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DRUG SAFETY

Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program

Statement of Marcia Crosse, Director
Health Care

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Highlights

Highlights of GAO-08-701T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

The Food and Drug Administration (FDA) is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments. FDA inspects foreign establishments to ensure that they meet the same standards required of domestic establishments. Ongoing concerns regarding FDA's foreign drug inspection program recently were heightened when FDA learned that contaminated doses of a common blood thinner had been manufactured at a Chinese establishment that the agency had never inspected. FDA has announced initiatives to improve its foreign drug inspection program.

In November 2007, GAO testified on weaknesses in FDA's foreign drug inspection program (GAO-08-224T). This statement presents preliminary findings on how FDA's initiatives address the weaknesses GAO identified. GAO interviewed FDA officials and analyzed FDA's initiatives. GAO examined reports and proposals prepared by the agency, as well as its plans to improve databases it uses to manage its foreign drug inspection program.

To view the full product, including the scope and methodology, click on GAO-08-701T. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

Recent FDA initiatives—some of which have been implemented and others proposed—could strengthen FDA's foreign drug inspection program, but these initiatives do not fully address the weaknesses that GAO previously identified.

- GAO testified in November 2007 that FDA's databases do not provide an accurate count of foreign establishments subject to inspection and do provide widely divergent counts. Through one recent initiative, FDA has taken steps to improve its database intended to include foreign establishments registered to market drugs in the United States. This initiative may reduce inaccuracies in FDA's count of foreign establishments. However, these steps will not prevent foreign establishments that do not manufacture drugs for the U.S. market from erroneously registering with FDA. Further, to reduce duplication in its import database, FDA has supported a proposal that would change the data it receives on products entering the United States. However, the implementation of this proposal is not certain and would require action from multiple federal agencies, in addition to FDA. Efforts to integrate these databases have the potential to provide FDA with a more accurate count of establishments subject to inspection, but it is too early to tell.

- GAO testified that gaps in information weaken FDA's processes for prioritizing the inspection of foreign establishments that pose the greatest risk to public health. While FDA recently expressed interest in obtaining useful information from foreign regulatory bodies that could help it prioritize foreign establishments for inspections, the agency has faced difficulties fully utilizing these arrangements in the past. For example, FDA had difficulties in determining whether the scope of other countries' inspection reports met its needs and these reports were not always readily available in English.

- GAO also testified that FDA inspected relatively few foreign establishments each year. FDA made progress in inspecting more foreign establishments in fiscal year 2007, but the agency still inspects far fewer of them than domestic establishments. FDA dedicated about $10 million to foreign drug inspections in fiscal year 2007 and plans to dedicate about $11 million to such inspections in fiscal year 2008.

- Finally, GAO testified that FDA faced certain logistical and staffing challenges unique to conducting foreign inspections. FDA is pursuing initiatives that could address some of the challenges that we identified as being unique to foreign inspections, such as volunteer inspection staff and lack of translators. FDA has proposed establishing a dedicated cadre of staff to conduct foreign inspections, but the timeframe associated with this initiative is unclear. FDA plans to open an office in China and is considering establishing offices in other countries, but the impact that this will have on the foreign drug inspection program is unknown.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you consider the Food and Drug Administration's (FDA) plans to improve its program for inspecting foreign drug manufacturers whose products are marketed in the United States. America has become increasingly dependent on drugs and drug ingredients manufactured in foreign countries. Ten years ago, we reported that FDA needed to improve its foreign drug inspection program.[1] Among other things, we noted that FDA had serious problems managing its foreign inspection data. We were also critical of the number of inspections FDA conducted at foreign manufacturers. In November 2007, we testified on the preliminary findings of our current work in which we identified weaknesses similar to those we found in our previous report.[2] Our preliminary findings suggested that FDA had weaknesses in its databases, including conflicting information on the number of foreign establishments subject to inspection;[3] had information gaps that weakened its process for selecting foreign establishments for inspection; conducted infrequent inspections of these establishments; and faced logistical and staffing challenges unique to foreign inspections. Recent developments involving heparin sodium, a commonly used blood thinner, have further heightened concerns about the safety of drugs and drug ingredients and FDA's ability to inspect foreign manufacturers of these products. In January 2008, FDA began an investigation after receiving reports of serious adverse events in people receiving this drug. The agency later learned that an active pharmaceutical ingredient (API) found in heparin sodium contained a

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

[2]GAO, *Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers*, GAO-08-224T (Washington, D.C.: Nov. 1, 2007). We also recently testified about similar weaknesses that we identified in FDA's program for inspecting foreign medical device manufacturers. GAO, *Medical Devices: Challenges for FDA in Conducting Manufacturer Inspections*, GAO-08-428T (Washington, D.C.: Jan. 29, 2008).

