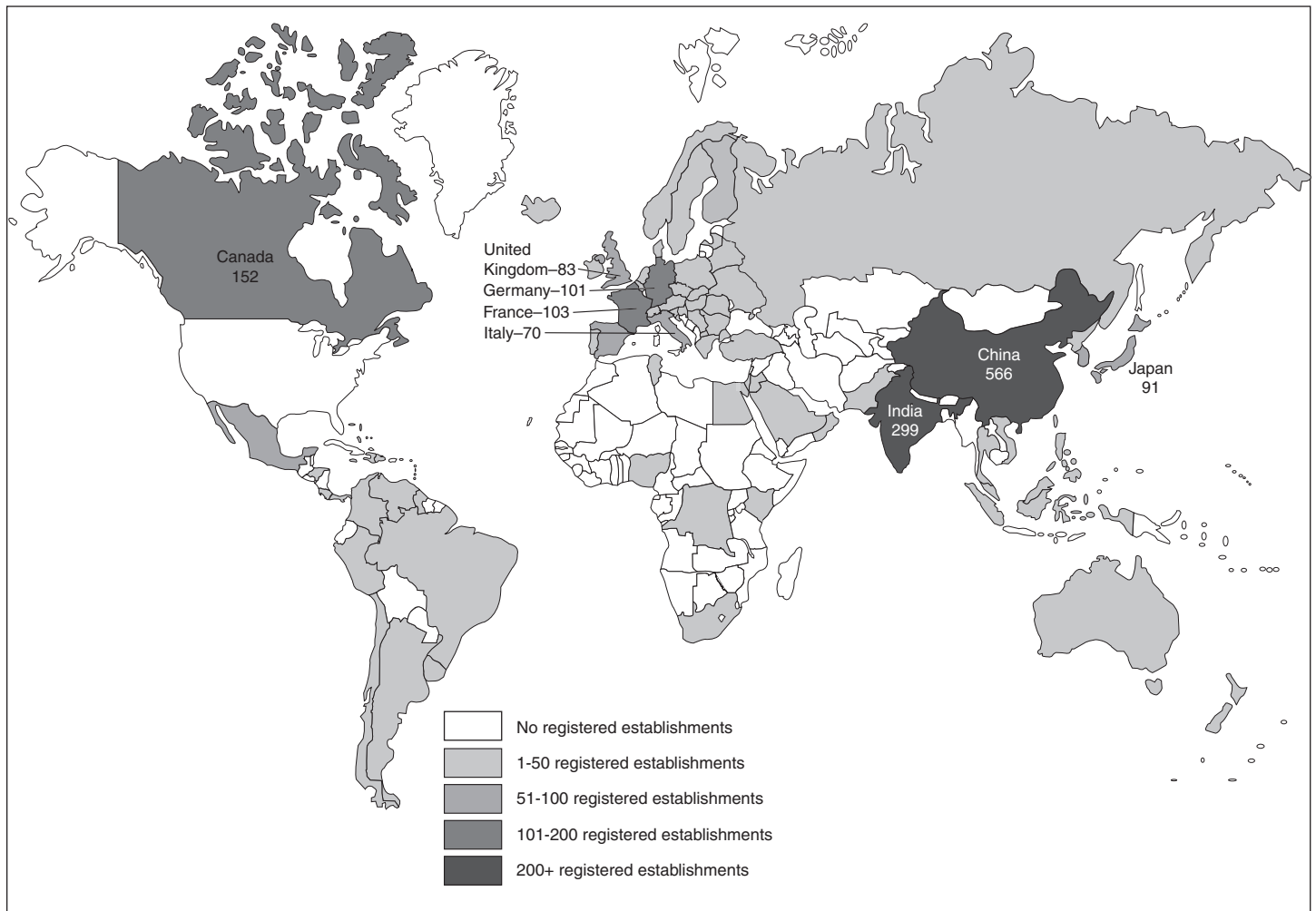
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- OASIS contains information on drugs and other FDA-regulated products imported into the United States, including information on the establishment that manufactured the drug. The information in OASIS is automatically generated from data managed by U.S. Customs and Border Protection, which are originally entered by customs brokers based on the information available from the importer.¹⁵ Each establishment is assigned a manufacturer identification number that is generated from key information entered about an establishment's name, address, and location.
 - FACTS contains information on FDA's inspections of domestic and foreign drug establishments. FDA investigators and laboratory analysts enter information into FACTS, following completion of an inspection.

