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DRUG SAFETY

FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed



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Why GAO Did This Study

Globalization has placed increasing demands on the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), in ensuring the safety and effectiveness of drugs marketed in the United States. Drugs manufactured in more than 100 countries were offered for entry into the United States in fiscal year 2009. FDA inspects drug manufacturing establishments in order to ensure that the safety and quality of drugs are not jeopardized by poor manufacturing practices.

In 1998 GAO identified weaknesses in FDA's foreign drug inspection program. In 2008 GAO found, among other things, that from fiscal years 2002 through 2007, FDA inspected relatively few foreign establishments each year. GAO also determined that, because of inaccurate information in its databases, FDA did not know how many foreign drug establishments were subject to inspection.

In 2008 GAO recommended that FDA increase inspections of foreign drug establishments and improve information it receives to manage the foreign drug inspection program. This report examines FDA's progress since 2008 in (1) conducting more foreign drug inspections, and (2) improving its information on foreign drug establishments. GAO analyzed information from FDA databases, reviewed documents related to FDA's efforts to both improve these databases and supplement its existing information on foreign drug establishments, examined staffing and funding information, and interviewed FDA officials.

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What GAO Found

FDA increased the number of foreign drug inspections it conducted from fiscal year 2007 to 2009, but still conducts relatively fewer foreign drug inspections each year than it conducts domestically. In fiscal year 2009, FDA conducted 424 foreign inspections, compared to 333 and 324 inspections conducted in fiscal years 2007 and 2008, respectively. Using a list FDA developed to prioritize foreign establishments for inspection, GAO estimated that FDA inspected 11 percent of foreign establishments on this list in fiscal year 2009. At this rate, GAO estimated it would take FDA about 9 years to inspect all establishments on this list once. In contrast, in that same year, FDA conducted 1,015 domestic inspections, inspecting approximately 40 percent of domestic establishments. GAO estimated that at this rate FDA inspects domestic establishments approximately once every 2.5 years. Further, FDA's approach in selecting establishments for inspection is inconsistent with GAO's 2008 recommendation that FDA inspect, at a comparable frequency, those establishments that are identified as having the greatest public health risk potential if they experience a manufacturing defect, regardless of whether they are a foreign or domestic establishment. Instead, its foreign inspections continue to be driven by the establishments listed on an application for a new drug, instead of those already producing drugs for the U.S. market.

FDA is taking steps to improve the information it receives from the drug establishment registration and import databases the agency uses to manage its foreign drug inspection program. For example, FDA is working to obtain more accurate information for its database that contains information about foreign establishments registered to market their drugs in the United States. In addition, FDA has an initiative underway to eliminate duplicate information from its database containing information about foreign establishments whose drugs are offered for import into the United States. However, these efforts are in the early stages. In addition, FDA is exploring other options for obtaining better information about foreign drug establishments, such as by collaborating with foreign regulatory authorities to exchange information about planned inspections and the results of completed inspections.

In 1998, and again in 2008, GAO reported that FDA needed to conduct more inspections of foreign establishments and that it was vital that the agency strengthen the data it uses to manage its foreign drug inspection program. FDA has begun to respond to GAO's recommendations; however, it has not yet fully addressed these weaknesses at a time when the volume of imported drugs and the number of foreign establishments producing these drugs have been increasing. Given the long-standing nature of these challenges and the nation's reliance on drugs manufactured overseas, it is urgent that FDA implement GAO's prior recommendations to better protect public health. HHS reviewed a draft of this report and agreed that more progress is needed in order to meet the challenge of safeguarding the nation's drug supply in today's global marketplace.

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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 |
| FTE | full-time equivalent |
| GMP | good manufacturing practice regulations |
| HHS | Department of Health and Human Services |
| OASIS | Operational and Administrative System for Import Support |
| ORA | Office of Regulatory Affairs |
| OTC | over-the-counter |

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United States Government Accountability Office
Washington, DC 20548

September 30, 2010

The Honorable Edolphus Towns
Chairman
The Honorable Darrell E. Issa
Ranking Member
Committee on Oversight and Government Reform
House of Representatives

Globalization has placed increasing demands on the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), in carrying out its role of ensuring the safety and effectiveness of drugs marketed in the United States.¹ The United States has come to depend on drug products and drug ingredients manufactured in foreign countries, and FDA is responsible for the oversight of drugs marketed in the United States, regardless of whether they are manufactured in foreign or domestic establishments.² In March 2010, an FDA official testified that while Americans once used drugs that were mostly manufactured domestically, this is no longer the case. The volume of imported drugs, the complexity of the drug supply chain, and the number of foreign establishments producing these drugs have all been increasing, making oversight significantly more difficult.³ According to FDA import data, drugs manufactured in more than 100 countries were offered for entry into the United States in fiscal year 2009. To assure that the safety and quality of drugs are not jeopardized by poor manufacturing

¹Drugs 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).

²FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. 21 C.F.R. § 207.3(a)(8) (2010). 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) (2010). Drug firms may have more than one establishment.

³Statement of Joshua M. Sharfstein, M.D., FDA Principal Deputy Commissioner, before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives (Washington, D.C.: Mar. 10, 2010).

practices, FDA relies on establishment inspections to determine compliance with current good manufacturing practice regulations (GMP).⁴

Concerns with FDA's foreign drug inspection program have been long-standing. More than 10 years ago, in 1998, we reported on weaknesses in FDA's foreign drug inspection program.⁵ Among other things, we noted that FDA had significant problems managing its foreign inspection data. We also found that FDA infrequently inspected foreign establishments to ensure the continued quality of drugs already on the market. In that same year, FDA expressed concern that, despite recent increases, its inspections of foreign drug establishments could not keep pace with the rapid growth of imported products.⁶ Our 1998 report also included information from two internal FDA reviews that indicated the agency was aware of problems with its inspection data and concerned with the number of foreign establishment inspections it was conducting as early as 1988. At the time our 1998 report was issued, the agency was planning to implement a new data system to establish a comprehensive inventory of foreign establishments shipping drug products to the United States. However, we recommended that, in addition, FDA conduct more foreign inspections.

In September 2008, we again reported on weaknesses in FDA's foreign drug inspection program.⁷ Among other things, we determined that, because of inaccurate information in FDA's databases, the agency did not know how many foreign drug establishments were subject to inspection. We also found that, from fiscal years 2002 through 2007, FDA inspected relatively few foreign establishments each year. Due in part to the concerns raised in our September 2008 report, in January 2009, we added

⁴GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210, 211 (2010). See also International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *ICH Harmonised Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7* (Geneva, Switzerland: Nov. 10, 2000).

⁵GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, [GAO/HEHS-98-21](#) (Washington, D.C.: Mar. 17, 1998).

⁶Statement of Sharon Smith Holston, FDA Deputy Commissioner for External Affairs, before the Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives (Washington, D.C.: Oct. 2, 1998).

⁷GAO, *Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program*, [GAO-08-970](#) (Washington, D.C.: Sept. 22, 2008).

FDA's oversight of medical products—drugs, biologics,⁸ and medical devices⁹—to our High-Risk Series, citing FDA's ability to ensure the quality of medical products manufactured overseas as an area of particular concern.¹⁰ Our subsequent reports have reinforced these designations of FDA as an agency in need of broad-based transformation by identifying additional concerns with FDA's ability to manage its growing responsibilities¹¹ and plans for modernizing the agency's information technology capabilities.¹²

Given continued questions about FDA's oversight of medical products, you asked for an update on the status of FDA's foreign drug inspection program. This report examines FDA's progress since our September 2008 report in (1) conducting more foreign drug inspections, and (2) improving its information on foreign drug establishments.

To determine the extent to which FDA has made progress in conducting more inspections of foreign drug establishments, we obtained information from FDA's Field Accomplishments and Compliance Tracking System (FACTS) and analyzed data on foreign and domestic drug manufacturing establishment inspections conducted from fiscal years 2007 to 2009.¹³ To

⁸Biologics are materials, such as vaccines, derived from living sources, such as humans, animals, and microorganisms. See 42 U.S.C. § 262(i); 21 C.F.R. § 600.3(h) (2010).

⁹Medical devices include instruments, apparatuses, machines, and implants that are intended for use to diagnose, cure, treat, or prevent disease, or to affect the structure or any function of the body. 21 U.S.C. § 321(h).

¹⁰GAO, *High-Risk Series: An Update*, [GAO-09-271](#) (Washington, D.C.: January 2009). The January 2009 addition of FDA's oversight of medical products to our High-Risk Series followed our inclusion of federal oversight—including FDA's oversight—of food safety in our High-Risk Series in 2007.