[3]FDA regulations define an establishment as a place of business under one management at one general physical location. 21 C.F.R. § 207.3(a)(7) (2007). Drug firms may have more than one establishment.

contaminant and had been manufactured at a Chinese establishment never inspected by FDA.[4]

Recently, FDA has begun or proposed initiatives to strengthen its foreign drug inspection program.[5] You asked us to assess whether FDA's initiatives will improve its management of this program. My testimony today will focus on these initiatives and how they address the weaknesses we previously identified.

To obtain information about FDA initiatives and how they address weaknesses in its program for inspecting foreign drug manufacturers, we interviewed officials from FDA, including from its Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA), which each have responsibilities for managing the foreign inspection program. We examined reports and proposals prepared by the agency on related initiatives. We also examined FDA's plans to improve databases it uses to manage its foreign drug inspection program, including its Field Accomplishments and Compliance Tracking System (FACTS), Operational and Administrative System for Import Support (OASIS), and Drug Registration and Listing System (DRLS).[6] Our November 2007 testimony included the number of inspections from FACTS as of September 26, 2007. To provide information to update those preliminary findings, we obtained FACTS data that contained information on fiscal year 2007 inspections conducted or entered into this database since our previous analysis. We also obtained fiscal year 2007 data from OASIS to determine the types of drug products manufactured in China and offered for entry into the United States. We assessed the reliability of these databases by (1) reviewing existing information about the data and the databases that produced them,

[4]An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product. According to FDA officials, the agency typically only inspects establishments manufacturing inactive ingredients on a for-cause basis.

[5]See, for example, Food and Drug Administration, *Revitalizing ORA: Protecting the Public Health Together In a Changing World* (Rockville, Md.: Jan. 2008).

[6]We also previously examined the reliability of DRLS. We found that DRLS was reliable, to the extent that it accurately reflects information provided by foreign drug manufacturing establishments that register with FDA. However, we determined that these data do not necessarily reflect all foreign establishments whose drugs are imported into the United States. We do not present new information from DRLS in this testimony.

(2) interviewing agency officials knowledgeable about the data, and (3) performing electronic testing of required data elements. We found the data in the FACTS database reliable for our purposes. In addition, we found that while OASIS is likely to over-estimate the number of foreign establishments involved in the manufacture of those drugs because of uncorrected errors in the data, it provides sufficiently reliable information about the types of drugs offered for entry into the United States. The information we present represents the best information available and is what FDA relies on to manage its foreign drug inspection activities. Our ongoing work is focused on human drugs regulated by CDER and not on biologics,[7] medical devices, veterinary medicines, food, or other items or products for which FDA conducts inspections. However, we obtained information from the center responsible for medical devices, the Center for Devices and Radiological Health (CDRH), to learn about a recent change to one of its databases that addresses problems similar to those in DRLS. We shared the facts contained in this statement with FDA officials. They provided technical comments, which we incorporated as appropriate. We conducted the work for our November 2007 testimony from September 2007 through October 2007, and we conducted our work for this statement from March 2008 through April 2008. All of our work is being performed in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

In summary, recent FDA initiatives—some of which have been implemented and others proposed—could strengthen FDA's foreign drug inspection program, but these initiatives do not fully address the weaknesses that we previously identified. For example, we found that FDA's databases do not provide an accurate count of foreign establishments subject to inspection. FDA plans to implement electronic registration for foreign establishments. Implementing such a process may reduce inaccuracies in FDA's database of registered establishments. However, this will not prevent foreign establishments that do not manufacture drugs for the U.S. market from erroneously registering with

