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DRUG SAFETY

COVID-19 Complicates Already Challenged FDA Foreign Inspection Program

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GAO Highlights

Highlights of [GAO-20-626T](#), a testimony before the Committee on Finance, U.S. Senate

Why GAO Did This Study

The outbreak of COVID-19 has called greater attention to the United States' reliance on foreign drug manufacturers and further highlighted the importance of ensuring a safe pharmaceutical supply chain. Much of the manufacturing of drugs for treating COVID-19 occurs overseas, which is also true of the majority of other drugs marketed in the United States. While the volume of drugs manufactured overseas for the U.S. market is not fully known, FDA reports that about 70 percent of establishments manufacturing active ingredients and more than 50 percent of establishments manufacturing finished drugs for the U.S. market were located overseas, as of August 2019.

FDA is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are produced, and conducts inspections of both foreign and domestic drug manufacturing establishments.

GAO has had long-standing concerns about FDA's ability to oversee the increasingly global pharmaceutical supply chain, an issue highlighted in GAO's High Risk Series since 2009. In particular:

- GAO recommended in 2008 ([GAO-08-970](#)) that FDA increase the number of inspections of foreign drug establishments.
- GAO found in 2010 ([GAO-10-961](#)) that FDA continued to conduct relatively few foreign inspections than domestic inspections.

View [GAO-20-626T](#). For more information, contact Mary Denigan-Macauley at (202) 512-7114 or deniganmacauleym@gao.gov.

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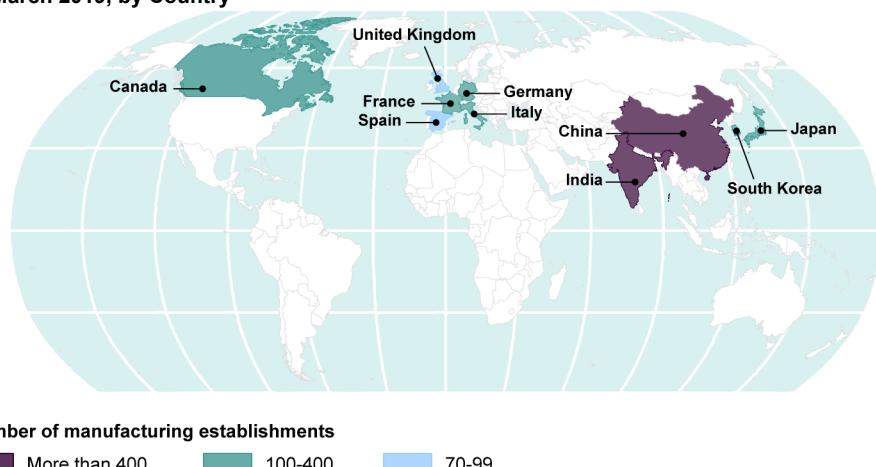
DRUG SAFETY

COVID-19 Complicates Already Challenged FDA Foreign Inspection Program

What GAO Found

In December 2019, GAO found that a growing number of foreign drug manufacturing inspections conducted by the Food and Drug Administration (FDA) were in China and India (43 percent in 2018), where most establishments that manufacture drugs for the United States were located. In fiscal year 2015, FDA, for the first time, conducted more foreign inspections than domestic inspections. However, from fiscal year 2016 through 2018, both foreign and domestic inspections decreased—by about 10 percent and 13 percent, respectively. FDA officials attributed the decline, in part, to vacancies among investigators available to conduct inspections. In March 2020, FDA announced that, due to Coronavirus Disease 2019 (COVID-19), it was postponing almost all inspections of foreign manufacturing establishments. While FDA has indicated it has other tools to ensure the safety of the U.S. drug supply, the lack of foreign inspections removes a critical source of information about the quality of drugs manufactured for the U.S. market.

The 10 Countries with the Most Foreign Drug Establishments Shipping to the United States as of March 2019, by Country



Number of manufacturing establishments

■ More than 400 ■ 100-400 ■ 70-99

Source: GAO analysis of Food and Drug Administration data (data); National Atlas (base map). | GAO-20-626T

GAO also found that FDA had vacancies among each of the groups of investigators who conduct foreign inspections. FDA had 190 investigators in the United States who conduct the majority of foreign inspections, but an additional 58 positions were vacant. At the time of GAO's December 2019 testimony, FDA was in the process filling 26 of these vacancies, with 32 remaining. However, according to FDA officials, it could be 2 to 3 years before new staff are experienced enough to conduct foreign inspections. FDA also faced persistent vacancies among investigators in its foreign offices.