¹¹GAO, *Food and Drug Administration: FDA Faces Challenges Meeting Its Growing Medical Product Responsibilities and Should Develop Complete Estimates of Its Resource Needs*, [GAO-09-581](#) (Washington, D.C.: June 19, 2009); *Food Safety: Agencies Need to Address Gaps in Enforcement and Collaboration to Enhance Safety of Imported Food*, [GAO-09-873](#) (Washington, D.C.: Sept. 15, 2009); and *Food and Drug Administration: Opportunities Exist to Better Address Management Challenges*, [GAO-10-279](#) (Washington, D.C.: Feb. 19, 2010).

¹²GAO, *Information Technology: FDA Needs to Establish Key Plans and Processes for Guiding Systems Modernization Efforts*, [GAO-09-523](#) (Washington, D.C.: June 2, 2009).

¹³Our September 2008 report included information on drug manufacturing establishment inspections conducted from fiscal years 2002 to 2007. For this report, we focused on drug manufacturing establishment inspections conducted from fiscal years 2007 through 2009. We obtained inspection data as of December 1, 2009, thus fiscal year 2009 represented the most recent complete fiscal year of data available at that time.

assess the reliability of these data we reviewed related documentation, interviewed knowledgeable agency officials, performed electronic data testing, and compared inspection counts to published data. 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. We obtained data FDA used to prioritize foreign and domestic establishments for inspection for fiscal years 2007 to 2009. To assess the reliability of these data we reviewed related documentation, interviewed knowledgeable agency officials, and performed electronic data testing. We found these data sufficiently reliable for the purposes of our report. Finally, we reviewed staffing and funding information for the foreign drug inspection program. To assess the reliability of FDA funding data, we reviewed related documentation, interviewed knowledgeable officials, and examined the data for consistency. We found these data sufficiently reliable for the purposes of our report.

To examine FDA's efforts to improve its information on foreign drug establishments, we reviewed FDA's initiatives for improving the accuracy of the agency's data on foreign establishments contained in its registration and import databases,¹⁴ which are both used to manage the foreign drug inspection program. We obtained data from FDA's Drug Registration and Listing System (DRLS) on the number of establishments registered to market their drugs in the United States. In addition, we interviewed representatives from FDA's Office of Critical Path Programs, which is responsible for managing aspects of the annual registration of drug establishments, and from FDA's Office of Information Management. We also obtained data from FDA's Operational and Administrative System for Import Support (OASIS) on the number of establishments that have manufactured drugs that were shipped to the United States. To assess the reliability of the data from both databases we reviewed related documentation, interviewed knowledgeable agency officials, and compared the data to published information from the same databases. Through this review, we identified inaccuracies with some aspects of FDA's registration and import databases. We found these data sufficiently reliable for illustrating the variability in information that FDA's databases provide to agency officials on the number of foreign drug establishments marketing drugs in the United States. Finally, to further examine FDA's

¹⁴Domestic and foreign establishments that manufacture drugs for the U.S. market are required to register annually with FDA. 21 U.S.C. § 360(b), (i)(1). FDA's import database 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.

efforts to improve its information on foreign drug establishments, we reviewed documents related to the agency's efforts to augment its existing information on foreign drug establishments, such as information obtained from foreign regulatory authorities.

To address both of our objectives, we interviewed officials from FDA, including its Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA), which each have responsibilities for managing the foreign drug inspection program. Our work focuses on human drugs regulated by CDER and not on biologics,¹⁵ medical devices, veterinary medicines, or other items or products for which FDA conducts inspections.¹⁶ Further, our work focuses on activities related specifically to the foreign drug inspection program. As part of its oversight of imported drugs, FDA undertakes other activities, such as providing capacity building to foreign regulatory authorities and working toward international harmonization of regulatory requirements, which are beyond the scope of our review.¹⁷ Our work also excludes FDA's efforts to screen imported drugs that enter the United States illegally.¹⁸

We conducted this performance audit from November 2009 to September 2010, in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to

¹⁵Biologics 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.

¹⁶While our work examines a major part of FDA's foreign drug inspection program, it does not examine all foreign drug inspections the agency conducts. Our work focuses on inspections related to the drug approval process or inspections conducted to determine an establishment's ongoing compliance with laws and regulations in the manufacture of drugs already marketed in the United States. FDA conducts additional foreign drug inspections that are beyond the scope of our review, 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, inspections conducted for the President's Emergency Plan for AIDS Relief, and inspections of clinical trial sites.

¹⁷For information on additional efforts FDA undertakes as part of its oversight of imported products, see GAO, *Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-term Planning is Needed*, [GAO-10-960](#) (Washington, D.C.: Sept. 30, 2010).

¹⁸In 2005, we reported on how federal agencies, including FDA, are addressing the illegal importation of prescription drugs. See GAO, *Prescription Drugs: Strategic Framework Would Promote Accountability and Enhance Efforts to Enforce the Prohibitions on Personal Importation*, [GAO-05-372](#) (Washington, D.C.: Sept. 8, 2005).

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.

Background

As part of its efforts to ensure the safety and quality of imported drugs, FDA may conduct inspections of foreign establishments manufacturing drug products and active pharmaceutical ingredients (API) that are imported into the United States.¹⁹ The purpose of these inspections is to ensure that foreign establishments meet the same requirements as domestic establishments to ensure the quality, purity, potency, safety, and efficacy of drugs marketed in the United States.

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 in the United States, but there is no comparable requirement for inspecting foreign establishments that market their drugs in the United States. However, drugs manufactured by foreign establishments that are offered for import may be refused entry to 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.²⁰

Within FDA, CDER establishes standards for the safety, quality, and effectiveness of and manufacturing processes for prescription and over-the-counter (OTC) drugs. ORA's activities are intended to assure that regulated establishments comply with laws and regulations. ORA supports CDER by, among other things, inspecting these establishments, conducting sample analysis on regulated products, and reviewing imported products offered for entry into the United States. 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. ORA investigators and, as needed, laboratory

¹⁹An API includes any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. See 21 C.F.R. § 210.3(b)(7) (2010). In this report, we refer both to drug products—drugs in their finished dosage form—and to APIs as “drugs.”

²⁰See 21 U.S.C. §§ 360(h), (i)(3); 381(a).

analysts,²¹ conduct two primary types of drug manufacturing establishment inspections, preapproval inspections and GMP inspections:

- Preapproval inspections of domestic and foreign establishments may be conducted before FDA will approve a new drug to be marketed in the United States. These inspections occur following FDA's receipt of a new drug application or an abbreviated new drug application²² and focus on the manufacture of a specific drug.²³ 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. Preapproval inspections also assess whether the establishment can manufacture the product in the application in conformance with GMPs. FDA's decision to inspect a particular establishment listed on the application is based on multiple factors, including the compliance history of the establishment—that is, the results of previous inspections, product recalls, and other compliance information—and the attributes of the product being proposed for manufacture.²⁴
- GMP inspections are conducted at establishments manufacturing drugs already marketed in the United States to determine ongoing compliance with laws and regulations. These inspections focus on an establishment's systemwide controls for ensuring that its manufacturing processes produce drugs that are of high quality. Systems examined during these inspections include those related to materials, quality control, production,

²¹ORA 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.

²²Approval of an abbreviated new drug application is necessary to market a generic drug.

²³While 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 through a different process. If a manufacturer determines that an OTC drug is in compliance with an FDA regulatory statement (called a monograph) that specifies such information as acceptable ingredients, dosage, labeling, and mode of administration, the drug may be marketed without FDA preapproval. Establishments that manufacture OTC drugs that reached the market through the monograph process may not receive a preapproval inspection.

²⁴The number of preapproval inspections conducted by FDA in a given year is dependent on the number of drug applications received. It is also affected by the number of establishments included on each application and the inspection history of the establishments.

facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drugs. For surveillance purposes, some establishments may be selected for GMP inspections through CDER's risk-based selection process, which draws on a variety of factors to identify those establishments that FDA considers to be a priority for inspection. Establishments may also be selected for GMP surveillance inspections for other reasons, such as FDA's focus on a particular product or geographic region. Establishments may also be the subject of a GMP inspection conducted for cause if FDA receives information indicating problems in the manufacture of marketed drugs or when FDA follows up on establishments that were not in compliance with GMPs during previous inspections.²⁵

While FDA may conduct a preapproval-only inspection or a GMP-only inspection, FDA may also conduct an inspection that combines both preapproval and GMP components in a single visit to an establishment. As the results of a GMP inspection can often be generalized to all drugs manufactured in a similar manner at a particular establishment, FDA can use the results of the combined inspection to make decisions in the future if the establishment is listed on another application. Therefore, when an establishment has already been selected to receive a preapproval inspection, FDA may also conduct a GMP inspection during the same visit.²⁶

FDA uses multiple databases to select foreign establishments for GMP surveillance inspections, including the following:

- DRLS contains information on foreign and domestic drug establishments that have registered with FDA to market their drugs in the United States. This information includes company name and address and the drugs they manufacture for commercial distribution in the United States, as reported by the establishment.

²⁵Although FDA considers nearly all drug establishment inspections to include an assessment of GMPs, to differentiate them from product specific, preapproval inspections, in this report we describe all systemwide, postapproval inspections as "GMP inspections."