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

FDA. For example, in some foreign markets, foreign drug manufacturers may register with FDA because registration may appear to convey an "approval" or endorsement by the agency. To reduce duplication in FDA's import database, FDA supported a proposal to create a unique governmentwide identifier for all establishments whose products are imported into the United States. However, the implementation of this identifier is not certain and would require action from multiple federal agencies in addition to FDA. Efforts to integrate these databases have the potential to provide FDA with a more accurate count of establishments subject to inspection, but it is too early to tell. FDA has also taken steps that could help it select foreign establishments for inspection by obtaining information from foreign regulatory bodies. However, the agency has not fully utilized arrangements with foreign regulatory bodies in the past that would allow it to obtain such information. FDA has also made progress in conducting more foreign inspections, but it still inspects relatively few establishments. FDA is pursuing initiatives that could address some of the challenges that we identified as unique to foreign inspections. For example, the agency has proposed establishing overseas offices, beginning in China, but the impact that these offices will have on the foreign drug inspection program is unknown. To date, it is unclear whether the agency's proposals will increase the frequency with which FDA inspects foreign establishments or the quality of information it uses to select establishments to inspect.

Background

FDA is responsible for overseeing the safety and effectiveness of human drugs that are marketed in the United States, whether they are manufactured in foreign or domestic establishments.[8] Foreign establishments that market their drugs in the United States must register with FDA. As part of its efforts to ensure the safety and quality of imported drugs, FDA may inspect foreign establishments whose products are imported into the United States. Regular inspections of manufacturing establishments are an essential component of ensuring drug safety. Conducting testing of finished dosage form drug products cannot reliably determine drug quality. Therefore, FDA relies on inspections to determine an establishment's compliance with current good manufacturing practice regulations (GMP).[9] These inspections are a critical mechanism in FDA's

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

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

process of assuring that the safety and quality of drugs are not jeopardized by poor manufacturing practices.

Requirements governing foreign and domestic inspections differ. Specifically, FDA is required to inspect every 2 years those domestic establishments that manufacture drugs marketed in the United States,[10] but there is no comparable requirement for inspecting foreign establishments. FDA does not have authority to require foreign establishments to allow the agency to inspect their facilities. However, FDA has the authority to conduct physical examinations of products offered for import, and if there is sufficient evidence of a violation, prevent their entry at the border.

Within FDA, CDER sets standards and evaluates the safety and effectiveness of prescription and over-the-counter drugs. Among other things, CDER requests that ORA inspect both foreign and domestic establishments to ensure that drugs are produced in conformance with federal statutes and regulations, including current GMPs. CDER requests that ORA conduct inspections of establishments that produce drugs in finished-dosage form as well as those that produce bulk drug substances,[11] including APIs used in finished drug products. These inspections are performed by investigators and, on occasion, laboratory analysts.[12] ORA conducts two primary types of drug manufacturing establishment inspections:

- Preapproval inspections of domestic and foreign establishments are conducted before FDA will approve a new drug to be marketed in the United States.[13] These inspections occur following FDA's receipt of a new drug application (NDA) or an abbreviated new drug application (ANDA)

[10]21 U.S.C. § 360(h).

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

[12]ORA 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.

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

and focus on the manufacture of a specific drug.[14] Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications to determine that the manufacturer is following commitments made in the application. FDA also determines that the manufacturer of the finished drug product, as well as each manufacturer of a bulk drug substance used in the finished product, manufactures, processes, packs, and labels the drug adequately to preserve its identity, strength, quality, and purity.

- Postapproval GMP surveillance inspections are conducted to ensure ongoing compliance with the laws and regulations pertaining to the manufacturing processes used by domestic and foreign establishments in the manufacture of drug products marketed in the United States and bulk drug substances used in the manufacture of those products. These inspections focus on a manufacturer's systemwide controls for ensuring that drug products are of high quality. Systems examined during these inspections include those related to materials, quality control, production, facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drug products.[15]

  FDA has established arrangements with regulatory bodies in other countries to facilitate the sharing of information about drug inspections. FDA has entered into arrangements related to GMP inspections with Canada, Japan, the European Union, and others. The scope of such arrangements can vary. Some arrangements may allow FDA to obtain reports of inspections conducted by other countries, for informational purposes. Other arrangements may involve more than the exchange of information. For example, FDA and another country may enter into an arrangement to work towards the mutual recognition of each other's inspection standards or the acceptance of one another's inspections, in lieu of their own.

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

[15]In addition, FDA conducts for-cause inspections when it receives information indicating problems in the manufacture of approved drug products, as well as when it follows up on manufacturers that were not in compliance with GMPs during previous inspections.