- GAO found in 2016 ([GAO-17-143](#)) that FDA was conducting more of these foreign drug inspections, and GAO closed its 2008 recommendation to conduct more foreign inspections. However, GAO also reported that FDA may have never inspected many foreign establishments manufacturing drugs for the U.S. market.

In addition, in the summer of 2018, FDA began announcing recalls of blood pressure medications manufactured overseas that were tainted with a potential carcinogen, raising further questions about FDA's oversight of foreign-manufactured drugs.

This statement is largely based on GAO's December 2019 testimony ([GAO-20-262T](#)) and discusses

- the number of foreign inspections FDA has conducted,
- inspection staffing levels, and
- challenges unique to foreign inspections.

For that testimony, GAO examined FDA data from fiscal years 2012 through 2018 and interviewed investigators from FDA's 2019 cadre of investigators (who are based in the United States but exclusively conduct foreign drug inspections) and from FDA's foreign offices in China and India.

GAO further found in December 2019 that FDA investigators identified persistent challenges conducting foreign inspections, raising questions about the equivalence of foreign to domestic inspections. Specifically, GAO found:

- While FDA inspections performed in the United States were almost always unannounced, FDA's practice of preannouncing foreign inspections up to 12 weeks in advance may have given manufacturers the opportunity to fix problems ahead of the inspection. Investigators from FDA's China and India offices had conducted some unannounced inspections, but these staff do not perform most of the inspections in these countries (27 percent and 10 percent, respectively).

FDA Estimates of the Amount of Notice Provided to Foreign Drug Establishments Prior to Inspection, Fiscal Year 2018

Type of investigator	Amount of notice provided	Percentage of inspections involving this investigator type
China office investigator	0-5 days	Involved in 27 percent of total number of inspections in China
India office investigator	0-5 days.	Involved in 10 percent of total number of inspections in India
U.S.-based investigator	Generally 12 weeks	Involved in: <ul style="list-style-type: none"> 73 percent of total number of inspections in China 90 percent of total number of inspections in India 100 percent of total number of inspections in other foreign countries

Source: Interviews with Food and Drug Administration (FDA) officials and GAO analysis of FDA data. | GAO-20-626T

- FDA was not generally providing translators on foreign inspections. Rather, FDA continued to rely on translators provided by the foreign establishments being inspected, which investigators said raised questions about the accuracy of information FDA investigators collected. For example, one investigator said there was more risk of conflict of interest if the establishment used its own employees to translate. In addition, the establishment representative providing the translation may be someone who does not have the technical language needed, which can make it harder to communicate with establishment staff and facilitate the inspection.
- The overseas travel schedule can present challenges for FDA's domestically based investigators, who conduct the majority of foreign inspections. Domestically based investigators told us there is little flexibility for them to extend foreign inspections during an overseas trip. The inspections they conduct on an overseas trip are scheduled back-to-back in 3-week trips and may involve three different countries. Therefore, extending one inspection would limit the amount of time the investigator has to complete their other scheduled inspections. FDA officials said that inspections conducted by investigators based in China or India (and domestic inspections in the United States) are generally scheduled one at a time and can thus more easily be extended if the investigator needs additional time to pursue potential deficiencies. However, these in-country investigators are not involved in the majority of FDA inspections conducted in China or India.

Chairman Grassley, Ranking Member Wyden, and Members of the Committee:

I am pleased to be here today to discuss our work on the Food and Drug Administration's (FDA) oversight of drugs manufactured overseas.¹ The outbreak of Coronavirus Disease 2019 (COVID-19) has called greater attention to the United States' reliance on foreign drug manufacturers and further highlighted the importance of ensuring a secure pharmaceutical supply chain. Like the majority of other drugs manufactured for the U.S. market, much of the manufacturing of drugs for treating COVID-19 occurs overseas.