According to DRLS, in fiscal year 2007, China and India had more establishments registered to manufacture drugs for the U.S. market than any other country.¹⁶ Other countries that had a large number of establishments registered to manufacture drugs for the U.S. market in this year were Canada, France, Germany, Italy, Japan, and the United Kingdom. (See fig. 1.) These countries are also listed in OASIS as having the largest number of manufacturers importing drugs into the United States.

¹⁵Customs brokers are private individuals, partnerships, associations, or corporations licensed, regulated, and empowered by U.S. Customs and Border Protection to assist in meeting federal requirements governing imports and exports.

¹⁶These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

Figure 1: Foreign Establishments Registered to Manufacture Drugs for the U.S. Market, by Country, Fiscal Year 2007



Source: GAO analysis of FDA data.

Note: These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments 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; including the number of establishments that are registered and whose products are currently imported into the United States and establishments that are not required to register but whose products are ultimately used in drugs that are marketed here. Instead of maintaining a list of such establishments, FDA relies on information from several databases that were not designed for this purpose.

DRLS, established in 1991, is intended to list the establishments registered that manufacture drugs for the U.S. market. However, requirements for the registration of foreign establishments were not implemented until 2002.¹⁷ FDA expected that requiring foreign establishments to register would provide it with a comprehensive list of such establishments. In fiscal year 2007, approximately 3,000 foreign establishments were registered with FDA that manufactured human drugs, biologics, or veterinary drugs; FDA was unable to determine from this database the number of registered establishments specifically manufacturing human drugs.

DRLS provides FDA with some information about establishments subject to inspection, but contains inaccuracies and does not provide a complete count. FDA officials told us that the count of registered foreign establishments in DRLS does not reflect the actual number whose products are being imported into the United States for several reasons. First, 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. Second, foreign establishments may not renew their registration information, although they are required by FDA to do so annually. Agency officials told us that if foreign establishments stop manufacturing drugs for the U.S. market or go out of business they may not report the change to FDA, even though it is required. FDA officials told us that the agency does not routinely verify the information provided by the establishment to ensure that it is accurate or confirm that the establishment actually manufactures

¹⁷See Pub. L. No. 105-115, §§ 417, 501, 111 Stat. 2296, 2379-80. FDA issued implementing regulations in 2001, which were effective February 11, 2002. 66 Fed. Reg. 59138 (Nov. 27, 2001).

drugs for the U.S. market.¹⁸ FDA does not know how many foreign establishments are erroneously registered. Third, foreign establishments that manufacture APIs are not required to register if their products are not directly imported into the United States.¹⁹

OASIS also provides FDA with some information about establishments subject to inspection, but this database contains inaccurate data on the count of foreign establishments manufacturing drugs imported into the United States. According to OASIS, 6,760 foreign establishments manufactured drugs that were imported into the United States in fiscal year 2007. However, FDA officials told us that errors in data entry result in inaccurate counts of establishments whose drugs are imported into the United States. FDA officials told us that if information about an establishment—such as its name—was entered by customs brokers incorrectly, a new manufacturer identification number, and thus a new FEI number, could be assigned to an establishment that already has an FEI number. For example, a customs broker may enter an establishment’s name slightly differently from the way it is displayed in OASIS, such as using “Inc.” instead of “Incorporated,” which would lead to the creation of a second FEI number for the establishment. Therefore, a single establishment may be counted more than once in OASIS, which would result in an artificially high count of foreign establishments importing drugs into the United States. FDA officials acknowledge this problem but were unable to provide us with an estimate of the extent of that error. 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 regional training to brokers as a way to improve accuracy. FDA officials also told us that the agency is pursuing a new government-wide initiative that would address this problem by providing a unique identifier for each foreign establishment involved in the import supply chain.