CDER uses a risk-based process to select some foreign and domestic establishments for postapproval GMP surveillance inspections. The process uses a risk-based model to identify those establishments that, based on characteristics of the establishment and of the product being manufactured, have the greatest public health risk potential should they experience a manufacturing defect. For example, FDA considers the risk to public health from poor quality over-the-counter drugs to be lower than for prescription drugs. Consequently establishments manufacturing only over-the-counter drugs receive a lower score on this factor in the risk-based process than other manufacturers. Through this process, CDER annually prepares a prioritized list of domestic establishments and a separate, prioritized list of foreign establishments.

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

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

- OASIS contains information on drugs and other FDA-regulated products offered for entry into the United States, including information on the establishment that manufactured the drug. The information in OASIS is automatically generated from data managed by Customs and Border Protection (CBP). The data are originally entered by customs brokers based on the information available from the importer.[16] CBP specifies an algorithm by which customs brokers generate a manufacturer identification number from information about an establishment's name, address, and location.

- FACTS contains information on FDA's inspections of foreign and domestic drug establishments. FDA investigators and laboratory analysts enter information into FACTS following completion of an inspection.

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

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

In November 2007, we testified on preliminary findings that identified weaknesses in FDA's program for inspecting foreign establishments manufacturing drugs for the U.S. market. Specifically, we found that, as in 1998, FDA's effectiveness in managing the foreign drug inspection program continued to be hindered by weaknesses in its data on foreign establishments. FDA did not know how many foreign establishments were subject to inspection. FDA relied on databases that were designed for purposes other than managing the foreign drug inspection program. Further, these databases contained inaccuracies that FDA could not easily reconcile. DRLS indicated there were about 3,000 foreign establishments registered with FDA in fiscal year 2007,[17] while OASIS indicated that about 6,800 foreign establishments actually offered drugs for entry in that year. FDA recognized these inconsistencies, but could not easily correct them partly because the databases could not exchange information. Any comparisons of the data must be performed manually, on a case-by-case basis.

We also testified that FDA inspected relatively few foreign establishments.[18] Data from FDA suggested that the agency may inspect about 8 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that no additional establishments require inspection. However, FDA could not provide an exact number of foreign

[17]This count includes foreign establishments that were registered to manufacture human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

[18]We updated information presented in our November 2007 testimony because that data did not include complete counts of inspections conducted in fiscal year 2007.

establishments that had never been inspected. From fiscal year 2002 through fiscal year 2007, FDA conducted 1,479 inspections of foreign establishments, and three quarters of these inspections were concentrated in 10 countries. (See table 1.) Because some establishments were inspected more than once during this time period, FDA actually inspected 1,119 unique establishments. For example, of the 94 inspections that FDA conducted of Chinese establishments, it inspected 80 unique establishments across this six year period. The lowest rate of inspections in these 10 countries was in China, for which FDA inspected 80 of its estimated 714 establishments, or fewer than 14 establishments per year, on average.

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

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

Source: GAO analysis of FDA data.

[a]This count represents the number of establishments FDA used to plan its fiscal year 2007 prioritized surveillance inspections. In preparing this list, FDA draws on information from DRLS. It also obtains information from previous inspections to help it identify establishments that are subject to inspection but are not required to register—such as the manufacturer of an API whose product is not directly imported into the United States. However, as a result of the inaccuracies in DRLS, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

We testified that, while enforcing GMP compliance through surveillance inspections was FDA's most comprehensive program for monitoring the quality of marketed drugs, most of FDA's inspections of foreign manufacturers occurred when they were listed in an NDA or ANDA. The majority of these preapproval inspections were combined with a GMP surveillance inspection. Although FDA used a risk-based process to develop a prioritized list of foreign establishments for GMP surveillance inspections, few were completed in a given year—about 30 in fiscal year 2007. The usefulness of the process was weakened by the incomplete and possibly inaccurate information on those foreign establishments that FDA had not inspected recently, as well as those that had never been the subject of a GMP surveillance inspection.