We have had long-standing concerns about FDA's ability to oversee the increasingly global pharmaceutical supply chain, an issue highlighted in our High Risk Series since 2009.² A critical element in FDA's oversight of overseas manufacturing is the inspections it conducts of foreign manufacturing establishments. For more than two decades, we have raised concerns about FDA's foreign drug inspection program. In 1998, and again in 2008, we found that FDA inspected relatively few foreign drug manufacturing establishments—an estimated 8 percent of those subject to inspection for our 2008 report—and that challenges unique to foreign inspections influenced the manner in which FDA conducted such inspections.³ In our 2008 report we recommended that FDA increase the

¹Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and include components of those articles. See 21 U.S.C. § 321(g)(1)(B), (D). An active pharmaceutical ingredient includes, among other things, any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. See 21 C.F.R. § 207.1 (2019). In this testimony, we refer both to drug products—drugs in their finished dosage forms—and to active pharmaceutical ingredients as “drugs.” Our work focuses on human drugs and not on most biologics, veterinary medicines, or other items or products for which FDA conducts inspections. (Biologics are materials, such as viruses, therapeutic sera, toxins, antitoxins, vaccines or analogous products, to prevent, treat, or cure human diseases or injuries and are derived from natural sources, such as humans, animals, and microorganisms. See 42 U.S.C. § 262(i); 21 C.F.R. § 600.3(h) (2019).)

²See GAO, *High-Risk Series: Substantial Efforts Needed to Achieve Greater Progress on High-Risk Areas*, GAO-19-157SP (Washington, D.C.: Mar. 6, 2019).

³See GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, GAO/HEHS-98-21 (Washington, D.C.: Mar. 17, 1998) and *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).

number of foreign inspections it conducts.⁴ In 2010, and again in 2016, we found that FDA was conducting more inspections of foreign establishments (inspecting about 11 percent and 21 percent of those subject to inspection for our 2010 and 2016 reports, respectively). However, in 2010 we reported that FDA continued to conduct relatively fewer foreign drug inspections than domestic inspections, and in 2016 we also reported that many foreign establishments manufacturing drugs for the U.S. market may never have been inspected by FDA.⁵ In addition, in the summer of 2018, FDA began announcing recalls of blood pressure medications manufactured overseas that were tainted with a potential carcinogen, raising further questions about FDA's oversight of foreign-manufactured drugs.⁶

My remarks today primarily discuss the findings from our December 2019 testimony on FDA's foreign drug inspection program.⁷ Accordingly, this statement provides observations on:

1. the number of FDA's foreign inspections,
2. inspection staffing levels, and
3. challenges unique to foreign inspections.

For our December 2019 testimony, we analyzed FDA data from fiscal year 2012 through fiscal year 2018 on inspections of foreign drug manufacturing establishments. We also interviewed FDA drug investigators from FDA's 2019 cadre of investigators, who are based in the United States but exclusively conduct foreign drug inspections, and investigators based in FDA's foreign offices in China and in India. More

⁴See GAO-08-970, 43. FDA agreed with our recommendation and then started conducting more foreign inspections and changed how it selects establishments for inspection to ensure that foreign establishments be inspected at a frequency comparable to domestic establishments with similar characteristics. As a result, we closed this recommendation.

⁵See 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, Drug Safety: FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices, GAO-17-143 (Washington, D.C.: Dec. 16, 2016).

⁶Food and Drug Administration, *FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)*, accessed December 1, 2019, <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan>

⁷See GAO, Drug Safety: Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections, GAO-20-262T (Washington, D.C.: Dec. 10, 2019).

detailed information on our objectives, scope, and methodology for that work can be found in the December 2019 testimony. The work on which this statement is based 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.

