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## DRUG SAFETY

# FDA Faces Challenges Overseeing the Foreign Drug Manufacturing Supply Chain

Statement of Marcia Crosse  
Director, Health Care

U.S. Government Accountability Office

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Highlights of [GAO-11-936T](#), a testimony before the Committee on Health, Education, Labor, and Pensions, U.S. Senate

## Why GAO Did This Study

Globalization has placed increasing demands on the Food and Drug Administration (FDA) in ensuring the safety and effectiveness of drugs marketed in the United States. The pharmaceutical industry has increasingly relied on global supply chains in which each manufacturing step may be outsourced to foreign establishments. As part of its efforts, FDA may conduct inspections of foreign drug manufacturing establishments, but there are concerns that the complexity of the drug manufacturing supply chain and the volume of imported drugs has created regulatory challenges for FDA. FDA has begun taking steps to address some of these concerns, such as the establishment of overseas offices.

This statement discusses (1) FDA's inspection of foreign drug manufacturing establishments, (2) the information FDA has on these establishments, and (3) recent FDA initiatives to improve its oversight of the supply chain. The statement presents findings based primarily on GAO reports since 2008 related to FDA's oversight of the supply chain. These reports include *Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning Is Needed* ([GAO-10-960](#), Sept. 30, 2010) and *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](#), Sept. 30, 2010). GAO supplemented this prior work with updated information obtained from FDA in August and September 2011.

View [GAO-11-936T](#). For more information, contact Marcia Crosse at (202) 512-7114 or [crosse@m@gao.gov](mailto:crosse@m@gao.gov).

September 14, 2011

## DRUG SAFETY

### FDA Faces Challenges Overseeing the Foreign Drug Manufacturing Supply Chain

## What GAO Found

Inspections of foreign drug manufacturers are an important element of FDA's oversight of the supply chain, but GAO's prior work showed that FDA conducts relatively few such inspections. In 2008, GAO reported that in fiscal year 2007 FDA inspected 8 percent of foreign establishments subject to inspection and estimated that, at that rate, it would take FDA about 13 years to inspect all such establishments. GAO recommended that FDA increase the number of foreign inspections it conducts at a frequency comparable to domestic establishments with similar characteristics. FDA subsequently increased the number of foreign establishment inspections. FDA's inspection efforts in fiscal year 2009 represent a 27 percent increase in the number of inspections it conducted, when compared to fiscal year 2007—424 and 333 inspections, respectively. However, FDA officials acknowledged that FDA is far from achieving foreign drug inspection rates comparable to domestic inspection rates—the agency inspected 1,015 domestic establishments in fiscal year 2009. Also, the types of inspections FDA conducts generally do not include all parts of the drug supply chain. Conducting inspections abroad also continues to pose unique challenges for the agency. For example, FDA faces limits on its ability to require foreign establishments to allow it to inspect their facilities. Furthermore, logistical issues preclude FDA from conducting unannounced inspections, as it does for domestic establishments.

GAO previously reported that FDA lacked complete and accurate information on foreign drug manufacturing establishments—information critical to understanding the supply chain. In 2008, GAO reported that FDA databases contained incorrect information about foreign establishments and did not contain an accurate count of foreign establishments manufacturing drugs for the U.S. market. FDA's lack of information hampers its ability to inspect foreign establishments. GAO recommended that FDA address these deficiencies. FDA has taken steps to do so, but has not yet fully addressed GAO's concerns.

Given the difficulties that FDA has faced in inspecting and obtaining information on foreign drug manufacturers, and recognizing that more inspections alone are not sufficient to meet the challenges posed by globalization, the agency has begun to implement other initiatives to improve its oversight of the drug supply chain. FDA's overseas offices have engaged in a variety of activities to help ensure the safety of imported products, such as training foreign stakeholders to help enhance their understanding of FDA regulations. GAO recommended that FDA enhance its strategic and workforce planning, which FDA agreed it would do. FDA has also taken other positive steps, such as developing initiatives that would assist its oversight of products at the border, although these are not yet fully implemented. Finally, FDA officials identified statutory changes that FDA believes it needs to help improve its oversight of drugs manufactured in foreign establishments. For example, in place of the current requirement that FDA inspect domestic establishments every 2 years, officials indicated the agency would benefit from a risk-based inspection process with flexibility to determine the frequency with which both foreign and domestic establishments are inspected. In light of the growing dependence upon drugs manufactured abroad and the potential for harm, FDA needs to act quickly to implement changes across a range of activities in order to better assure the safety and availability of drugs for the U.S. market.