We also testified that FDA's foreign inspection process involves unique circumstances that are not encountered domestically. For example, FDA relies on staff that inspect domestic establishments to volunteer for foreign inspections. Unlike domestic inspections, FDA does not arrive unannounced at a foreign establishment. It also lacks the flexibility to easily extend foreign inspections if problems are encountered. Finally, language barriers can make foreign inspections more difficult than domestic ones. FDA does not generally provide translators to its inspection teams. Instead, they may have to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

Recent Initiatives May Help FDA Select Foreign Establishments for Inspection, but Weaknesses in Its Foreign Drug Inspection Program Are Not Fully Addressed

FDA has initiated several recent changes to its foreign drug inspection program, but the changes do not fully address the weaknesses that we previously identified. FDA has initiatives underway to reduce the inaccuracies in its registration and import databases that make it difficult to determine the number of foreign establishments subject to inspection, although to date these databases still do not provide an accurate count of such establishments. FDA has taken steps that could help it select foreign establishments for inspection by obtaining information from foreign regulatory bodies. However, the agency has not fully utilized arrangements with foreign regulatory bodies in the past that would allow it to obtain such information. FDA has made progress in conducting more foreign inspections, but it still inspects relatively few establishments. FDA is also pursuing initiatives that could address some of the challenges that we identified as being unique to foreign inspections, but implementation details and timeframes associated with these initiatives are unclear.

FDA Initiatives Could Improve Its Data, but Will Not Ensure an Accurate Count of Foreign Establishments Subject to Inspection

FDA has initiatives underway to reduce inaccuracies in its databases, but actions taken thus far will not ensure that the agency has an accurate count of establishments subject to inspection. As we previously testified, DRLS does not provide FDA with an accurate count of foreign establishments manufacturing drugs for the U.S. market. For example, foreign establishments may register with FDA, whether or not they actually manufacture drugs for the U.S. market,[19] and the agency does not routinely verify the information provided by the establishment. Beginning in late 2008, CDER plans to implement an electronic registration and listing system that could improve the accuracy of information the agency maintains on registered establishments. The new system will allow drug manufacturing establishments to submit registration and listing information electronically, rather than submitting it on paper forms. FDA hopes that electronic registration will result in efficiencies allowing the agency to shift resources from data entry to assuring the quality of the databases. However, electronic registration alone will not prevent foreign establishments that do not manufacture drugs for the U.S. market from registering, thus still presenting the problem of an inaccurate count.

Recently, another FDA center implemented changes affecting the registration of medical device manufacturers, an activity for which we previously identified problems similar to those found in CDER.[20] In fiscal year 2008, CDRH implemented, in addition to electronic registration, an annual user fee of $1,706 per registration for certain medical device establishments[21] and an active re-registration process.[22] According to CDRH, as of early April 2008, about half of the previously registered establishments have reregistered using the new system. While CDRH

[19]FDA officials pointed out that some foreign establishments register, for example, because registration may erroneously appear to convey an "approval" or endorsement by FDA in foreign markets.

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

[21]21 U.S.C. §§ 379i(13); 379j(a)(3), (b), (h). The registration user fee is $1,706 in fiscal year 2008 and will increase by 8.5 percent per year, to $2,364 in fiscal year 2012. Fees are available for obligation only to the extent and in the amount provided in annual appropriations acts. FDA's authority to assess registration fees terminates on October 1, 2012.

[22]CDRH indicated that the center will deactivate the registrations of those establishments that fail to complete the annual registration. Officials noted that, in the past, many establishments that had previously registered had not updated those registrations in several years.

officials expect that this number will increase,[23] they expect that the elimination of establishments that do not manufacture medical devices for the U.S. market—and thus should not be registered—will result in a smaller, more accurate database of medical device establishments. CDRH officials indicated that implementation of electronic registration and the annual user fee seems to have improved the data so CDRH can more accurately identify the type of establishment registered, the devices manufactured at an establishment, and whether or not an establishment should be registered. According to CDRH officials, the revenue from device registration user fees is applied to the process for the review of device applications,[24] including establishment inspections undertaken as part of the application review process. CDER does not currently have the authority to assess a user fee for registration of drug establishments, but officials indicated that such a fee could discourage registrations of foreign manufacturers that are not ready, are not actively importing, or have not been approved to market drug products in the United States. Officials also suggested that such fees could be used to supplement the resources available for conducting inspections.

FDA has proposed, but not yet implemented, the Foreign Vendor Registration Verification Program, which could help improve the accuracy of information FDA maintains on registered establishments. Through this program, FDA plans to contract with an external organization to conduct on-site verification of the registration data and product listing information of foreign establishments shipping drugs and other FDA-regulated products to the United States. As of April 2008, FDA had solicited proposals for this contract but was still developing the specifics of the program. For example, the agency had not yet established the criteria it would use to determine which establishments would be visited for verification purposes or determined how many establishments it would verify annually. FDA currently plans to award this contract in May 2008. Given the early stages of this process, it is too soon to determine whether this program will improve the accuracy of the data FDA maintains on foreign drug establishments.