²⁶Most combined inspections occur when FDA conducts a GMP inspection at an establishment that was already selected to receive a preapproval inspection. However, officials told us that if a combined inspection was conducted at an establishment selected for inspection through CDER's risk-based selection process, the preapproval inspection was generally added after the establishment had already been selected for a GMP surveillance inspection.

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- FACTS contains information on foreign and domestic establishments inspected by ORA, the type of inspection conducted, and the outcome of those inspections. ORA investigators and laboratory analysts enter information into FACTS following completion of an inspection.
 - OASIS contains information on drugs 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), within the Department of Homeland Security. The data are originally entered by customs brokers based on the information available from the importer.²⁷ CBP specifies an algorithm by which customs brokers generate a manufacturer identification number from information about an establishment's name and address.

In September 2008 we reported that FDA did not maintain a list of foreign drug establishments subject to inspection, instead relying on information from DRLS and OASIS to help select establishments for inspection. However, we noted that these databases contained incorrect information about foreign establishments and did not contain an accurate count of foreign establishments manufacturing drugs for the U.S. market. For example, some establishments included in DRLS did not actually manufacture drugs for the U.S. market.²⁸ As a result, FDA did not know how many foreign establishments were subject to inspection.

To select foreign establishments for GMP surveillance inspections, CDER continues to rely on information from multiple databases, including those with which we previously identified inaccuracies. CDER uses data from DRLS and FACTS to annually compile an inventory of foreign establishments that may be subject to inspection; it does not maintain a list of such establishments. While DRLS provides information on all registered establishments, FACTS provides information about additional

²⁷ 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.

²⁸ Such establishments may have gone out of business, but not informed FDA, or the establishments may not actually ship drugs to the United States. Some foreign establishments may register with FDA, but never ship drugs to the United States. FDA officials told us that such foreign establishments may register because, in foreign markets, registration may erroneously convey an "approval" or endorsement by FDA.

establishments that may not appear in DRLS.²⁹ To prioritize establishments for GMP surveillance inspections, CDER applies a risk-based model to this inventory of establishments each year to identify those establishments that, based on the characteristics of the establishments and of the drugs being manufactured, pose the greatest public health risk potential should they experience a manufacturing defect. Establishments are further prioritized based on whether, according to OASIS data, they are actively importing their products to the United States. Establishments that have not shipped a product to the United States in the previous 3 years are not scheduled for inspection. Through this process, CDER annually prepares a list of a selected set of foreign establishments from this inventory that it forwards to ORA,³⁰ requesting that ORA staff conduct GMP surveillance inspections at a certain number of establishments on this prioritized list. In order to use resources efficiently, officials told us that ORA staff may select establishments for inspection from CDER's prioritized list based on geographic proximity to other planned inspection trips.

In September 2008 we also reported that FDA inspected fewer foreign drug establishments than it inspected domestically. We noted that while the majority of domestic establishments inspected were selected to examine the manufacture of drugs already marketed in the United States, FDA generally only selected foreign establishments for inspection if they were named in an application for new drug approval. As a result of our findings, we made a number of recommendations to the FDA Commissioner, including that FDA should improve the accuracy of the data it uses to manage its foreign inspection program. We also recommended that FDA increase the number of foreign inspections so that foreign establishments are inspected at a frequency comparable to domestic establishments with similar characteristics. In response, FDA described plans to improve the databases it uses to manage the foreign

²⁹FACTS provides information about establishments that have previously been inspected, including: registered establishments; establishments that are required to register, but have not done so; and establishments that are not required to register. Foreign establishments that manufacture APIs are not required to register with FDA if their products are not directly imported into the United States. For 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 would not be required to register.

³⁰CDER applies the same risk-based model to its inventory of domestic establishments to prepare a prioritized list of domestic establishments to be forwarded to ORA.

drug inspection program and agreed that it should conduct more inspections of foreign drug establishments.

FDA Conducted More Foreign Inspections in Fiscal Year 2009, but Continued to Conduct Relatively Fewer Foreign than Domestic Inspections

FDA conducted more foreign drug inspections in fiscal year 2009 than in prior fiscal years through staffing changes and dedicating additional resources to conducting foreign inspections. However, FDA continued to conduct relatively fewer foreign drug establishment inspections than domestic inspections. FDA's selection of foreign establishments for inspection was mainly for preapproval purposes, while domestic establishments were mainly inspected to examine the manufacturing of drugs already marketed in the United States.

FDA Increased the Number of Foreign Drug Inspections Conducted in Fiscal Year 2009

FDA increased the number of foreign drug inspections conducted in fiscal year 2009 compared to previous fiscal years. In fiscal year 2009, FDA conducted 424 foreign inspections, an increase from the 333 and 324 inspections conducted in fiscal years 2007 and 2008, respectively. The rate at which FDA increased foreign drug inspections from fiscal year 2007 to fiscal year 2009 was higher than the increase in the annual inventory FDA compiled of foreign drug establishments during the same period. In fiscal year 2009, FDA conducted 27 percent more inspections than in fiscal year 2007.³¹ In comparison, the total number of foreign establishments in FDA's inventory increased by 16 percent—from 3,249 to 3,765—during the same period.³² FDA conducted inspections in 37 countries in fiscal year 2009, with 77 percent of the inspections conducted in 10 countries, as shown in table 1.

³¹We are using the number of foreign inspections conducted in a fiscal year in our calculations, rather than the number of unique foreign establishments inspected. Although FDA can inspect an establishment more than once a year, during this time period there was not a sizeable difference between the number of foreign inspections conducted and the number of unique establishments inspected. For example, in fiscal year 2009, FDA conducted 424 inspections at 416 unique establishments.

³²FDA does not know the exact number of foreign drug establishments that are subject to inspection. Instead of maintaining a list of such establishments, FDA officials told us they annually draw on information from multiple databases to compile an inventory of foreign establishments to which FDA applies its risk-based model. We are using the count of establishments in this inventory for our calculations because it represents the best available data on the number of foreign drug establishments subject to inspection.

Table 1: Total Number of FDA Inspections of Foreign Establishments, Fiscal Year 2007 through Fiscal Year 2009

| Most frequently inspected countries | Number of inspections | | | | Estimated number of establishments in FDA's inventory, fiscal year 2009 ^a |
|-------------------------------------|-----------------------|------------------|------------------|--------------|--|
| | Fiscal year 2007 | Fiscal year 2008 | Fiscal year 2009 | Total | |
| India | 64 | 64 | 59 | 187 | 502 |
| China | 19 | 36 | 52 | 107 | 920 |
| Germany | 26 | 34 | 36 | 96 | 228 |
| Italy | 28 | 28 | 30 | 86 | 168 |
| Canada | 20 | 19 | 35 | 74 | 310 |
| United Kingdom | 16 | 17 | 32 | 65 | 191 |
| France | 24 | 14 | 26 | 64 | 188 |
| Japan | 22 | 17 | 20 | 59 | 207 |
| Switzerland | 17 | 15 | 18 | 50 | 100 |
| Ireland | 14 | 11 | 19 | 44 | 63 |
| All other countries | 83 | 69 | 97 | 249 | 888 |
| Total | 333 | 324 | 424 | 1,081 | 3,765 |

Source: GAO analysis of FDA FACTS and risk-based process data.

Note: The number of inspections includes preapproval inspections, GMP inspections, and inspections that include both preapproval and GMP components. The number of inspections does not include a small number of other foreign drug inspections, such as inspections for the President's Emergency Plan for AIDS Relief, inspections of clinical trial sites, and 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, which were not included in the scope of our review.

^aThere were an estimated 3,249 and 3,559 foreign drug establishments in FDA's inventory in fiscal years 2007 and 2008, respectively.

According to FDA officials, the agency has made two types of staffing changes—by creating a drug cadre based in the United States and by staffing overseas offices with investigators—to increase the number of foreign drug establishment inspections it conducted in fiscal year 2009. First, FDA created a foreign drug cadre consisting of 15 domestically based members in January 2009.³³ Cadre members are specifically

³³Members of the 2009 foreign drug cadre signed on for a 1-year commitment, which ended in January 2010. Three members returned to their original positions at the end of the year and were subsequently replaced.

dedicated to conducting foreign drug inspections. The cadre members began conducting foreign inspections in January 2009 and conducted 152 foreign inspections in 27 countries by the end of fiscal year 2009.³⁴ The countries most frequently inspected by the foreign cadre were China and India, with 23 and 19 inspections, respectively. Second, in late 2008 FDA opened overseas offices in China and India and, since the middle of 2009, has had two medical product investigators staffed to each office to conduct drug inspections.³⁵ These investigators receive a mix of inspection assignments, including GMP inspections, and have additional responsibilities not related to conducting inspections.³⁶ FDA officials told us that investigators in the overseas offices will not conduct the majority of the inspections of foreign drug establishments in these two countries.³⁷ According to our FACTS analysis, investigators in the overseas offices conducted one drug manufacturing establishment inspection in China and two in India in fiscal year 2009.³⁸ These staffing changes have provided FDA officials with a larger pool of investigators to conduct foreign

³⁴For fiscal year 2009, one member of the foreign drug cadre exclusively conducted inspections of clinical trial sites, which are not within the scope of our review. We have therefore excluded these inspections from the reported number of inspections conducted by cadre members. It is also important to note that not all inspections in fiscal year 2009 were conducted by a single cadre member; some inspections were conducted by two members of the cadre at the same time.