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Chairman Harkin, Ranking Member Enzi, and Members of the Committee:

I am pleased to be here today to discuss the Food and Drug Administration's (FDA) oversight of the nation's drug supply chain.<sup>1</sup> Globalization has placed increasing demands on FDA, which is responsible for the oversight of drugs marketed in the United States, regardless of whether they are manufactured in foreign or domestic establishments.<sup>2</sup> While Americans once used drugs that were mostly manufactured domestically, this is no longer the case. According to FDA, the number of drug products manufactured at foreign establishments has more than doubled since 2002, with China and India accounting for the greatest shares of this growth. In addition, the pharmaceutical industry has increasingly relied on global supply chains in which each manufacturing step may be outsourced to foreign establishments. The complexity of the drug supply chain, the volume of imported drugs, and the number of foreign establishments producing these drugs have created regulatory challenges for FDA. The danger associated with an insecure supply chain was highlighted in January 2008, when FDA responded to a crisis involving the contamination of the active pharmaceutical ingredient (API) used to manufacture heparin,<sup>3</sup> a medication used to prevent and treat blood clots. The contaminated heparin, which was associated with numerous adverse events—including deaths—came from a facility in

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<sup>1</sup>Drugs 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).

<sup>2</sup>FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. 21 C.F.R. § 207.3(a)(8) (2011). 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) (2011). Drug manufacturers may have more than one establishment.

<sup>3</sup>An API includes any component of a drug 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) (2011). In this statement, we refer both to drug products—drugs in their finished dosage form—and to APIs as “drugs.”

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China. During its investigation, FDA determined that some manufacturers were not adequately safeguarding their heparin supply chains.<sup>4</sup>

In recent years we have reported on several aspects of FDA's ability to protect Americans from unsafe and ineffective drugs entering our supply chain.<sup>5</sup> Amidst growing concerns with the increasing demands placed on the agency, including its ability to ensure the quality of drugs manufactured overseas, we added FDA's oversight of medical products to our High-Risk Series.<sup>6</sup> FDA has acknowledged that globalization has fundamentally changed the environment for regulating pharmaceutical products and the agency has begun taking steps to address some of these concerns, such as the establishment of overseas offices.<sup>7</sup>

My remarks today will focus primarily on information collected for several reports we issued since 2008 that specifically cite concerns we identified related to FDA's oversight of the manufacturing side of the supply chain for drugs produced by overseas establishments for marketing in the

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<sup>4</sup>The heparin supply chain starts with a raw source material, primarily derived from the intestines of pigs, that is processed into crude heparin. Thousands of small pig farms in Chinese villages extract and process pig intestines in small workshops called casing facilities. Consolidators collect different batches of heparin from various workshops and sell these batches to manufacturers, who further refine the crude heparin into heparin API, the active ingredient used in heparin drug products and heparin containing devices. More than half of the finished heparin products in the United States and globally are made from Chinese-sourced materials.

<sup>5</sup>See the *Related GAO Products* page at the end of this statement.

<sup>6</sup>GAO, *High-Risk Series: An Update*, [GAO-11-278](#) (Washington, D.C.: February 2011). We first added FDA's oversight of medical products to our High-Risk Series in January 2009.

<sup>7</sup>In late 2008 and early 2009, FDA established overseas offices comprised of staff covering particular countries or regions. FDA has staff located overseas in Beijing, Shanghai, and Guangzhou, China; New Delhi and Mumbai, India; San Jose, Costa Rica; Mexico City, Mexico; and Santiago, Chile. In June 2011, FDA also located staff in Amman, Jordan and Pretoria, South Africa.