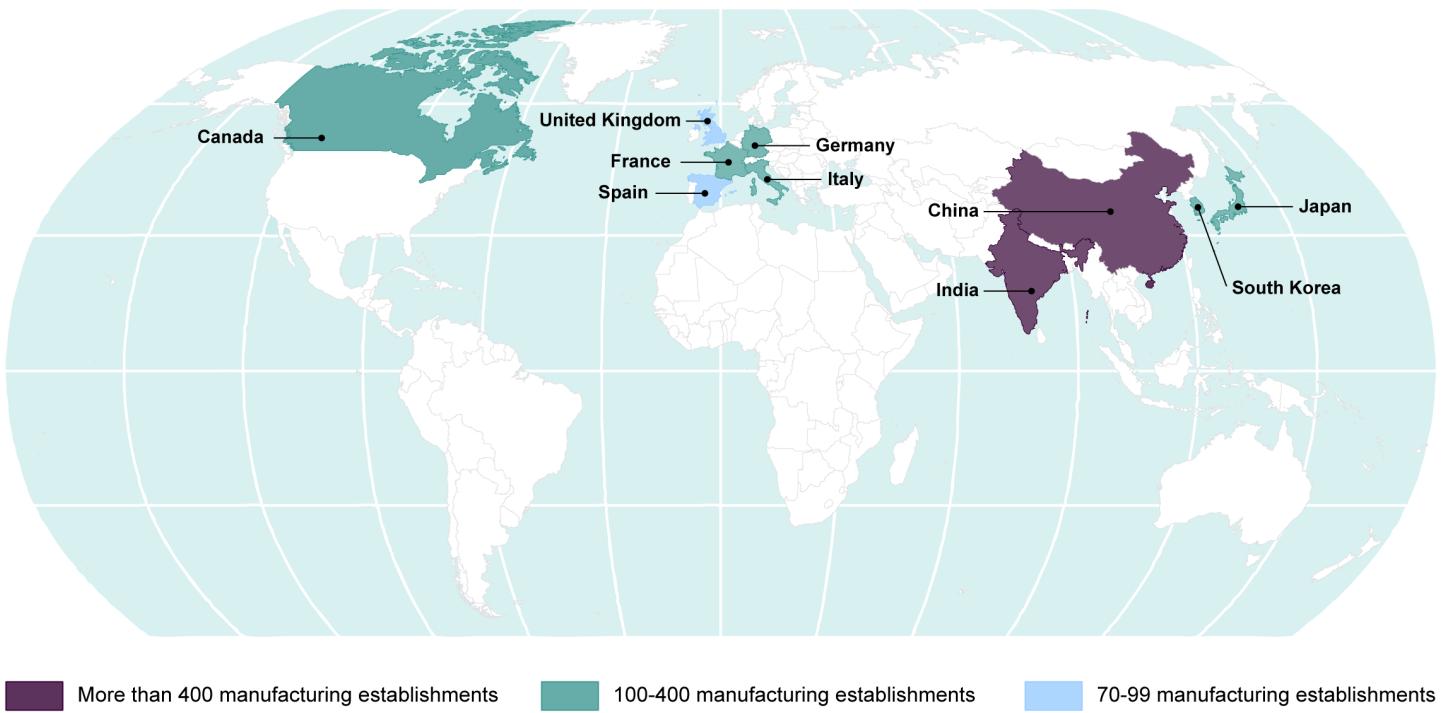
Background

Globalization of Drug Manufacturing

Drugs sold in the United States—including active pharmaceutical ingredients (APIs) and finished dosage forms—are manufactured throughout the world. According to FDA, as of August 2019 about 70 percent of establishments manufacturing APIs and more than 50 percent of establishments manufacturing finished drugs for the U.S. market were located overseas.⁸ As of March 2019, FDA data showed that India and China had the most manufacturing establishments shipping drugs to the United States, with about 40 percent of all foreign establishments in these two countries. (See fig. 1.)

⁸Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration, *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program*, testimony before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, 116th Congress, December 10, 2019. According to FDA, although the agency has information on the location of drug manufacturing establishments, it does not have information on the volume of drug ingredients these establishments manufacture for the U.S. market.

Figure 1: The 10 Countries with the Most Foreign Drug Establishments Shipping to the United States as of March 2019, by Country



■ More than 400 manufacturing establishments ■ 100-400 manufacturing establishments ■ 70-99 manufacturing establishments

Source: GAO analysis of Food and Drug Administration data (data); National Atlas (base map). | GAO-20-626T

Note: This figure includes the 10 countries with the most foreign drug establishments shipping to the United States and does not include those countries with fewer than 70 establishments. The count of foreign establishments represents the number of establishments that were known to ship or likely would ship a drug to the United States as of March 2019. This count excludes about 380 establishments that participate in some aspect of the manufacturing process, such as sterilizers and analytical labs, but would not ship products to the United States directly. Such establishments are also subject to inspection.