³⁵According to FDA officials, one investigator in the China office conducts drug inspections and one investigator primarily conducts device inspections, but may conduct drug inspections as well. Two investigators in the India Office are responsible for drug inspections. In addition to these investigators, the China Office has two investigators who focus on food inspections and the India Office has one investigator who focuses on medical device inspections.

³⁶In addition to conducting inspections, investigators in the overseas offices have other responsibilities to aid in FDA's oversight of imported products. These responsibilities include establishing relationships with local governments, gathering information about regulated products from local sources, and initiating investigations to confirm registration information about local establishments. Overseas office staff have periodically provided information regarding foreign drug establishments to officials in FDA's headquarters. However, as of August 2010, FDA had not yet established a formal or systematic process for reviewing this information and incorporating it into the process for selecting foreign drug establishments for inspection. FDA officials told us that the agency is still developing such a process and that it is also working to better utilize the information it receives to improve its knowledge of foreign drug establishments.

³⁷FDA officials told us that the foreign drug cadre and other domestically based staff from ORA will conduct the majority of foreign inspections.

³⁸The investigators assigned to the China and India offices conducted an additional three drug manufacturing establishment inspections in fiscal year 2009 that had not been entered into FACTS by December 1, 2009, the date on which we received our data.

inspections. According to FDA officials, the agency plans to sustain the increases in foreign inspections by maintaining the foreign drug cadre and the overseas offices.

In addition to staffing changes, FDA has increased the resources dedicated to conducting foreign drug inspections, with the largest increase occurring in fiscal year 2009. FDA dedicated approximately \$10 million to foreign drug inspections in fiscal year 2007,³⁹ and approximately \$12 million for this purpose in fiscal year 2008. In fiscal year 2009, FDA dedicated approximately \$41 million to foreign drug inspections, which includes a portion of the supplemental appropriation FDA received in fiscal year 2008.⁴⁰ According to FDA officials, the supplemental appropriation allowed the agency to conduct more inspections in fiscal year 2009.⁴¹ The supplemental appropriation also allowed FDA to hire additional investigators to conduct foreign inspections. FDA officials told us that although the agency hired additional investigators, the effect of this hiring will not be fully realized until fiscal year 2011 due to the time it takes to train investigators to become qualified to conduct foreign drug inspections. FDA estimates it will dedicate about \$42 million in fiscal year 2010 to foreign drug inspections, and approximately \$50 million in fiscal year 2011.

³⁹This amount includes funding for the entire foreign drug inspection program, including foreign drug inspections beyond the scope of our review.

⁴⁰The fiscal year 2008 supplemental appropriation provided \$150 million to FDA in June 2008 and was available through the end of fiscal year 2009. See Pub. L. No. 110-252, 122 Stat. 2323, 2345 (2008).

⁴¹For fiscal year 2009, FDA estimated that the average cost for ORA to conduct a foreign inspection ranged from \$60,000 to \$62,500. This is an increase from the estimated range of \$41,000 to \$44,000 we previously reported for fiscal year 2007. The fiscal year 2009 estimate includes inflation of the average cost of an ORA full-time equivalent (FTE) staff, inflation of travel and per diem costs, and a higher average number of hours per inspection in fiscal year 2009 than in fiscal year 2007. (One FTE represents 40 hours of work per week conducted by a federal government employee over the course of a year.) The fiscal year 2009 estimate also includes ORA's share of rent and rent-related expenditures, which was not included in the previous calculation for fiscal year 2007. There are additional costs, such as costs associated with CDER's review of inspection reports, which are not included in this estimate.

FDA Continues to Inspect Few Foreign Establishments Relative to Its Inspection of Domestic Establishments

Although FDA increased the number of foreign drug establishment inspections it conducted in fiscal year 2009, the agency continues to inspect relatively few foreign establishments compared to its inspection of domestic establishments. The number of foreign establishments the agency inspected in fiscal year 2009 remained a small portion of the total number of foreign establishments in FDA's inventory, compared to the portion of domestic establishments inspected. FDA inspected 11 percent of the total number of foreign establishments in its inventory in fiscal year 2009, an increase from the 10 percent and 9 percent of foreign establishments inspected in fiscal year 2007 and fiscal year 2008, respectively.⁴² In comparison, FDA inspected approximately 40 percent of domestic establishments in fiscal year 2009. If FDA continued to conduct foreign inspections at the rate it adhered to in fiscal year 2009—424 a year—it would take FDA about 9 years to inspect each of the 3,765 foreign establishments in FDA's inventory in fiscal year 2009 at least one time.⁴³ In contrast, FDA conducted 1,015 domestic inspections in fiscal year 2009.⁴⁴ If FDA continued to conduct domestic inspections at this rate, it would inspect the 2,498 establishments in its fiscal year 2009 domestic inventory about once every 2.5 years.

However, the rate at which FDA inspects establishments within any given country differs. For example, in fiscal year 2009, FDA conducted 59 inspections in India and 52 in China. If FDA continued to inspect

⁴²We previously reported that comparing the average number of foreign establishment inspections per year from fiscal years 2002 through 2007—247—to the 3,249 foreign establishments in FDA's inventory in fiscal year 2007 suggests that the agency inspects about 8 percent of foreign establishments in a given year. We noted that at the average rate of inspections conducted from fiscal years 2002 to 2007, it would take FDA more than 13 years to inspect this group of establishments once, assuming that no additional establishments enter the U.S. marketplace and no establishments go out of business. See [GAO-08-970](#), 23.

⁴³It is important to note that FDA may inspect a unique establishment more than once a year. Although we have determined that another calculation can be done using the number of unique establishments inspected, the result is the same. The 424 inspections conducted in fiscal year 2009 were conducted at 416 unique establishments. If FDA continued to inspect 416 unique establishments each year, it would take FDA about 9 years to inspect each of the 3,765 establishments in FDA's inventory in fiscal year 2009. Both calculations assume that no additional establishments enter the U.S. marketplace and no establishments go out of business in the future. If more foreign establishments are subject to inspection in subsequent years, the length of time it would take FDA to inspect each establishment once would also increase.

⁴⁴This is a decrease from the 1,122 domestic inspections conducted in fiscal year 2007 and the 1,033 inspections conducted in fiscal year 2008.

establishments in its fiscal year 2009 inventory in these two countries at the rate at which it inspected establishments in these countries in fiscal year 2009, it would take FDA about 8.5 years to inspect all of the 502 establishments in India once and about 18 years to inspect all of the 920 establishments in China once.

FDA officials acknowledged that the agency is far from achieving foreign inspection rates comparable to domestic inspection rates and, without significantly increased inspectional capacity, its ability to close this gap is highly unlikely. FDA also indicated that the agency cannot respond to the nation's increasing reliance on the globalization of the drug supply chain, in which manufacturing steps may be outsourced to multiple foreign establishments, at its expected fiscal year 2011 funding level. According to FDA, the sheer number of foreign establishments, the complexity of the drug supply chain, and the rapidly changing use of suppliers all pose formidable challenges to its ability to gather comprehensive information about foreign establishments and take action against them when necessary. In addition, FDA noted that its current legal authorities limit the agency's ability to improve its oversight of imported products.⁴⁵

FDA's concern about its ability to close the gap in foreign and domestic inspection rates is underscored by the proportion of establishments in the agency's inventory that FDA may never have inspected. A majority of foreign establishments in FDA's inventory may never have been inspected by the agency, and almost half of these establishments are in China and India. According to agency officials, after compiling its inventory of foreign establishments that may be subject to inspection, FDA identifies establishments in the inventory that may never have received an FDA inspection. Of the 3,765 foreign establishments in FDA's inventory for fiscal year 2009, there were 2,394 foreign establishments that may never

⁴⁵FDA officials outlined legal authorities that they believe the agency currently does not have which would be helpful in improving its oversight of drugs manufactured in foreign establishments. For example, these include authorizing FDA to: (1) suspend or cancel drug establishment registrations to address concerns, including inaccurate or out-of-date information; (2) require drug establishments to submit a unique establishment identifier; and (3) implement a risk-based inspection process, with flexibility to determine the frequency with which both foreign and domestic establishments are inspected, in place of the current requirement that FDA inspect domestic establishments every 2 years. As of August 2010, FDA had not completed a formal analysis to determine the appropriate inspection frequency for foreign and domestic drug establishments. However, in response to our inquiries and those of congressional staff, FDA has undertaken such a review.

have been inspected by FDA (see table 2).⁴⁶ This is an increase from the 2,133 foreign establishments that may have never been inspected in fiscal year 2007. In fiscal year 2009, 47 percent of the foreign establishments in FDA's inventory that may never have been inspected by FDA were in China and India. In comparison, 10 percent, or 253, of the 2,498 domestic establishments in FDA's inventory for fiscal year 2009 may never have been inspected.⁴⁷ Agency officials told us that the count of foreign establishments that FDA may never have inspected includes registered establishments whose drugs are being imported into the United States,⁴⁸ as well as establishments that may not actually be subject to inspection.⁴⁹

⁴⁶FDA officials told us that this count could include establishments that received an inspection other than a GMP inspection prior to fiscal year 2000, but for which inspection data may not have been transferred when the agency began using FACTS in 2000.