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United States.<sup>8</sup> Specifically, I will discuss (1) FDA's inspections of foreign drug manufacturing establishments, which are intended to assure that the safety and quality of drugs are not jeopardized by poor manufacturing practices; (2) the information FDA has on these establishments; and (3) recent FDA initiatives to improve its oversight of the supply chain.

For our work reviewing FDA's inspections of foreign drug manufacturing establishments, we obtained and analyzed FDA data on foreign and domestic drug manufacturing establishment inspections conducted from fiscal years 2007 to 2009. We also examined methods used by FDA to select establishments for inspection. For our work examining how FDA responded to the heparin crisis, we reviewed actions FDA took during the crisis period, which FDA defined as January 2008 through May 2008. We also interviewed FDA officials and drug manufacturers and reviewed FDA documents, such as inspection reports and internally produced summaries (e.g., a time line of events related to the crisis).

For our work reviewing the information FDA has on foreign drug manufacturing establishments, we obtained data from FDA's registration database on the number of establishments registered to market their drugs in the United States.<sup>9</sup> We also obtained data from FDA's import database on the number of establishments that have manufactured drugs that were shipped to the United States.<sup>10</sup> We reviewed FDA's initiatives for improving the accuracy of the agency's data on foreign establishments contained in these databases, which are both used to manage the foreign drug inspection program.

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<sup>8</sup>GAO, *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); 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); GAO, *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](#) (Washington, D.C.: Sept. 30, 2010); and GAO, *Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added*, [GAO-11-95](#) (Washington, D.C.: Oct. 29, 2010).

<sup>9</sup>Domestic 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).

<sup>10</sup>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.

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For our work reviewing recent FDA initiatives intended to improve the agency's oversight of foreign drug manufacturing establishments, we reviewed documentation and interviewed FDA officials from each of FDA's five overseas offices to learn about their activities, challenges, accomplishments, and strategic and workforce planning. For three of the overseas offices—China, India, and Latin America—we interviewed office staff and others, such as officials from FDA's foreign regulatory counterparts, during on-site visits in February and March 2010. We also 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. We supplemented that prior work with updated information that we received from FDA in August and September 2011.

We conducted the work for the performance audits on which this statement is based from September 2007 to September 2008, June 2009 to September 2010, and from August to September 2011 for selected updates. Our work was conducted 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.

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## Background

As part of its efforts to ensure the safety and quality of imported drugs, FDA may conduct inspections of foreign establishments manufacturing drugs, including APIs, that are imported into the United States. FDA relies on these establishment inspections to determine compliance with current good manufacturing practice regulations (GMP).<sup>11</sup> 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.

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<sup>11</sup>GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210, 211 (2011). 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).

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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.<sup>12</sup>

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 when they are offered for import at a point of entry, or otherwise—that there is sufficient evidence of a violation of applicable laws or regulations.<sup>13</sup>

FDA conducts two primary types of drug manufacturing establishment 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. In addition, FDA conducts GMP inspections at establishments manufacturing drugs already marketed in the United States to determine ongoing compliance with laws and regulations.

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## FDA Conducts Relatively Few Inspections of Foreign Drug Establishments

Although inspections of foreign drug manufacturing establishments—which are intended to assure that the safety and quality of drugs are not jeopardized by poor manufacturing practices—are an important element of FDA's oversight of the supply chain, our previous work has shown that FDA conducts relatively few inspections of the establishments that it considers subject to inspection. Specifically, in our 2008 report, we estimated that FDA inspected 8 percent of such foreign drug establishments in fiscal year 2007. At this rate, we estimated that it would take FDA about 13 years to inspect all foreign establishments the agency considers subject to inspection. In 2010, we reported that FDA had increased its inspection efforts in fiscal year 2009. We estimated that FDA inspected 11 percent of foreign establishments subject to inspection and it would take FDA about 9 years to inspect all such establishments at this rate. FDA's inspection efforts in fiscal year 2009 represent a 27 percent increase in the number of inspections the agency conducted when compared to fiscal year 2007—424 and 333 inspections,

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<sup>12</sup>See 21 U.S.C. § 360(h), (i)(3).

<sup>13</sup>See 21 U.S.C. § 381(a).