FDA’s data suggest that between 3,000 and 6,760 establishments could be subject to FDA inspection. However, FDA officials told us that the two

¹⁸If the agency learns of an error, it would ask the establishment to submit corrected information.

¹⁹For 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.

databases—DRLS and OASIS—cannot be electronically integrated or interact with one another, so any comparisons are done manually for each individual establishment. Because comparisons of the data and error identification are done manually, the databases are not conducive to routine data analysis. FDA officials told us that they have not generated an accurate count of the establishments whose drugs are imported into the United States.

Because FDA does not have a list of all foreign establishments subject to inspection, in fiscal year 2007 it created a list of such establishments for the purpose of applying its risk-based process.²⁰ In preparing this list, FDA draws on information from DRLS. It also obtains information from previous inspections to help it identify establishments that are subject to inspections but are not required to register—such as the manufacturer of an API whose product is not directly imported into the United States. For fiscal year 2007, this list consisted of 3,249 foreign establishments. However, as a result of the inaccuracies in DRLS, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

²⁰In addition to establishments identified for the purposes of conducting its risk-based analysis, FDA also identifies establishments subject to inspection that are named in NDAs or ANDAs using its Establishment Evaluation System database. This database identifies the multiple establishments involved in drug manufacturing, including the establishments manufacturing a finished product for import into the United States and the establishments manufacturing any APIs for that finished product.

FDA Conducts Relatively Few Foreign Establishment Inspections and Relies on the NDA and ANDA Review Process as the Primary Selection Factor

FDA conducts relatively few inspections of foreign drug establishments. However, because FDA is not certain how many foreign establishments are actually subject to inspection, the percentage of foreign establishments that have been inspected cannot be calculated with certainty. Most foreign establishments are selected for inspection as part of the agency's review process associated with an NDA or ANDA. Therefore, the vast majority of foreign inspections include a preapproval inspection. In addition, although FDA has implemented a risk-based process in selecting foreign establishments for GMP surveillance inspections, relatively few such inspections are conducted. FDA tries to make efficient use of its resources by selecting establishments for these inspections that allow it to coordinate travel with preapproval inspections.

Relatively Few Foreign Establishments Are Inspected by FDA Each Year

In each year we examined, FDA inspected a small portion of foreign establishments through either preapproval or GMP surveillance inspections. However, its lack of a list of foreign establishments subject to inspection makes it difficult to determine an exact percentage. Based on our review of data on inspections, FDA conducted an average of 241 foreign establishment inspections per year from fiscal year 2002 through fiscal year 2007.²¹ Comparing this average number of inspections with FDA's count of 3,249 foreign establishments it used to plan its fiscal year 2007 prioritized GMP surveillance inspections suggests that the agency inspects about 7 percent of foreign establishments in a given year. 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.

FDA's data indicate that some foreign drug manufacturers have not received an inspection, but the exact number of establishments not inspected was 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

²¹Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year. Our analysis includes all foreign and domestic inspections that were identified in FDA's data as being either related to the drug application approval process or GMP. It does not include a small number of other inspections, such as those related to problems identified by consumers or health care professionals.

registered establishments whose drugs are being imported into the United States that have never been inspected but also included other types of establishments, such as those whose products 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 surveillance inspection since fiscal year 2000,²² and 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 from fiscal year 2000 through fiscal year 2002.

FDA has increased the number of foreign establishments it inspects, most of which are concentrated in a small number of countries. From fiscal year 2002 through fiscal year 2007, the number of foreign establishment inspections FDA conducted annually varied from year to year, but increased overall from 222 in fiscal year 2002 to 295 in fiscal year 2007. During this period, FDA inspected establishments in a total of 51 countries. More than three quarters of the 1,445 foreign inspections the agency conducted during this period were of establishments in ten countries, as shown in table 2. The country with the most inspections during this period was India, which had 200 inspections. Inspections of establishments located in India increased from 11 in fiscal year 2002 to 65 in fiscal year 2007.