⁴⁷According to FDA officials, domestic establishments that may never have been inspected could be new establishments or those that are not generally subject to GMP inspections.

⁴⁸Registered establishments whose drugs are being imported, but which have never been inspected, include OTC manufacturing establishments. However, FDA has not conducted a formal analysis to determine how many such establishments are in its inventory.

⁴⁹Establishments that may not actually be subject to inspection include those whose drugs were never imported into the United States or those that have stopped shipping drugs into the United States without notifying FDA. In addition, some establishments may have gone out of business without informing FDA. Establishments that have never shipped drugs to the United States or have not done so recently remain in FDA's inventory. FDA cannot be certain that these establishments will not ship products to the United States.

Table 2: Number of Establishments in FDA’s Inventory That May Never Have Been Inspected by FDA and the Total Estimated Number of Establishments in Its Inventory, by Country, Fiscal Year 2009

| Countries with the largest number of establishments in FDA’s inventory that may never have been inspected | Number of establishments in FDA’s inventory that may never have been inspected ^a | Estimated number of establishments in FDA’s inventory | Percent of establishments in FDA’s inventory that may never have been inspected |
|---|---|---|---|
| China | 811 | 920 | 88 |
| India | 323 | 502 | 64 |
| Canada | 206 | 310 | 66 |
| France | 107 | 188 | 57 |
| Japan | 99 | 207 | 48 |
| Germany | 97 | 228 | 43 |
| United Kingdom | 82 | 191 | 43 |
| South Korea | 69 | 75 | 92 |
| Mexico | 57 | 76 | 75 |
| Italy | 55 | 168 | 33 |
| All other countries | 488 | 900 | 54 |
| Foreign total | 2,394 | 3,765 | 64 |
| Domestic total | 253 | 2,498 | 10 |

Source: GAO analysis of FDA risk-based process data.

^aThis count represents the number of establishments for which FDA could not identify a previous inspection when FDA compiled its inventory in fiscal year 2009. Officials told us that this count could include establishments that received an inspection other than a GMP inspection prior to fiscal year 2000, but that these data may not have been transferred when the agency began using FACTS in fiscal year 2000. This count could also include establishments that are not subject to inspection, such as those establishments that may have gone out of business or those that have never shipped to the United States.

Inspections Conducted for Preapproval Purposes Continued to Drive the Selection of Foreign Establishments for Inspection in Fiscal Year 2009

While FDA mainly selected domestic establishments for inspection to examine the manufacture of drugs already marketed in the United States, it mainly selected foreign establishments for inspection for preapproval purposes. Unless a foreign establishment is listed on an application for a new drug, FDA is still unlikely to select that establishment for inspection. In fiscal year 2009, 83 percent of foreign drug establishment inspections contained preapproval components—preapproval-only inspections and inspections including both preapproval and GMP components—compared to 18 percent of domestic drug establishment inspections. When a foreign

establishment was already selected to receive a preapproval inspection, FDA often included a GMP inspection.⁵⁰ However, relatively few foreign establishments are selected for inspection solely to examine the manufacture of drugs already marketed in the United States. In fiscal year 2009, 17 percent of the 424 foreign inspections were GMP-only inspections—that is, GMP inspections that do not include a preapproval component (see fig. 1).⁵¹ In comparison, for fiscal year 2009, GMP-only inspections continued to make up about 82 percent of domestic establishment inspections. This approach—in which foreign establishments are primarily selected for inspection for preapproval purposes while domestic establishments are primarily selected to examine the manufacture of drugs already marketed in the United States—is inconsistent with one of the recommendations we made in 2008. Specifically, we recommended that FDA inspect, at a comparable frequency, those establishments that are identified as having the greatest public health risk potential if they experience a manufacturing defect, regardless of whether they are a foreign or domestic establishment.

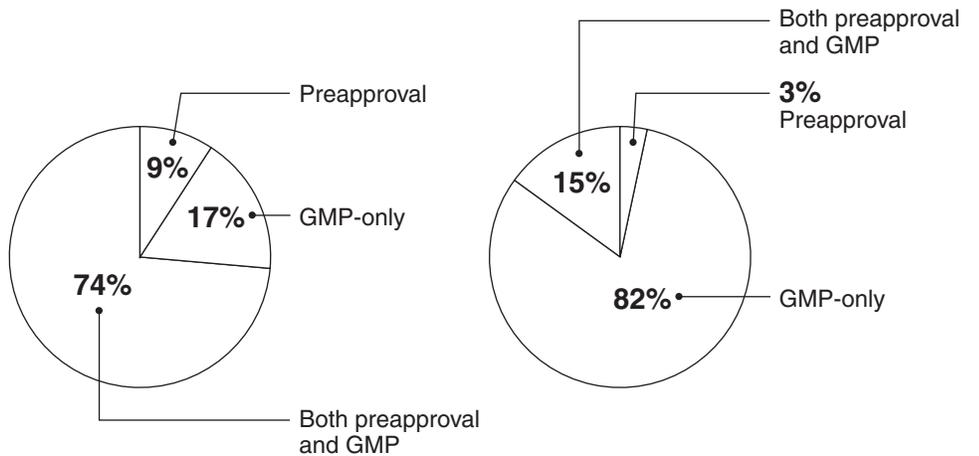
⁵⁰According to FDA officials, the agency combines preapproval and GMP inspections because foreign establishments are inspected infrequently, and it increases efficiency to conduct preapproval inspections and GMP inspections during the same visit to a foreign establishment. When an establishment has already been selected to receive a preapproval inspection, FDA may also conduct a GMP inspection during the same visit. Although this is the case for most combined inspections, officials told us that if a combined inspection was conducted at an establishment selected for inspection through CDER's risk-based selection process, the preapproval inspection was generally added after the establishment had already been selected for a GMP surveillance inspection. In fiscal year 2009, of the 312 combined preapproval and GMP inspections conducted by FDA, 61 inspections were conducted at establishments selected through the risk-based process.

⁵¹We previously reported that for fiscal years 2002 through 2007, about 13 percent of the foreign inspections FDA conducted were GMP-only inspections, either surveillance or for-cause, compared to about 85 percent of domestic inspections during the same period. See [GAO-08-970](#), 27.

Figure 1: FDA Foreign and Domestic Drug Establishment Inspections by Type of Inspection, Fiscal Year 2009

Foreign drug establishment inspections:
total 424

Domestic drug establishment inspections:
total 1,015



Source: GAO analysis of FDA FACTS data.

The majority of foreign inspections conducted in the 10 most frequently inspected countries in fiscal year 2009 had a preapproval component (see table 3). For example, of the 59 inspections conducted in India in fiscal year 2009, 50 had a preapproval component; that is, these included both preapproval-only inspections and inspections including both preapproval and GMP components. In China, 35 of the 52 inspections conducted had a preapproval component.

Table 3: Number of Inspections Conducted by Inspection Type for the Most Frequently Inspected Countries in Fiscal Year 2009

| Most frequently inspected countries | Number of preapproval-only inspections | Number of both preapproval and GMP inspections | Number of GMP-only inspections | Total number of inspections |
|-------------------------------------|--|--|--------------------------------|-----------------------------|
| India | 5 | 45 | 9 | 59 |
| China | 7 | 28 | 17 | 52 |
| Germany | 6 | 24 | 6 | 36 |
| Canada | 0 | 30 | 5 | 35 |
| United Kingdom | 3 | 26 | 3 | 32 |
| Italy | 5 | 20 | 5 | 30 |
| France | 1 | 23 | 2 | 26 |
| Japan | 0 | 14 | 6 | 20 |
| Ireland | 0 | 16 | 3 | 19 |
| Switzerland | 4 | 13 | 1 | 18 |
| All other countries | 9 | 73 | 15 | 97 |
| Foreign total | 40 | 312 | 72 | 424 |
| Domestic total | 35 | 151 | 829 | 1,015 |

Source: GAO analysis of FDA FACTS data.