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respectively.<sup>14</sup> In contrast, FDA conducts more inspections of domestic establishments and the agency inspects these establishments more frequently. For example, in fiscal year 2009, FDA conducted 1,015 domestic inspections, inspecting approximately 40 percent of domestic establishments. We estimated that at this rate FDA inspects domestic establishments approximately once every 2.5 years. To address these discrepancies, we recommended that FDA conduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics.<sup>15</sup> FDA agreed that the agency should be conducting more foreign inspections, but FDA officials have since acknowledged that the agency is far from achieving foreign drug inspection rates comparable to domestic inspection rates and, without significant increases to its inspectional capacity, the agency's ability to close this gap is highly unlikely.<sup>16</sup>

In addition to conducting few foreign drug manufacturing inspections, the types of inspections FDA conducts generally do not include all parts of the drug supply chain. For example, FDA officials told us during our review of the contaminated heparin crisis that the agency typically does not inspect manufacturers of source material<sup>17</sup>—which are not required to be listed on applications to market drugs in the United States—and generally limits its inspections to manufacturers of the finished product and APIs. Furthermore, once FDA conducts an inspection of a foreign drug manufacturer, it is unlikely that the agency will inspect it again, as the majority of the foreign inspections FDA conducts are to inform decisions about the approval of new drugs before they are marketed for sale in the United States.

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<sup>14</sup>FDA attributes this increase in fiscal year 2009 foreign drug inspections to staffing changes—the creation of a drug inspection cadre and the placement of investigators overseas—and increased resources dedicated to these types of inspections.

<sup>15</sup>See [GAO-08-970](#).

<sup>16</sup>We noted in our September 2010 report that, in response to our inquiries and those of congressional staff, FDA had undertaken a review to determine the appropriate inspection frequency for foreign and domestic drug establishments. However, as of September 2011, this review had not been completed.

<sup>17</sup>For example, in the case of the heparin supply chain, the source material is primarily derived from the intestines of pigs, which is processed into the crude heparin that is refined into heparin API.



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Despite increases in foreign drug establishment inspections in recent years, FDA continues to face unique challenges conducting inspections abroad. Specifically, as we identified in our 2008 report on FDA's foreign drug inspections, FDA continues to experience challenges related to limits on the agency's ability to require foreign establishments to allow the agency to inspect their facilities.<sup>18</sup> For example, while inspecting establishments in China during the heparin crisis, Chinese crude heparin consolidators refused to provide FDA full access during inspections—in particular, one consolidator refused to let FDA inspectors walk through its laboratory and refused FDA access to its records. As a result, FDA officials said they focused on the manufacturers' responsibilities to ensure that these establishments could trace their crude heparin back to qualified suppliers that produce an uncontaminated product and requested that manufacturers conduct their own investigations of any heparin products for which they received complaints or that did not meet specifications. Furthermore, FDA faces other challenges conducting foreign inspections, such as logistical issues that necessitate the agency notifying the manufacturer of the agency's intention to inspect the establishment in advance. In contrast to domestic inspections which are conducted without prior notice, FDA contacts foreign manufacturers prior to inspection to ensure that the appropriate personnel are present and that the establishment is manufacturing its product during the time of the inspection. In some cases, FDA must obtain permission from the foreign government of the country in which an establishment is located in order to conduct an inspection. FDA officials report that inspections may be conducted several months after an establishment has been notified of FDA's intent to conduct an inspection due to the need to obtain visas and other delays. As a result of such advance notice, FDA staff conducting inspections may not observe an accurate picture of the manufacturer's day-to-day operations.

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## FDA Lacks Complete Information on Foreign Drug Establishments

Our previous reports indicated that FDA has experienced challenges maintaining complete information on foreign drug manufacturing establishments. This lack of information, which is critical to understanding the supply chain, hampers the agency's ability to inspect foreign establishments. In 2008, we reported that FDA did not maintain a list of foreign drug establishments subject to inspection, but rather the agency

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<sup>18</sup>See [GAO-08-970](#).