Types of Inspections

FDA is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are manufactured. Drugs manufactured overseas must meet the same statutory and regulatory requirements as those manufactured in the United States. FDA's Center for Drug Evaluation and Research (CDER) establishes standards for the safety, quality, and effectiveness of, and manufacturing processes for, over-the-counter and prescription drugs. CDER requests that FDA's Office of Regulatory Affairs (ORA) inspect both domestic and foreign establishments to ensure that drugs are

produced in conformance with applicable laws of the United States, including current good manufacturing practice (CGMP) regulations.⁹

FDA investigators generally conduct three main types of drug manufacturing establishment inspections: preapproval inspections, surveillance inspections, and for-cause inspections, as described in table 1. At times, FDA may conduct an inspection that combines both preapproval and surveillance inspection components in a single visit to an establishment.¹⁰

Table 1: Types of Drug Manufacturing Establishment Inspections Conducted by the Food and Drug Administration (FDA)

Type of inspection	Purpose of inspection
Preapproval inspections	FDA conducts preapproval inspections before approving a new brand name or generic drug to be marketed in the United States. These inspections are designed to verify the accuracy and authenticity of drug application data (such as manufacturing records) and assess whether the establishment can manufacture the product in the application in conformance with applicable regulations to assure a drug's identity, strength, quality, and purity. ^a
Surveillance inspections	Surveillance inspections are conducted at establishments when drugs are already marketed in the United States—either after FDA approval or after marketing for drugs that do not require FDA preapproval—and focus on compliance with system-wide controls for ensuring that the manufacturing processes produce high-quality drugs. ^b Systems examined during these inspections include those related to materials, quality control, production, facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drugs.
For-cause inspections	For-cause inspections are conducted to investigate specific issues, such as those raised in consumer complaints, indications of potential manufacturing problems submitted by the manufacturers themselves, or to follow-up on previous FDA regulatory action, among other reasons.

Source: GAO analysis of FDA information. | GAO-20-626T

^aWhen FDA receives an application for drug approval (or a supplement to that application related to a manufacturing change), officials review the inspection history of each establishment listed on the application, among other things. According to FDA officials, if an establishment listed on the application has received a satisfactory good manufacturing practices inspection in the previous 2 years for a similar or more complex product, and the agency has no new concerns, FDA may consider this inspection sufficient and not perform a preapproval inspection of this establishment.

^bCertain drugs, such as some over-the-counter drugs, may not require FDA approval before marketing in the United States.

FDA uses multiple databases to select foreign and domestic establishments for surveillance inspections, including its registration database and inspection database. Because the establishments are

⁹CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. See 21 C.F.R. pts. 210, 211, 212 (2019). FDA considers nearly all drug establishment inspections to include an assessment of CGMPs.

¹⁰Most combined inspections occur when FDA conducts a surveillance inspection at an establishment where a preapproval inspection was also being conducted.

continuously changing as they begin, stop, or resume marketing products in the United States, CDER creates a monthly catalog of establishments. The establishments in the catalog are prioritized for inspection twice each year.

In our 2008 report we found that, because of inaccurate information in FDA's databases, the agency did not know how many foreign drug establishments were subject to inspection.¹¹ For example, some establishments included in FDA's registration database may have gone out of business and did not inform FDA that they had done so, or they did not actually manufacture drugs for the U.S. market. In our report, we noted that some foreign establishments may register because, in foreign markets, registration may erroneously convey an "approval" or endorsement by FDA, when in fact the establishment may never have been inspected by FDA.¹² We recommended that FDA take steps to improve the accuracy of this registration information. In our 2010 and 2016 reports we found that FDA had taken steps to improve the accuracy and completeness of information in its catalog of drug establishments subject to inspection, such as using contractors to conduct site visits to verify the existence of registered foreign establishments and confirm that they manufacture the products that are recorded in U.S. import records.¹³

To prioritize establishments for surveillance inspections, CDER applies a risk-based site selection model to its catalog of establishments to identify those establishments (both domestic and foreign) that, based on the characteristics of the drugs being manufactured, pose the greatest potential public health risk should they experience a manufacturing defect. This model analyzes several factors, including inherent product risk, establishment type, inspection history, and time since last inspection, to develop a list of establishments that FDA considers to be a priority for inspection.¹⁴ Through this process, CDER develops a ranked list of foreign and domestic establishments selected for inspection that is

¹¹[GAO-08-970](#).