²²According to FDA officials, some of these establishments may have received an inspection for another type of product, such as a veterinary drug.

Table 2: 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 Year 2002 through Fiscal Year 2007

Country	Number of inspections						Total	Number of establishments ^b
	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007 ^a		
India	11	19	38	33	34	65	200	410
Germany	24	15	35	25	19	22	140	199
Italy	17	30	26	21	18	19	131	150
Canada	29	12	17	23	23	19	123	288
United Kingdom	19	22	15	18	15	13	102	169
France	14	15	13	12	16	24	94	162
China	11	9	17	21	17	13	88	714
Japan	11	13	14	21	13	15	87	196
Switzerland	12	12	11	17	9	14	75	83
Ireland	11	5	11	14	3	11	55	61
All other countries	63	38	63	61	45	80	350	817
Total	222	190	260	266	212	295	1,445	3,249

Source: GAO analysis of FDA data.

^aInspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

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

The Need to Conduct Preapproval Inspections Associated with NDAs and ANDAs Drives FDA's Selection of Foreign Establishments

While enforcing GMP compliance through surveillance inspections is FDA's most comprehensive program for monitoring the quality of marketed drugs, FDA's inspections of most foreign establishments occur as part of the agency's review of an NDA or ANDA. Agency officials said that FDA may need to inspect establishments involved in the manufacture of the drug referenced in an NDA or ANDA in order to meet specific goals for the timely review of these applications. As we reported in 1998 and we still found in 2007, most inspections of foreign manufacturers occur only when they are listed in an NDA or ANDA. For fiscal years 2002 through 2007, 88 percent of FDA's inspections of foreign establishments were conducted as part of the preapproval process. When FDA receives an NDA or ANDA, CDER officials review the inspection history of each establishment listed on the application. According to FDA officials, if an establishment listed on the NDA or ANDA has received a satisfactory GMP inspection in the previous 2 years and the agency has no new concerns,

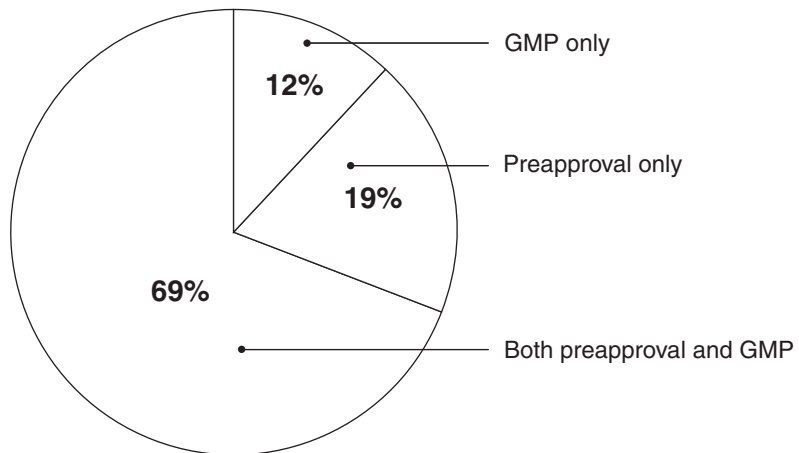
FDA will consider this inspection sufficient and will not perform a preapproval inspection of this establishment.²³

FDA often includes a GMP inspection when it visits an establishment for a preapproval inspection. As presented in figure 2, from fiscal year 2002 through fiscal year 2007, the majority of FDA's foreign inspections combined a preapproval inspection with a GMP inspection. According to FDA officials, because foreign establishments are inspected infrequently, it is expedient for investigators and laboratory analysts to conduct preapproval inspections and GMP inspections during the same visit to a foreign establishment. During one establishment visit, FDA investigators can conduct inspections related to multiple compliance programs.²⁴ Because a GMP surveillance inspection examines the major manufacturing systems at an establishment, the results of such an inspection can be generalized to all products 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 again in another NDA or ANDA.