Although preapproval inspections drove the selection of establishments for inspection, FDA increased the number of foreign establishments inspected from the agency’s annual prioritized list. Based on the application of its risk-based process, CDER forwarded to ORA a list of 104 and 120 foreign establishments that it considered to be a priority for inspection in fiscal years 2007 and 2008, respectively. In fiscal year 2007, ORA inspected 29 establishments from the prioritized list, and FDA increased this number of establishments inspected in fiscal year 2008 to 56. CDER followed the same process in fiscal year 2009, submitting a list of 220 foreign establishments. ORA inspected 88 establishments from the fiscal year 2009 prioritized list.⁵²

⁵²FDA officials told us that since fiscal year 2008, therapeutic biologic manufacturing establishments have been included in the agency’s annual prioritized list. Therefore, the number of establishments inspected from the prioritized list in fiscal year 2007 is not directly comparable to the number inspected in fiscal years 2008 and 2009. However, FDA inspects relatively few foreign therapeutic biologic manufacturing establishments per year. Therapeutic biologics are produced using living organisms, such as yeast, bacteria, or mammalian cells.

FDA Is Taking Steps to Improve Its Information on Foreign Drug Establishments, but These Efforts Are in the Early Stages

FDA is pursuing initiatives to improve the information it receives from its drug establishment registration and import databases, DRLS and OASIS, respectively, but these efforts are in the early stages. FDA is taking additional steps to improve its information on foreign drug establishments.

FDA Is Pursuing Initiatives to Improve Its Information on Registered Foreign Drug Establishments, but Efforts Are Preliminary and Inaccuracies Remain

FDA is taking steps to improve the information it obtains from establishments through the registration process by moving from a paper-based registration system—DRLS—to an electronic registration and listing system, known as eLIST. In June 2009, FDA began requiring all drug establishments marketing their products in the United States to submit their annual registration and listing information electronically through eLIST, rather than submitting the information on paper forms to be entered into DRLS.⁵³ The intent of eLIST is to provide FDA with more accurate information on foreign establishments by reducing the potential for human error associated with the transcription of information from paper forms to electronic files. According to an FDA official, the agency currently does not have enough data to tell whether the implementation of electronic registration has improved the agency's foreign establishment registration data.⁵⁴ However, FDA will continue to study the effect that the

⁵³During 2009, mandatory electronic registration was implemented after some establishments had already submitted their registration information on paper forms for the year. According to an FDA official, establishments that updated their registration on paper prior to June 1, 2009, were considered registered for 2009 and were not asked by FDA to update their registration again for this year. The information contained in the agency's paper-based registration system—DRLS—will still exist for archival purposes, but no new information will be added to this system after December 31, 2010. If an establishment does not register electronically, its information will not be in FDA's registration database.

⁵⁴Both foreign and domestic establishments are required to register with FDA once each calendar year. FDA has instructed establishments to complete their annual registrations between January and July. However, according to agency officials, if an establishment has not registered in accordance with the schedule FDA does not consider it to be out of compliance until December 31. Therefore, eLIST may not be fully populated until January 2011.

implementation of electronic registration has had on the accuracy of data obtained from establishments.⁵⁵

In another initiative designed to improve registration information, FDA issued guidance that requests that establishments voluntarily submit a unique identification number—a Dun and Bradstreet Data Universal Numbering System (D-U-N-S®) Number—as a part of their electronic registration.⁵⁶ The D-U-N-S® Number is intended to serve as a recognized identifier to avoid duplications and errors in FDA’s data systems. Also, the D-U-N-S® Number and the associated data to which it is linked should allow FDA to verify information about foreign establishments, including whether they have gone out of business or relocated.

According to FDA officials, as the first part of a larger planned verification effort using the D-U-N-S® Number, when an establishment submits a D-U-N-S® Number with its registration data, FDA verifies the country code in the establishment’s address and has done so since the fall of 2009.⁵⁷ If the country code submitted with an establishment’s registration does not match the country code on file for that establishment in the Dun and Bradstreet database, the registration file is returned to the establishment for correction. FDA and Dun and Bradstreet are developing an algorithm that is intended to allow FDA to implement a more complete verification process that will include additional aspects of an establishment’s registration information, such as the establishment’s full name, city, and street address. The time frame for implementing this more complete

⁵⁵FDA will continue to use DRLS to help select establishments for inspection until eLIST is fully integrated with other FDA databases.

⁵⁶The 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.

⁵⁷FDA performs this verification by comparing the country code in the establishment’s registration file to the country code associated with the D-U-N-S® Number in Dun and Bradstreet’s Global Business Database, which contains information that the company collects on foreign businesses. According to Dun and Bradstreet officials, this database contains approximately 170 million records from businesses located in more than 200 countries and provides Dun and Bradstreet with information on data elements, such as business names, addresses, and phone numbers.

verification procedure is unclear, although FDA officials told us that they hoped to implement the algorithm by the end of calendar year 2010.⁵⁸

FDA acknowledged that the implementation of eLIST and the related guidance requesting that establishments submit a D-U-N-S® Number at the time of registration do not represent a comprehensive solution to the problems we previously identified regarding the accuracy of FDA's registration information. For example, in 2008 we reported that FDA did not enforce the requirement that establishments submit their registration information annually. Some foreign establishments may not report to FDA if they stop manufacturing drugs for the U.S. market or go out of business, although establishments are required to do so. Because FDA did not enforce the annual registration requirement, these establishments may still be listed as actively registered establishments. Also, we reported that FDA's registration data contained information on foreign establishments that may have registered with FDA whether or not they actually manufacture drugs for the U.S. market. DRLS, which in fiscal year 2009 contained information on approximately 3,200 foreign drug establishments, still does not provide FDA with a complete count of establishments subject to inspection.⁵⁹ FDA confirmed that establishments that do not need to register with FDA continue to submit registration files, that those required to update their registration information annually do not always do so, and that FDA still relies on multiple databases to estimate the number of foreign establishments actually shipping drugs to the United States.

⁵⁸According to FDA officials, once the algorithm is implemented, establishment registration information submitted to FDA will be verified before being recorded in eLIST. The agency also plans to use the algorithm to verify existing electronic registration data collected prior to implementation of the algorithm. If errors are found in existing registration data, FDA plans to request that establishments submit corrected information.

⁵⁹We previously reported that in fiscal year 2007, about 3,000 foreign drug establishments were registered with FDA. See [GAO-08-970](#), 17.

OASIS Continues to Contain Inaccurate Data on the Number of Establishments Offering Drugs for Import, but FDA Is Exploring Options to Prevent Future Inaccuracies

According to FDA officials, OASIS still provides an inaccurate count of foreign establishments manufacturing drugs offered for import into the United States, and the agency is exploring options for preventing this problem in the future. In fiscal year 2009, OASIS contained information on about 7,000 foreign establishments that offered drugs for import into the United States, compared with the approximately 3,200 foreign drug establishments that were registered with FDA in that year.⁶⁰ As we previously reported, this inaccurate count of establishments in OASIS is the result of unreliable manufacturer identification numbers generated by customs brokers when a drug is offered for import.⁶¹

FDA has initiated a project to identify and resolve duplication of existing data, including duplication of data on foreign drug establishments offering their products for import into the United States. It is taking steps to identify and remove all duplicate drug establishment records from existing import data within the next couple of years. As a result of this effort, FDA expects that it may be easier to more precisely identify the total number of establishments that have offered drugs for import into the United States. Identifying and resolving duplicates in existing import data is important because FDA uses information on establishment shipping history from OASIS to select establishments for inspection.⁶²

In addition to its project to resolve existing duplications in OASIS data, FDA officials told us that the agency continues to support a proposal that could help prevent future duplication errors in OASIS across all product areas, but FDA does not control the implementation of this proposal. FDA, in conjunction with 20 of the nearly 50 federal agencies involved in the oversight of products imported into the United States, requested that CBP use the D-U-N-S® Number as a unique establishment identifier for all establishments whose products, including drugs, are imported into the United States. The implementation of this unique establishment identifier

⁶⁰In September 2008 we reported that, on the basis of the information contained in OASIS, 6,760 foreign establishments manufactured drugs that were offered for import into the United States in fiscal year 2007. See [GAO-08-970](#), 20.

⁶¹The 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. Consequently, according to FDA officials, multiple records may be created for a single establishment, resulting in an inflated count of the number of establishments.

⁶²Establishments that have not shipped a product to the United States in the previous 3 years are not scheduled for inspection.

depends on changes to CBP's import and export system. In 2009, CBP agreed to modify its import and export system to accept the D-U-N-S® Number for all FDA-regulated products (e.g., foods, drugs, and medical devices). However, as of March 2010, the system had not been modified, and CBP had not established a schedule and target date to do so.