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relied on information from their drug establishment registration and import databases to help select establishments for inspection.<sup>19</sup> However, we found 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, in our 2008 report, we identified that for fiscal year 2007, FDA's registration database contained information on approximately 3,000 foreign drug establishments that registered with FDA to market drugs in the United States, while the import database contained information on about 6,800 foreign establishments that offered drugs for import into the United States.<sup>20</sup> Some of the inaccuracies in the registration database reflected the fact that, despite being registered, some foreign establishments did not actually manufacture drugs for the U.S. market.<sup>21</sup> Additionally, the inaccurate count of establishments in the import database was the result of unreliable manufacturer identification numbers generated by customs brokers when a drug is offered for import.<sup>22</sup> As a result of these inaccuracies, FDA did not know how many foreign establishments were subject to inspection. To address these inaccuracies, we recommended that FDA enforce the requirement that establishments manufacturing drugs for the U.S. market update their registration annually and establish mechanisms for verifying information provided by the establishment at the time of registration.

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<sup>19</sup>See [GAO-08-970](#).

<sup>20</sup>In our 2010 report, we indicated that, in fiscal year 2009, FDA's import database contained information for about 7,000 foreign establishments, compared with the approximately 3,200 foreign drug establishments that were registered with FDA in that year. See [GAO-10-961](#).

<sup>21</sup>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.

<sup>22</sup>As we reported in 2010, the algorithm 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. See [GAO-10-961](#).

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Since then, FDA has taken steps to address these deficiencies and improve the information it receives from both the registration and import databases, though these efforts have not yet fully addressed the concerns we raised in 2008. For example, 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, rather than submitting the information on paper forms to be entered into the registration database. FDA indicated that, as of September 2011, the implementation of this requirement has eliminated the human error that has been associated with the transcription of information from paper forms to electronic files. As part of electronic registration, FDA has also requested the each establishment provide a unique identification number—a Dun and Bradstreet Data Universal Numbering System (D-U-N-S®) Number<sup>23</sup>—as a way to help avoid duplications and errors in FDA’s data systems.<sup>24</sup> In addition, in September 2011, FDA officials reported that the agency had begun to take steps to enforce its annual registration requirement. They indicated that FDA will now conduct outreach to establishments that have not submitted an annual registration to confirm that they are no longer producing drugs for the U.S. market or to ensure they register, as required, if they are continuing to manufacture drugs for the U.S. market. They said that if an establishment does not respond to FDA’s outreach, it is to be removed from the registration database. To further address concerns with the import database, FDA has an initiative underway to eliminate duplicate information by taking steps to identify and remove all duplicate drug establishment records from existing import data over the next few years.

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<sup>23</sup>The 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.

<sup>24</sup>Additionally, FDA, in conjunction with 20 of the nearly 50 federal agencies involved in the oversight of products imported into the United States, supports efforts for Customs and Border Protection—which control the implementation of this proposal—to adopt unique establishment identifiers for all establishments whose products, including drugs, are imported into the United States.

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## Recent FDA Initiatives to Improve Oversight of the Supply Chain

Given the difficulties that FDA has faced in inspecting and obtaining information on foreign drug manufacturers, and recognizing that more inspections alone are not sufficient to meet the challenges posed by globalization, the agency has begun to explore other initiatives to improve its oversight of the drug supply chain. We reported that FDA's overseas offices had engaged in a variety of activities to help ensure the safety of imported products. These included establishing relationships with foreign regulators, industry, and U.S. agencies overseas; gathering information about regulated products to assist with decision making; and, in China and India, conducting inspections of foreign establishments.<sup>25</sup> Although we noted that the impact of the offices on the safety of imported products was not yet clear, FDA staff, foreign regulators, and others pointed to several immediate benefits, such as building relationships. However, they also described challenges related to some of their collaborations with domestic FDA offices and the potential for increasing demands that could lead to an unmanageable workload. We reported that FDA was in the process of long-term strategic planning for the overseas offices, but had not developed a long-term workforce plan to help ensure that it is prepared to address potential overseas office staffing challenges, such as recruiting and retaining skilled staff. We recommended that FDA enhance its strategic planning and develop a workforce plan to help recruit and retain overseas staff and FDA concurred with our recommendations. In September 2011, FDA indicated that it had developed a 2011 to 2015 strategic plan and was in the process of updating it, and it had initiated a workforce planning process.