[23]According to CDRH, in April, the center will send letters to establishments that have registered in the past but have not completed their registration for fiscal year 2008 advising them that they must register using the new system and must pay the registration fee, if applicable, to be considered registered.

[24]21 U.S.C. § 379i(8).

In addition to changes to improve DRLS, FDA has supported a proposal that has the potential to address weaknesses in OASIS, but FDA does not control the implementation of this change. As we previously testified, OASIS contains an inaccurate count of foreign establishments manufacturing drugs imported to the United States as a result of unreliable identification numbers generated by customs brokers when the product is offered for entry.[25] FDA officials told us that these errors result in the creation of multiple records for a single establishment, which results in inflated counts of establishments offering drugs for entry into the U.S. market. FDA is pursuing the creation of a governmentwide unique establishment identifier, as part of the Shared Establishment Data Service (SEDS), to address these inaccuracies.[26] Rather than relying on the creation and entry of an identifier at the time of import, SEDS would provide a unique establishment identifier and a centralized service to provide commercially verified information about establishments. The standard identifier would be submitted as part of import entry data where required by FDA or other government agencies. SEDS could thus eliminate the problem of having multiple identifiers associated with an individual establishment. The implementation of SEDS is dependent on action from multiple federal agencies, including the integration of the concept into a CBP import and export system currently under development and scheduled for implementation in 2010. In addition, once implemented by CBP, participating federal agencies would be responsible for bearing the cost of integrating SEDS with their own operations and systems. FDA officials are not aware of a specific timeline for the implementation of SEDS. Developing an implementation plan for SEDS is a recommendation of the Interagency Working Group on Import Safety's *Action Plan for Import Safety: A Roadmap for Continual Improvement*.

Finally, FDA is in the process of implementing additional initiatives to improve the integration of its current data systems, which could make it easier for the agency to establish an accurate count of foreign drug manufacturing establishments subject to inspection. The agency's Mission Accomplishments and Regulatory Compliance Services (MARCS) is intended to help FDA electronically integrate data from multiple systems.

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

[26]The SEDS concept was developed by a working group with representatives from FDA, the Environmental Protection Agency, and the departments of Agriculture, Commerce, Defense, and Homeland Security.

It is specifically designed to give individual users a more complete picture of establishments. FDA officials estimate that MARCS, which is being implemented in stages, could be fully implemented by 2011 or 2012. However, FDA officials told us that implementation has been slow because the agency has been forced to shift resources away from MARCS and toward the maintenance of current systems that are still heavily used, such as FACTS and OASIS. Taken together, electronic registration, the Foreign Vendor Registration Verification Program, SEDS, and MARCS could provide the agency with more accurate information on the number of establishments subject to inspection. However, it is too early to tell.

FDA Initiatives to Obtain Information on Foreign Establishments May Have Limited Impact on Its Selection of Establishments to Inspect

FDA has taken steps to help it select establishments for inspection by obtaining information on foreign establishments from regulatory bodies in other countries, despite encountering difficulties in fully utilizing these arrangements in the past. FDA has recognized the importance of receiving information about foreign establishments from other countries and has taken steps to develop new, or strengthen existing, information-sharing arrangements to do so. For example, according to FDA, the agency is enhancing an arrangement to exchange information with the Swiss drug regulatory agency. FDA officials have highlighted such arrangements as a means of improving the agency's oversight of drugs manufactured in foreign countries. For example, they told us that in selecting establishments for GMP surveillance inspections, they sometimes use the results of an establishment inspection conducted by a foreign government to determine whether to inspect an establishment.[27] FDA told us that it received drug inspection information from foreign regulatory bodies six times in 2007.