²³ According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis. 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.

²⁴ Compliance programs outline procedures for conducting different types of inspections, including preapproval inspections for drugs that are the subject of an NDA or ANDA, drug manufacturing inspections, and drug repacker and relabeler inspections.

Figure 2: FDA Foreign Establishment Inspections by Type of Inspection, Fiscal Year 2002 through Fiscal Year 2007

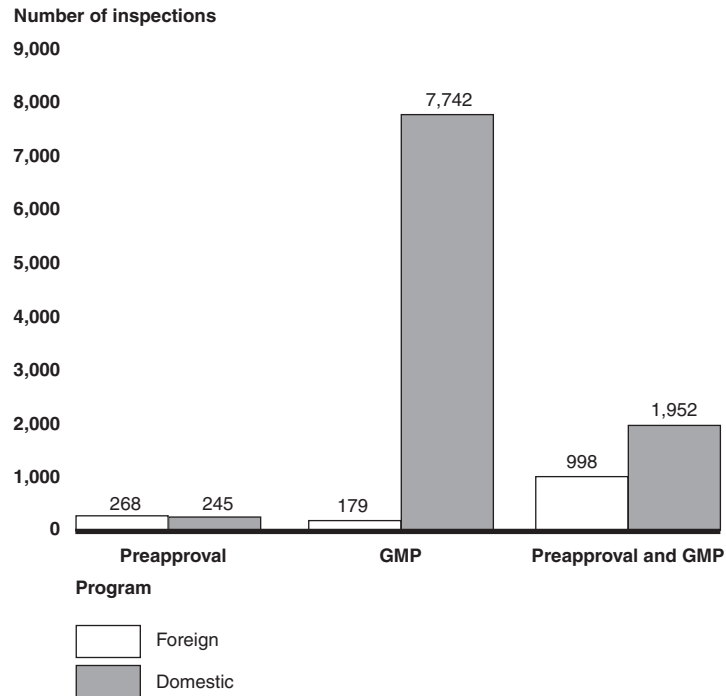


Source: GAO analysis of FDA data.

Note: Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA conducts fewer GMP surveillance inspections of foreign establishments than it does of domestic ones. Of the 1,445 foreign establishment inspections conducted from fiscal year 2002 through fiscal year 2007, 1,177 inspections included a GMP component, of which 998 were conducted in conjunction with a preapproval inspection. In contrast, FDA conducted 9,694 domestic establishment inspections that included a GMP component, of which 7,742 were not conducted in conjunction with a preapproval inspection. Figure 3 shows a comparison of foreign and domestic inspections, by type of inspection.

Figure 3: Number of FDA Foreign and Domestic Establishment Inspections, by Type of Inspection, Fiscal Year 2002 through Fiscal Year 2007



Source: GAO analysis of FDA data.

Note: Inspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA's funding for its domestic and foreign inspection programs is consistent with this approach. From fiscal year 2002 through fiscal year 2007, FDA dedicated more funding to domestic establishment inspections than foreign establishment inspections. The agency dedicated more funding to conduct foreign preapproval inspections than foreign GMP surveillance inspections, as shown in table 3.

Table 3: FDA Funding for Foreign and Domestic Inspections Related to Human Drugs, Fiscal Year 2002 through Fiscal Year 2007

Activity (dollars in thousands)	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007 ^a
Foreign						
Preapproval inspections	\$8,274	\$8,515	\$8,406	\$8,604	\$7,544	\$7,558
Postapproval inspections	5,256	5,177	5,150	5,224	5,261	5,191
Domestic						
Preapproval inspections	21,846	23,008	23,965	25,213	21,775	23,532
Postapproval inspections	23,102	28,601	27,989	28,270	27,607	28,452

Source: GAO analysis of FDA data.

^aFiscal year 2007 funding is estimated.