¹²Foreign and domestic establishments that manufacture drugs for the U.S. market are required to register annually with FDA. Establishments provide FDA with, among other things, their names and addresses and a listing of the drugs that they manufacture for the U.S. market. 21 U.S.C. § 360(b), (i), (j).

¹³See [GAO-10-961](#) and [GAO-17-143](#).

¹⁴Establishments may also be selected for surveillance inspections for other reasons, such as FDA's focus on a particular product.

submitted to ORA. To be efficient with its resources, ORA staff may shift the order of establishments to be inspected on CDER's prioritized list based on geographic proximity to other planned inspection trips, according to FDA officials.

FDA Inspection Workforce	<p>Investigators from ORA and, as needed, ORA laboratory analysts with certain expertise are responsible for inspecting drug manufacturing establishments.¹⁵ FDA primarily relies on three groups of investigators to conduct foreign inspections:</p> <ul style="list-style-type: none">• ORA investigators based in the United States, who primarily conduct domestic drug establishment inspections but may sometimes conduct foreign inspections.• Members of ORA's dedicated foreign drug cadre, a group of domestically based investigators, who exclusively conduct foreign inspections.• Investigators assigned to and living in the countries where FDA has foreign offices, who include both staff based in the foreign offices full time and those on temporary duty assignment to the foreign offices. FDA began opening offices around the world in 2008 to obtain better information on the increasing number of products coming into the United States from overseas, to build relationships with foreign stakeholders, and to perform inspections.¹⁶ FDA full-time foreign office staff are posted overseas for 2-year assignments. FDA staff can also be assigned to the foreign offices on temporary duty assignments for up to 120 days. In fiscal year 2019, there were full-time and temporary duty drug investigators assigned to FDA foreign offices in China and India.
Post-Inspection Activities	FDA's process for determining whether a foreign establishment complies with CGMPs involves both CDER and ORA. During an inspection, ORA investigators are responsible for identifying any significant objectionable conditions and practices and reporting these to the establishment's management. Investigators suggest that the establishment respond to

¹⁵ORA investigators lead inspections and are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing. In some instances, staff from CDER, such as subject matter experts or drug application reviewers, may participate in inspections.

¹⁶Currently, FDA has foreign offices in China, Europe, India, and Latin America but does not have drug investigators in the Europe or Latin America offices.

FDA in writing concerning all actions taken to address the issues identified during the inspection.

Once ORA investigators complete an inspection, they are responsible for preparing an establishment inspection report to document their inspection findings. Inspection reports describe the manufacturing operations observed during the inspection and any conditions that may violate U.S. statutes and regulations. Based on their inspection findings, ORA investigators make an initial recommendation regarding whether regulatory actions are needed to address identified deficiencies using one of three classifications: no action indicated (NAI); voluntary action indicated (VAI); or official action indicated (OAI).¹⁷ Inspection reports and initial classification recommendations for regulatory action are to be reviewed within ORA. For inspections classified as OAI—where ORA identified serious deficiencies—such inspection reports and classification recommendations are to be reviewed within CDER. CDER is to review the ORA recommendations and determine whether regulatory action is necessary. CDER also is to review inspection reports and initial classification recommendations for all for-cause inspections, regardless of whether regulatory action is recommended by ORA.

According to FDA policy, inspections classified as OAI may result in regulatory action, such as the issuance of a warning letter. FDA issues warning letters to those establishments manufacturing drugs for the U.S. market that are in violation of applicable U.S. laws and regulations and may be subject to enforcement action if the violations are not promptly and adequately corrected. In addition, warning letters may notify foreign establishments that FDA may refuse entry of their drugs at the border or recommend disapproval of any new drug applications listing the establishment until sufficient corrections are made.¹⁸ FDA may take other regulatory actions if it identifies serious deficiencies during the inspection of a foreign establishment. For example, FDA may issue an import alert,

¹⁷FDA officials told us that investigators are responsible for checking on previously identified deficiencies in any subsequent inspections of the same establishment. Officials told us that repeated identification of the same deficiency could result in regulatory action.