FDA has previously encountered difficulties which prevented it from taking full advantage of information-sharing arrangements with other countries. Obtaining inspection reports from other countries and using this information has proved challenging. In order for FDA to determine the value of inspection reports from a particular country, it must consider whether the scope of that country's inspections is sufficient for FDA's needs. Evaluation of inspections conducted by foreign regulatory bodies can be complex and may include on-site review of regulatory systems and audit inspections. Further, to obtain results of inspections conducted by

[27]FDA officials told us that they do not use the results of an inspection conducted by a foreign regulatory body to make decisions about whether to approve a new drug.

its foreign counterparts, FDA must specifically request them—they are not automatically provided. While FDA has provided certain foreign regulatory bodies access to its Compliance Status Information System—which provides information from the results of FDA's inspections—foreign regulatory bodies have not established similar systems to provide FDA access to data about their inspections. FDA indicated that such systems are under development in some countries and FDA has been promised access when they are available. However, currently, FDA cannot routinely incorporate the results of inspections conducted by foreign regulatory authorities into its risk-based selection process.[28] FDA officials stated that, in the past, they encountered difficulties using inspection reports from other countries that were not readily available in English. Consequently, the existence of such information-sharing arrangements alone may not help FDA systematically address identified weaknesses in its foreign inspection program.

Arrangements that have the potential to allow FDA to formally accept the results of inspections conducted by other countries have been prohibitively challenging to implement. Although these arrangements allow countries to leverage their own inspection resources, according to FDA officials, assessing the equivalence of other countries' inspections and the relevance of the information available is difficult. They added that complete reliance on another country's inspection results is risky. The activities associated with establishing these agreements may be resource intensive, which may slow FDA's implementation of them. For example, FDA told us that a lack of funding for establishing such an arrangement with the European Union effectively stopped progress. Although FDA has completed preliminary work associated with this arrangement, the agency has concluded that it will be more beneficial to pursue other methods of cooperating with the European Union. The agency has no plans at this time to enter into other such arrangements.

FDA's current efforts to obtain more information from foreign regulatory bodies may help it better assess the risk of foreign establishments when prioritizing establishments for GMP surveillance inspections. However, most foreign inspections are conducted to examine an establishment referenced in an NDA or ANDA. The agency conducts relatively few

[28]In addition to challenges in obtaining inspection reports, FDA may also be limited by the type of information available. For example, FDA may not be able to obtain inspection reports on API manufacturing establishments because other regulatory bodies may only inspect finished-dosage manufacturers.

foreign GMP surveillance inspections selected through its risk-based process. Therefore, these efforts may be of limited value to the foreign inspection program if the agency does not increase the number of such inspections.

FDA Has Increased Its Inspections of Foreign Establishments, but Still Inspects Relatively Few

FDA has made progress in conducting more foreign inspections, but it still inspects relatively few establishments. FDA conducted more foreign establishment inspections in fiscal year 2007 than it had in each of the 5 previous fiscal years. However, the agency still inspected less than 11 percent of the foreign establishments on the prioritized list that it used to plan its fiscal year 2007 GMP surveillance inspections.[29] The agency also still conducts far fewer inspections of foreign establishments than domestic establishments. Its budget calls for incremental increases in funding for foreign inspections. FDA officials told us that, for fiscal year 2008, the agency plans to conduct more GMP surveillance inspections based on its prioritized list of foreign establishments. FDA officials estimated that the agency conducted about 30 such inspections in fiscal year 2007 and plans to conduct at least 50 in fiscal year 2008.

If FDA were to inspect foreign establishments biennially, as is required for domestic establishments, this would require FDA to dedicate substantially more funding than it has dedicated to such inspections in the past. In fiscal year 2007, FDA dedicated about $10 million to inspections of foreign establishments.[30] FDA estimates that, based on the time spent conducting inspections of foreign drug manufacturing establishments in fiscal year 2007, the average cost of such an inspection ranges from approximately $41,000 to $44,000.[31] Our analysis suggests that it could cost the agency $67 million to $71 million each year to biennially inspect each of the 3,249 foreign drug establishments on the list that FDA used to plan its fiscal year 2007 GMP surveillance inspections. Based on these same estimates, it would take the agency $15 million to $16 million each year to inspect the estimated 714 drug manufacturing establishments in China

[29]As a result of the inaccuracies in its data, FDA recognizes that this list does not provide an accurate count of establishments subject to inspection.

[30]According to FDA budget documents, the agency dedicated about $43 million to inspecting domestic drug manufacturers in fiscal year 2007.

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

every 2 years. According to FDA budget documents, the agency estimates that it will dedicate a total of about $11 million in fiscal year 2008 and $13 million in fiscal year 2009 to all foreign inspections.