FDA's Risk-Based Process Is Used to Select Relatively Few Foreign Establishments for GMP Surveillance Inspections

Relatively few foreign establishments identified through CDER's risk-based site selection process are selected for GMP surveillance inspections. 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. Of these, CDER requested that ORA complete GMP surveillance inspections of 25 establishments and FDA officials estimated that about 30 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 negotiated target of at least 50 inspections.

The application of the risk-based site selection process does not ensure that the foreign establishments posing the greatest potential risk are selected for GMP surveillance inspections. First, FDA officials acknowledge that they do not have an accurate list of foreign establishments manufacturing drugs for the U.S. market to use in the application of the risk-based process. Second, the usefulness of the risk-based process is weakened by the incomplete and possibly inaccurate information on those foreign establishments that FDA has not inspected recently, as well as those that have never been the subject of a GMP surveillance inspection. As a consequence, FDA lacks sufficient data to make an accurate assessment of the potential risk of such establishments. FDA recognized the effect of such data limitations on the domestic application of the risk-based process and undertook a data quality improvement initiative in fiscal year 2005, but it has yet to make a comparable effort to improve its data on foreign establishments.

To help account for the differences in information available to FDA between foreign establishments that have and have not been inspected, the agency categorizes establishments into one of three groups for the purposes of examining risk scores: (1) those that have received a GMP surveillance inspection since fiscal year 2000; (2) those that have not received a GMP surveillance inspection since fiscal year 2000, but have received another type of inspection in that time (for example, a preapproval inspection or a veterinary drugs inspection); and (3) those that may never have received an inspection.²⁵ These groups were created to account for limitations in the data and are not designed to indicate relative risk among groups. FDA officials told us that risk scores can be more readily compared within a group, than among groups. In 2007, FDA selected 33 establishments from the first group, 31 from the second group, and 40 from the third group to create the list of 104 establishments it submitted to ORA.

FDA officials indicated that they do not know if the establishments on the prioritized list forwarded to ORA differ significantly from each other in risk level. Consequently, they do not necessarily select the highest ranked establishments and therefore consider the locations of other planned inspections in making a final determination of foreign establishments from the prioritized list for GMP surveillance inspections. According to FDA officials, this gives them needed flexibility to make selections that will make efficient use of available resources. For example, if ORA is sending an investigator and laboratory analyst to a particular region in China for a preapproval inspection and an establishment in the same region appears on the prioritized list for GMP surveillance inspections, ORA might add this establishment to the inspection itinerary.

²⁵This third group may include registered establishments whose drugs are imported into the United States. However, some establishments in this group may have received an inspection under a different FEI number, be shippers rather than manufacturers, only manufacture products other than human drugs, or never have or no longer have their drugs imported. FDA was unable to provide counts of how many establishments fall into each of these subcategories.

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. For example, unlike domestic inspections, FDA does not have a dedicated staff devoted to conducting foreign inspections and relies on volunteers. In addition, unlike domestic GMP surveillance inspections, foreign establishment GMP 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.

According to FDA officials, the agency does not have a dedicated staff to conduct foreign inspections. They 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 to conduct inspections of foreign establishments. For example, they are required to take certain training courses and have at least 3 years of experience conducting domestic inspections before they can be considered to conduct a foreign inspection. FDA reported that it currently has approximately 335 employees who are qualified to conduct foreign inspections of drug manufacturers. Approximately 250 of these employees are investigators and 85 are laboratory analysts. These counts do not represent the number of individuals that 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 others may perform multiple inspections during the same period. Using data from FACTS, we found that the total number of employees conducting pre-approval and GMP surveillance inspections of drug manufacturing establishments, either foreign or domestic, decreased from 587 in fiscal year 2002 to 446 in fiscal year 2007, as shown in table 4. However, of these, the number of employees who conducted foreign inspections of drug manufacturers increased from 100 to 141 during that same period. While an investigator and 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.