Inspection classifications are publicly available for some inspections on FDA's website: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-classification-database/>

¹⁸Warning letters are publicly available on FDA's website: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>.

which instructs FDA staff that they may detain drugs manufactured by the violative establishment that have been offered for entry into the United States.¹⁹ In addition, FDA may conduct regulatory meetings with the violative establishment. Regulatory meetings may be held in a variety of situations, such as a follow-up to the issuance of a warning letter to emphasize the significance of the deficiencies or to communicate documented deficiencies that do not warrant the issuance of a warning letter.

The Number of Foreign Inspections Declined in Recent Years, and the Majority of Such Inspections Identified Deficiencies

Total Number of FDA Foreign Drug Inspections Has Decreased Since Fiscal Year 2016 after Several Years of Increases

In December 2019, we found that from fiscal year 2012 through fiscal year 2016, the number of FDA foreign drug manufacturing establishment inspections increased but then began to decline after fiscal year 2016. In fiscal year 2015, the total number of foreign inspections surpassed the number of domestic inspections for the first time. However, from fiscal year 2016 through 2018, both foreign and domestic inspections decreased—by about 10 percent and 13 percent, respectively. FDA officials attributed this decrease to vacancies in the number of investigators available to conduct inspections (which we discuss later in this testimony statement) and to inaccurate data used to select establishments for inspection in fiscal years 2017 and 2018.

Despite steps taken to improve the accuracy and completeness of FDA data on foreign establishments, in December 2019, we found that the data challenges we identified in our 2008 report continue to make it difficult for FDA to accurately identify establishments subject to inspection. Specifically, since 2017, FDA had pursued an initiative to inspect approximately 1,000 foreign establishments that lacked an

¹⁹An import alert can apply to specific drugs or all drugs manufactured by an establishment. Import alerts are publicly available on FDA's website: <https://www.fda.gov/industry/actions-enforcement/import-alerts>.

inspection history. As of November 2019, officials said all of these establishments had either been inspected or were determined not to be subject to inspection because it was determined they did not actually manufacture drugs for the U.S. market, or had not recently shipped drugs to the United States.²⁰ However, officials told us that this effort contributed to the decline in the number of foreign inspections conducted because of how data inaccuracies affected the process for selecting establishments for inspection. Specifically, after selecting uninspected foreign establishments for inspection, FDA determined that a sizeable percentage of these establishments were not actually subject to inspection (e.g., about 40 percent of those assigned to the China Office in fiscal years 2017 and 2018).²¹ These foreign establishments were thus removed from the list for inspection for the given year. FDA officials told us that the next highest priority establishments identified through the risk-based model to replace those establishments were domestic establishments. As a result, the number of foreign establishments actually inspected decreased. As part of our ongoing work, we plan to examine the accuracy and completeness of information FDA maintains about foreign establishments and the application of its risk-based site selection process.

We further found that FDA continued to conduct the largest number of foreign inspections in India and China, with inspections in these two countries representing about 40 percent of all foreign drug inspections from fiscal year 2016 through 2018. (See table 2.) In addition to India and China, the rest of the countries in which FDA most frequently conducted inspections has generally been the same since our 2008 report.

²⁰We previously reported that as of 2016, FDA lacked the inspection history of 33 percent of the foreign establishments in its catalog of establishments subject to inspection.

²¹FDA officials said that some of these establishments were registered with FDA but did not actually manufacture drugs for the U.S. market, and others were drug manufacturers but had not shipped drugs to the United States in the previous 3 years. FDA officials told us that, once identified, they removed such establishments from the catalog of establishments subject to surveillance inspection to which the agency applies its risk-based model each year, but they retained information on these establishments in the larger inventory of establishments should these establishments begin shipping drugs to the United States in the future.

Table 2: Total Number of FDA Foreign Drug Inspections, by Country, Fiscal Years 2012 through 2018

Country	2012	2013	2014	2015	2016	2017	2018
India	140	110	114	204	207	219	252
China	59	74	113	127	173	165	153
Germany	59	60	72	68	72	69	68
Canada	49	51	39	52	56	72	48
Italy	38	45	50	41	69	46	45
Japan	49	28	47	31	65	46	43
South Korea	4	7	8	5	13	56	40
France	25	37	44	45	55	42	36
Switzerland	23	23	37	31	37	25	32
United Kingdom	29	27	33	43	41	40	12
All other countries	150	175	222	193	247	213	206
Total foreign	625	637	779	840	1,035	993	935
Total domestic	1,184	1,030	897	784	882	772	742

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-626T

Note: The total number of inspections includes those conducted for preapproval, surveillance, and for-cause purposes.