FDA officials told us that they are developing a pilot program to study the feasibility of obtaining and validating additional information from establishments during the import process, such as the D-U-N-S® Number, in the event that CBP does not adopt changes to its import and export system. This may help FDA address the problems with information on the number of foreign drug establishments in OASIS. As of July 2010, FDA had not yet developed an implementation plan for the pilot program. The agency has, however, identified 10 potential participants for the program, but some of these participants had not yet submitted their updated electronic annual registration as of May 2010. In addition, FDA is in the process of updating some of its information-technology infrastructure, further delaying implementation of the pilot program.

FDA Is Taking Additional Steps to Improve Its Information on Foreign Drug Establishments

In addition to initiatives to enhance DRLS and OASIS, FDA is taking other steps to improve the information that the agency maintains on foreign establishments shipping drugs to the United States. In August 2008, FDA contracted with two external organizations to implement the Foreign Registration Verification Program.⁶³ Through this program, contractors conduct site visits to verify the existence of foreign establishments that are registered with FDA and confirm that they manufacture the products that are recorded in U.S. import records. According to FDA officials, establishments that are new to the U.S. market or are importing products not typically manufactured at the same establishment are considered candidates for the verification program.⁶⁴ For example, FDA officials told us about an establishment that was selected for the program because, according to agency records, it was offering for import into the United States pickles and an API—two products not normally manufactured at the same establishment.

⁶³FDA previously referred to this program as the Foreign Vendor Registration Verification Program (see [GAO-08-970](#), 19).

⁶⁴To select establishments for the Foreign Registration Verification Program, FDA uses information from OASIS to determine the products that establishments are shipping to the United States and to identify establishments that are importing a variety of products.

As of July 2010, the contractors had visited 43 foreign drug establishments located in Canada, Europe, and Asia, 7 of which did not appear to exist at the address provided by the establishments at the time of registration.⁶⁵ According to agency officials, FDA took action against 2 of the establishments that appeared not to exist by deactivating their registration and alerting FDA import staff so they can detain any products offered for import by these establishments, thus preventing these products from being imported into the United States.⁶⁶ FDA officials noted that most of the drug establishments visited under the Foreign Registration Verification Program were OTC manufacturing establishments, which are infrequently inspected under FDA's foreign drug inspection program, and API manufacturing establishments.

FDA has also implemented collaborative efforts with foreign regulatory authorities to exchange information about planned inspections as well as the results of completed inspections. In December 2008, FDA, along with its counterpart regulatory authorities of the European Union and Australia, initiated a pilot program under which the three regulators share their preliminary plans for and results of inspections of API manufacturing establishments in 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 this information will allow these regulatory bodies to more efficiently use their resources by minimizing the overlap in their inspection plans. Since September 2008, FDA had requested 47 inspection reports for API manufacturing establishments. As of July 2010, it had received 13 of the 47 reports requested. According to agency officials, this information was used by FDA to improve its knowledge of establishments, most of which had not been inspected in the last 3 years, but that it was interested in inspecting due to a pending drug application. In addition to the inspection reports received through this pilot program, FDA also received 13 additional inspection reports from various foreign drug regulatory authorities, including New Zealand and

⁶⁵ According to FDA officials, the Foreign Registration Verification Program covers establishments manufacturing all FDA-regulated products. In addition to the 43 drug establishments, FDA's contractors visited 130 foreign food manufacturing establishments located in North America, South America, Asia, Europe, Australia, Africa, and the Middle East.

⁶⁶ According to agency officials, as of July 2010, FDA had not yet determined the type of action to take against the other five establishments that appeared not to exist.

Canada. These reports helped FDA evaluate the GMP compliance status of several API and finished drug product manufacturing establishments.

Concluding Observations

Our work over the last decade has identified long-standing concerns regarding FDA's ability to respond to the challenges posed by the globalization of drug manufacturing. In 1998, and again in 2008, we reported that FDA needed to conduct more inspections of foreign establishments and that it was vital that the agency strengthen the data it uses to manage its foreign drug inspection program. Among other things, our 2008 report recommended that FDA conduct more inspections of foreign establishments and that it address weaknesses in the data systems it uses to help select establishments for inspection. FDA has acknowledged that its approach to inspecting foreign drug manufacturing establishments has not kept pace with the realities of the global marketplace.

We recognize that FDA has made improvements in its foreign drug inspection program since our 2008 report was issued by increasing the number of foreign inspections it conducted. However, we recommended that FDA inspect, at a comparable frequency, those establishments that are identified as having the greatest public health risk potential if they experience a manufacturing defect, regardless of whether they are a foreign or domestic establishment. FDA has not done so. Instead, its foreign inspections continue to be driven by the establishments listed on an application for a new drug, instead of inspections of establishments already producing drugs for the U.S. market. FDA is also taking steps to obtain more complete and accurate information on foreign establishments marketing drugs in the United States. We believe that these efforts to collect and maintain more complete and accurate information on foreign establishments may be instrumental in helping FDA improve its oversight. However, these steps appear to involve long-term efforts that are in their early stages and it is unclear if these efforts will prove successful. In the meantime, FDA's data systems continue to contain inaccurate information on foreign establishments, compromising the agency's oversight of the nation's drug supply.

The challenges FDA faces in managing its foreign drug inspection program are not new, as our prior work shows. Given the long-standing nature of these challenges and the nation's reliance on drugs manufactured overseas, we believe that there is an urgent need for FDA to better protect the public health by implementing our prior recommendations.

Agency Comments and Our Evaluation

HHS reviewed a draft of this report and agreed that more progress is needed in order to meet the challenge of safeguarding the nation's drug supply in today's global marketplace. HHS underscored FDA's position that relying solely on inspections is insufficient to secure the drug supply chain and noted that, due to globalization and outsourcing, the drug supply chain has become more nebulous and complex. According to HHS, drug products are more likely to change hands during manufacture and distribution without adequate traceability. As a consequence, HHS said that FDA faces challenges from a proliferation of new entry points through which contaminated, adulterated, and otherwise violative products can infiltrate the drug supply. In addition, HHS described several practical and jurisdictional issues that affect FDA's ability to gather information during foreign inspections, such as the need to obtain permission from the foreign government of the country in which an establishment is located in order to conduct an inspection. HHS emphasized that, to be effective, inspections must be informed by relevant data from other sources. To that end, it elaborated on FDA's efforts to enhance its global presence and cited additional efforts that FDA has initiated that may lead to greater international cooperation on drug safety issues, such as the opening of FDA offices in several foreign countries and conducting joint inspections with foreign regulatory authorities.

HHS also stressed that FDA has made many of the improvements recommended in our 2008 report, such as enhancing its registration data. However, it also specifically cited obstacles related to one of our 2008 recommendations regarding the varying rates of inspections between foreign and domestic establishments. HHS pointed out that, if FDA were to conduct foreign GMP surveillance inspections at a rate comparable to domestic GMP surveillance inspections, given current resources, the inspection frequency for both would be, at most, about once every 7 years. However, we did not recommend that FDA inspect all foreign and domestic establishments at a comparable frequency, rather, we recommended that FDA inspect foreign establishments at a frequency comparable to domestic establishments with similar characteristics. We continue to maintain that FDA should 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.

HHS's comments are reprinted in appendix I. HHS also provided us with one technical comment, which we incorporated.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, the Commissioner of FDA, and other interested parties. The report also 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 key contributions to this report are listed in appendix II.



Marcia Crosse
Director, Health Care

Appendix I: 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 09 2010

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street N.W.
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled: "Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve its Information on Foreign Establishments, but More Progress Is Needed" (GAO-10-961).

The Department appreciates the opportunity to review this report before its publication.

Sincerely,

A handwritten signature in cursive script that reads "Jim Esquea".

Jim Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "DRUG SAFETY: FDA HAS CONDUCTED MORE INSPECTIONS AND BEGUN TO IMPROVE ITS INFORMATION ON FOREIGN ESTABLISHMENTS, BUT MORE PROGRESS IS NEEDED" (GAO-10-961)

The Department appreciates the opportunity to comment on the GAO's findings in this draft report. HHS and FDA appreciate GAO's recognition of the progress FDA has made toward strengthening its foreign inspection capability within the past two years, and agree that more progress is needed in order to meet the challenge of safeguarding the nation's drug supply in today's globalized marketplace.

In 2008, GAO published a report recommending that, among other things, FDA conduct more inspections of foreign establishments and address weaknesses in the data systems FDA uses to manage its foreign inspection program. Since then, FDA has made many of the recommended improvements and initiated additional efforts that may lead to greater international cooperation on drug safety issues.

As a result of these initiatives, FDA's presence abroad is greater today than it has ever been, and FDA's foreign inspection capacity is on the rise. In 2009, FDA conducted 424 foreign inspections concerning drugs intended for human use, the highest number of inspections to date, representing nearly a 31 percent increase over the 324 foreign inspections that FDA conducted in 2008.