In its fiscal year 2009 budget, FDA proposed instituting a reinspection user fee.[32] Reinspections are conducted to verify that corrective actions the agency has required establishments to take in response to previously identified violations have been implemented. FDA's proposal to institute a reinspection user fee would allow it to charge establishments a fee when the agency determines a reinspection is warranted. However, as proposed, the reinspection user fee would be budget neutral, meaning that the other appropriated funds the agency receives would be offset by the amount of collected reinspection fees. As a result, this proposal would not provide the agency with an increase in funds that could be used to pay for additional foreign inspections.

FDA Initiatives May Address Some Challenges Unique to Foreign Inspections, but It Is Too Early to Determine Their Effectiveness

FDA has recently announced proposals to address some of the challenges unique to conducting foreign inspections, but specific implementation steps and associated time frames are unclear. We previously identified the lack of a dedicated staff devoted to conducting foreign inspections as a challenge for the agency. FDA noted in its report on the revitalization of ORA that it is exploring the creation of a cadre of investigators who would be dedicated to conducting foreign inspections.[33] However, the report does not provide any additional details or timeframes about this proposal. In addition, FDA recently announced plans to establish a permanent foreign presence overseas, although little information about these plans is available. Through an initiative known as "Beyond our Borders," FDA intends that its foreign offices will improve cooperation and information exchange with foreign regulatory bodies, improve procedures for expanded inspections, allow it to inspect facilities quickly in an emergency, and facilitate work with private and government agencies to assure standards for quality. FDA's proposed foreign offices are intended to expand the agency's capacity for regulating, among other things, drugs, medical devices, and food. The extent to which the activities conducted by foreign offices are relevant to FDA's foreign drug inspection program is

[32]FDA also proposed a reinspection user fee in its fiscal year 2007 and fiscal year 2008 budgets, but these proposals were not enacted.

[33]See, for example, Food and Drug Administration, *Revitalizing ORA: Protecting the Public Health Together In a Changing World* (Rockville, Md.: Jan. 2008).

uncertain. Initially, FDA plans to establish a foreign office in China with three locations—Beijing, Shanghai, and Guangzhou—comprised of a total of eight FDA employees and five Chinese nationals. The Beijing office, which the agency expects will be partially staffed by the end of 2008, will be responsible for coordination between FDA and the Chinese regulatory agencies. FDA staff located in Shanghai and Guangzhou, who will be hired in 2009, will be focused on conducting inspections and working with Chinese inspectors to provide training as necessary. FDA has noted that the Chinese nationals will primarily provide support to FDA staff including translation and interpretation. The agency is also considering setting up offices in other locations, such as India, the Middle East, Latin America, and Europe, but no dates have been specified. While the establishment of both a foreign inspection cadre and offices overseas have the potential for improving FDA's oversight of foreign establishments and providing the agency with better data on foreign establishments, it is too early to tell whether these steps will be effective or will increase the number of foreign drug inspections.

Agreements with foreign governments, such as one recently reached with China's State Food and Drug Administration, may help the agency address certain logistical issues unique to conducting inspections of foreign establishments. We previously testified that one challenge faced by FDA involved the need for its staff to obtain a visa or letter of invitation to enter a foreign country to conduct an inspection. However, FDA officials told us that their agreement with China recently helped FDA expedite this process when it learned of the adverse events associated with a Chinese heparin manufacturer. According to these officials, the agreement with China greatly facilitated its inspection of this manufacturer by helping FDA send investigators much more quickly than was previously possible.

Concluding Observations

Americans depend on FDA to ensure the safety and effectiveness of the drugs they take. The recent incident involving heparin underscores the importance of FDA's initiatives and its steps to obtain more information about foreign drug establishments, conduct more inspections overseas, and improve its overall management of its foreign drug inspection program. FDA has identified actions that, if fully implemented, could address some, but not all, of the concerns we first identified 10 years ago and reiterated 5 months ago in our testimony before this subcommittee. Given the growth in foreign drug manufacturing for the U.S. market and the current large gaps in FDA's foreign drug inspections, FDA will need to devote considerable resources to this area if it is to increase the rate of inspections. However, FDA's plans currently call for incremental increases

that will have little impact in the near future to reduce the interval between inspections for these establishments. In addition, many of FDA's initiatives will take several years to implement and require funding and certain interagency or intergovernmental agreements that are not yet in place. Taken together, FDA's plans represent a step forward in filling the large gaps in FDA's foreign drug inspection program, but do little to accomplish short-term change.

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

Contacts and Acknowledgments

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