Table 4: Number of FDA Employees Conducting Inspections, Fiscal Year 2002 through Fiscal Year 2007

Location of inspection	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007 ^a
Employees who conducted foreign inspections	100	94	117	114	102	141
Employees who conducted foreign or domestic inspections	587	595	539	512	478	446

Source: GAO analysis of FDA data.

^aInspection data for fiscal year 2007 may not be complete because FDA provided GAO with these data as of September 26, 2007, prior to the end of the fiscal year.

FDA relies on investigators and laboratory analysts to volunteer to conduct foreign inspections. FDA officials told us that it is difficult to recruit investigators and laboratory analysts to voluntarily travel to certain countries. However, officials noted that the agency provides various incentives to recruit employees for foreign inspection assignments. For example, employees receive a \$300 bonus for each three week trip completed. FDA indicated that if the agency could not find an individual to volunteer for a foreign inspection trip, it would mandate the travel. However, FDA does not typically send investigators and laboratory analysts to countries for which the U.S. Department of State has issued a travel warning nor would it mandate travel to such a country.²⁶ 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 2007.²⁷ However, FDA officials told us that in the past 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 U.S. 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 at foreign facilities are to be approached in the same manner as domestic inspections. However, the guidance notes that one main difference posing a significant challenge to the inspection team abroad is the logistics borne by the program itself. For example, FDA is unable to conduct unannounced inspections of foreign drug manufacturers, as it sometimes does with domestic manufacturers. FDA policy states that the

²⁶Travel warnings are issued when the U.S. Department of State recommends that Americans avoid travel to a certain country.

²⁷These ten countries are Colombia, the Democratic Republic of the Congo, Haiti, Indonesia, Israel, Kenya, Nigeria, Pakistan, the Philippines, and Saudi Arabia.

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.²⁸ However, prior notification is routinely provided to foreign establishments. FDA recognizes that the time and expense associated with foreign travel requires them to ensure that the foreign establishment's managers are available and that the production line being inspected is operational during the inspection. In addition, FDA does not have explicit authority to inspect establishments in foreign countries, and it therefore may have to obtain permission from the government and company 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. In addition, FDA does not have the same flexibility to extend 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.

FDA officials also told us that language barriers can make foreign inspections more difficult to conduct than domestic inspections. The agency does not generally provide translators in foreign countries, nor does it require that foreign establishments provide independent interpreters. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, who may not be a translator by training, rather than rely on an independent translator.

Concluding Observations

Millions of Americans depend on the safety and effectiveness of the drugs they take. More than nine years ago we reported that FDA needed to make improvements in its foreign drug inspection program. Yet, our preliminary work indicates that fundamental flaws that we identified in the management of this program in 1998, continue to persist. FDA still does not have a reliable list of foreign establishments that are subject to inspection. As more imported drugs enter the United States, it becomes increasingly important that foreign establishments receive appropriate

²⁸ORA Field Management Directive No. 112A, Prior Notification to FDA Regulated Industries of Impending Inspections, August 1996. However, for both domestic and foreign preapproval inspections, FDA provides prior notification to the establishment.

scrutiny. We understand that FDA currently cannot inspect all foreign establishments every few years. We also recognize that FDA has taken steps to improve its management of the foreign drug inspection program by enhancing the risk-based process it uses to select establishments for GMP surveillance inspections. In addition, FDA is pursuing an initiative that is intended to improve its identification of foreign drug establishments. However, until FDA responds to systemic weaknesses in the management of this important program, it cannot provide the needed assurance that the drug supply reaching our citizens is appropriately scrutinized, and safe.

Mr. Chairman, this completes my prepared statement, I would be happy to respond to any questions you or the other Members of the subcommittee may have at this time.

Contacts and Acknowledgments

For further information about this testimony, please contact Marcia Crosse 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 testimony. Geraldine Redican-Bigott, Assistant Director; Katherine Clark; Robert Copeland; William Hadley; Cathleen Hamann; Julian Klazkin; Romonda McKinney; Lisa Motley; and Suzanne Worth made key contributions to this testimony.

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