Establishment inspections -- both domestic and foreign -- provide a system for determining that a firm's manufacturing practices comply with U.S. legal standards for assuring the safety, quality and purity of active pharmaceutical ingredients (APIs) and drug products. Although establishment inspections are an essential element of FDA's drug safety efforts, given the ever-increasing scope and ever-changing design of the drug production and distribution systems, FDA cannot rely solely on inspections to secure the drug supply chain, and to be effective, inspections must be informed by relevant data from other sources.

In the past decade or so, the pharmaceutical industry has shifted a large part of its manufacturing operations and supply sourcing overseas. Today, nearly 40 percent of the finished dosage form drugs Americans take are imported, and nearly 80 percent of the active ingredients used to formulate the drugs on the American market come from overseas sources. Furthermore, due to globalization and outsourcing, the supply chain -- from raw material to finished product -- has become more nebulous and complex, so that drug products are more likely to change hands during manufacture and distribution without adequate traceability. Like any chain, the drug supply chain is only as strong as its weakest link, and the proliferation of additional handlers, suppliers and middlemen creates new entry points through which contaminated, adulterated, counterfeit, and otherwise violative products can infiltrate the drug supply.

FDA protects the American people from unsafe and poor quality drug products by holding the industry accountable for the integrity, purity, quality and safety of its drug products. A drug company's obligation does not begin or end in its manufacturing

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facility; it extends from the first filing of a new drug application or an abbreviated new application to every single link in the firm's supply chain until the product reaches the consumer. The same is true for products not covered by applications (e.g., over-the-counter products).

Challenges in Meeting GAO's Goals for the Foreign Inspection Program

Despite the significant progress FDA has made toward improving the Agency's foreign inspection operations and capacity, it is important to acknowledge the nature and the depth of the challenges FDA faces in the foreign inspection arena. The sheer number of foreign facilities, the complexity of the drug supply chain, and the rapidly changing use of suppliers all pose formidable obstacles to implementing GAO's recommendation that FDA conduct foreign inspections at a rate comparable to domestic inspections. FDA has estimated that if it were to conduct foreign Good Manufacturing Practices (GMP) surveillance inspections at a rate comparable to domestic GMP surveillance inspections, the inspection frequency for both, under current resources, would be, at most, about once every 7 years. This lower bound estimate does not take into consideration several practical matters, and so overestimates how often FDA would be able to conduct such inspections. For example, FDA does not currently have sufficient trained and experienced investigators to conduct inspections at these rates, and it would take several years of sustained effort to develop sufficient numbers of such investigators.

As GAO recognized in 2008, the Agency also faces a number of practical and other jurisdictional issues that affect its ability to gather information during foreign inspections. For instance, during domestic inspections, FDA inspectors arrive unannounced to observe drug establishments under conditions that represent normal day-to-day activities. In contrast and for a variety of reasons, FDA is generally unable to conduct foreign inspections unannounced. First, the time and expense associated with foreign travel necessitate that inspectors ensure that managers of foreign establishments are available at the time of the inspection and that the production lines being inspected are operational during the inspection. Second, FDA often needs permission from the foreign government of the country in which the establishment is located in order to conduct the inspection. In some countries, visas or letters of invitation are required for the inspectors to enter the country in which the establishment is located. Third, there is little flexibility to extend inspections in foreign countries when the Agency encounters difficulties in an establishment because of the need to adhere to a tight schedule. As a consequence, FDA generally must contact establishments it identifies for surveillance inspections to arrange the inspections, and establishments are [far] more likely to schedule the inspections with the Agency when they have, or know they will soon have, a drug application under review at the Agency for a preapproval inspection.

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Finally, we note that many of the issues raised in GAO's report would be affected by legislation currently under consideration by Congress to grant FDA new authorities to ensure the safety of our nation's drug supply. The Administration has not yet taken a position on additional authorities for drugs; however, the Administration strongly supports passage of pending food safety legislation that would require food manufacturers to have controls and systems in place to prevent safety problems, and would provide FDA with several important enforcement authorities, including civil money penalties, subpoena authority, registration of importers, unique identifiers for food facilities, explicit authority to refuse entry of food from a facility that has refused or delayed an inspection, and mandatory recall authority.

Increasing Global Presence and International Collaboration and Capacity

Given the challenges that it faces in the foreign inspections arena, FDA has undertaken efforts to more effectively secure the drug supply chain by complementing its inspections through additional measures, such as enhancing its global presence and international collaboration and capacity.

Among other things, such efforts include establishing a physical presence in countries that are ever more active in the production of raw materials and drug components; creating cooperative agreements to leverage inspection capabilities among international regulators; and working to create more uniformity among drug safety standards throughout the world. Over the past two years, FDA has made significant progress toward these mutually supportable goals.

Foreign Offices: In November 2008 the Agency began posting FDA employees in foreign posts in key locations overseas. FDA has opened offices in several countries where an FDA presence can help to improve product safety and quality, and leverage resources. To date, FDA has offices in India (Mumbai and New Delhi), China (Shanghai, Guangzhou, and Beijing), Europe (Brussels, Belgium), and Latin America (San Jose, Costa Rica; Santiago, Chile; and Mexico City, Mexico), and the Agency has plans for a Middle East office. FDA has investigators posted in Mumbai, Shanghai, and Guangzhou. The establishment of these foreign offices has enabled FDA to enhance its relationships with foreign counterpart regulatory officials to obtain more accurate and robust information about foreign drug establishments and has facilitated FDA access to drug establishments for inspection.

Dedicated Foreign Cadre: The Agency also has established a specialized foreign cadre of investigators located in FDA district offices in the United States who are dedicated to foreign inspection assignments. The program selects investigators with professional experience specifically related to pharmaceutical inspections and other relevant

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knowledge and skills. Now in its second year, the program has 15 investigators and has already significantly increased the number of foreign inspections as it has grown.

International Collaboration: In addition, FDA has substantially increased its collaboration with foreign regulatory authorities. For example, FDA participates in the API Pilot Program with the European Medicines Agency (EMA) and Australia's Therapeutic Goods Administration (TGA), which calls for participants to share information, as permitted by law, about API inspections and to use this information to leverage the inspectional resources of each regulatory body.

Through this pilot program, FDA has participated in two successful joint inspections, one with the EMA in Croatia and one with the TGA in Mexico. FDA's goal for the pilot program this fiscal year is to conduct four joint inspections (two with each participating authority) and to increase the number of information exchanges with the participating authorities. In 2009, FDA also conducted joint inspections with the drug regulatory authorities of Ireland and the United Kingdom and collaborated on investigations with regulatory officials in Norway, Canada, Australia, Austria, Israel and New Zealand. FDA also continues to work with other regulatory partners to establish more consistent guidelines and standards for good manufacturing practices in many countries throughout the world.

FDA also maintains Memoranda of Understanding with countries to facilitate cooperation and Confidentiality Commitments that allow the exchange of non-public information relating to product safety, quality and effectiveness.

Improvements in FDA's Databases

The 2008 GAO report highlighted deficiencies in FDA's registration data and inspection information systems. FDA's old drug registration and listing system (DRLS), for example, relied on manual entry of hard copy data, a cumbersome process that required reviewers to add hard copy data manually into an electronic database. As GAO noted in its prior report, this process created opportunities for human error and often resulted in a lag between the time FDA received registration information and the time that information was entered into the electronic database.

In keeping with GAO's observations about DRLS, FDA has implemented the electronic drug registration and listing system (eDRLS). With the implementation of eDRLS, it is mandatory for all drug establishments shipping drugs to the United States to register with FDA electronically. The implementation of eDRLS helps FDA more quickly to assemble information about drug establishments. Also, given that eDRLS is updated on a daily basis, FDA's import entry reviewers have near real-time access to registration

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information, and they quickly flag unregistered foreign firms and unlisted drugs when offered for importation at ports and borders.

The new registration system also requires that importing firms submit more comprehensive information. As the Agency fully implements the electronic registration system, reviewers will be able to quickly and easily validate information required as part of importation.

In conjunction with the rollout of eDRLS, FDA also has taken steps to use secondary verification of drug establishments in eDRLS through a widely used universal establishment identifier. In May 2009, FDA published a guidance requesting the submission of a Data Universal Number System (D-U-N-S) number during the electronic registration process. Each DUNS number is unique to a particular business establishment and is available free of charge from Dun & Bradstreet, which maintains a database of all DUNS numbers and their corresponding business entities. As these DUNS numbers begin to populate eDRLS, they can assist FDA in verifying information about foreign establishments.

Over the last two years, FDA substantially has increased its inspection capacity, improved its databases, and expanded its infrastructure to increase its global presence. FDA remains dedicated to addressing the multiple challenges posed by the globalization of the pharmaceutical industry. Building on the progress FDA has made since 2008 will require the commitment and engagement of FDA as well as its stakeholders.

Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114, crossem@gao.gov

Staff Acknowledgments

In addition to the contact named above, Geraldine Redican-Bigott, Assistant Director; Katherine L. Amoroso; Amyre Barker; Cathleen Hamann; Julian Klazkin; and Sarah Resavy made key contributions to this report.

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