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 could allow these regulatory bodies to more efficiently use their resources by minimizing the

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<sup>25</sup>We also reported that FDA overseas officials had started to provide training, responses to queries, and other assistance to foreign stakeholders to help them improve their regulatory systems and better understand FDA regulations.

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overlap in their inspection plans. According to agency officials, the agency had used inspection reports from the other regulators to improve its knowledge of a small number of API manufacturing 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.

FDA has also taken 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. 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.<sup>26</sup> 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.<sup>27</sup> 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. As of September 2011, the contractors had visited 142 foreign drug establishments located in Asia, Australia, Africa, Canada, and Europe, 27 of which did not appear to exist at the address provided by the establishments at the time of registration.<sup>28</sup> According to FDA, the agency uses the information obtained from the contractors as screening criteria to target drug products from those establishments for review at the border.<sup>29</sup>

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<sup>26</sup>According to FDA officials, the Foreign Registration Verification Program covers establishments manufacturing all FDA-regulated products.

<sup>27</sup>To select establishments for the Foreign Registration Verification Program, FDA uses information from its import database to determine the products that establishments are shipping to the United States and to identify establishments that are importing a variety of products.

<sup>28</sup>According to FDA, the agency has engaged contractors to conduct at least 125 more such visits of foreign drug manufacturing establishments during the coming year.

<sup>29</sup>In our 2010 report, we noted that FDA had taken action against 2 of the establishments that appeared not to exist by deactivating their registration and alerting FDA import staff so that they could detain any products offered for import by these establishments, thus preventing these products from being imported into the United States.

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FDA is also developing initiatives that would assist its oversight of products at the border. For example, FDA is in the process of establishing its Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) import screening system. The system is intended to automatically score each entry based on a range of risk factors and identify high-risk items for review. FDA piloted this system on seafood products in the summer of 2007. FDA determined that the system expedited the entry of lower-risk products, while identifying a higher rate of violations among products that were tested when they were offered for import. The agency planned to have the system implemented in all locations and for all FDA-regulated products by June 2011, although its deployment has been delayed. According to FDA, full deployment of PREDICT is currently slated for December 2011.

FDA also identified statutory changes that would help improve its oversight of drugs manufactured in foreign establishments. These include authority to (1) suspend or cancel drug establishment registrations to address concerns, including inaccurate or out-of-date information; (2) require drug establishments to use 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.

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## Concluding Observations

Globalization has fundamentally altered the drug supply chain and created regulatory challenges for FDA. In our prior reports we identified several concerns that demonstrate the regulatory difficulties that FDA faces conducting inspections of, and maintaining accurate information about, foreign drug establishments. While inspections provide FDA with critical information, we recognize that inspections alone are not sufficient to meet all the challenges of globalization. FDA should be credited for recent actions, such as collaborating with and exchanging information on drug establishments with foreign governments, that represent important initial steps toward addressing these challenges. However, as the agency has acknowledged, there are additional steps that it still needs to take. We have previously made recommendations to address some challenges, such as poor information and planning, and the agency has identified additional authorities that could provide it with necessary enforcement tools. In light of the growing dependence upon drugs manufactured abroad and the potential for harm, FDA needs to act quickly to implement changes across a range of activities in order to better assure the safety and availability of drugs for the U.S. market.

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Chairman Harkin, Ranking Member Enzi, and Members of the Committee, this concludes my prepared statement. I would be pleased to respond to any questions you may have at this time.

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## GAO Contact and Staff Acknowledgments

For further information about this testimony, please contact Marcia Crosse at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. GAO staff who made key contributions to this testimony include Geraldine Redican-Bigott, Assistant Director; William Hadley; Cathleen Hamann; Rebecca Hendrickson; and Lisa Motley.

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# Related GAO Products

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*High-Risk Series: An Update.* [GAO-11-278](#). Washington, D.C.: February 2011.

*Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added.* [GAO-11-95](#). Washington, D.C.: October 29, 2010.

*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](#). Washington, D.C.: September 30, 2010.

*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.: September 30, 2010.

*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.

*High-Risk Series: An Update.* [GAO-09-271](#). Washington, D.C.: January 2009.

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

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

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

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

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



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**Related GAO Products**

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

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