Since we last reported on this issue, FDA announced in March 2020 that, due to COVID-19, it was postponing most inspections of foreign manufacturing establishments. Only inspections deemed mission-critical would still be considered on a case-by-case basis.²² According to the announcement, while the pandemic has added new complexities, FDA has other tools to ensure the safety of the U.S. drug supply. For example, FDA announced that it was evaluating additional ways to conduct its inspectional work that would not jeopardize public safety and would protect both the establishments and the FDA staff. Such ways, according to FDA, could include reviewing the compliance histories of establishments, using information shared by foreign regulatory partners, and evaluating establishment records in lieu of an onsite inspection. In addition, the FDA Commissioner's May 11, 2020 press statement stated that while FDA's regulatory oversight is vital to the long-term health of America, product safety and quality are ultimately the establishment's

²²According to FDA, the agency's assessment of mission-critical drug inspections includes consideration for whether the products are innovative breakthrough products or are considered medically necessary. FDA indicated that both for-cause and pre-approval inspections can be deemed mission critical

responsibility.²³ Most firms, according to FDA, strive to reliably provide quality products and maintain the integrity of the supply chain. However, the lack of foreign inspections removes a critical source of information about the quality of drugs manufactured for the U.S. market.

It is not clear when FDA will resume regular inspections. The agency originally announced the postponement would last through April 2020. However, on May 11, 2020, it stated that the postponement would continue. According to FDA, the agency continues to closely monitor the global situation. FDA stated that it remains in contact with its foreign regulatory counterparts and would work with the Centers for Disease Control and Prevention to develop a process that would govern how and where to return to on-site facility inspections as conditions improve.

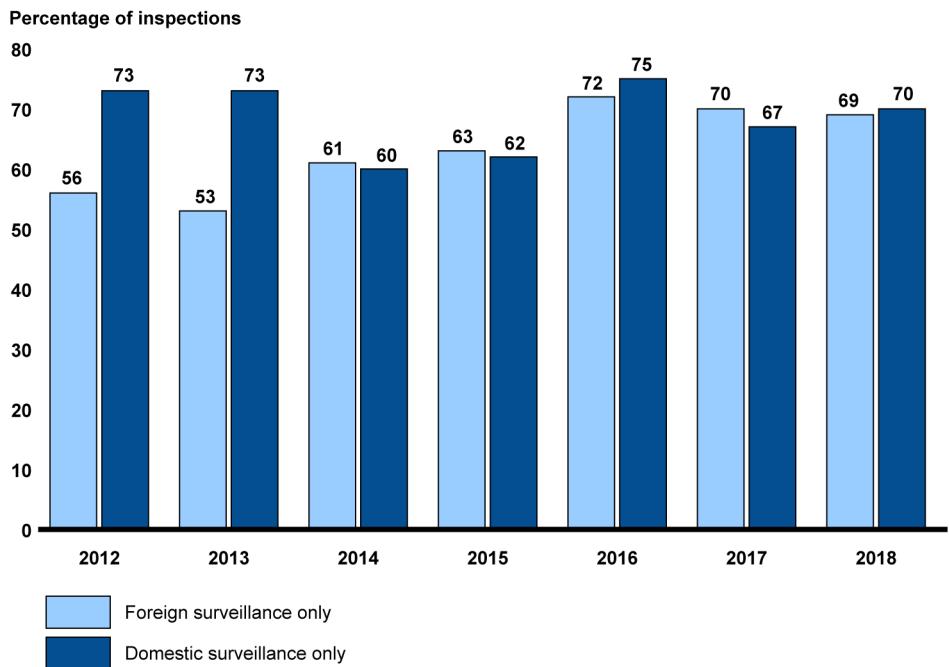
Most Foreign Inspections Were for Surveillance

In December 2019, we found that each year from fiscal year 2012 through 2018 at least 50 percent of FDA's foreign inspections were surveillance inspections. In contrast to preapproval inspections, surveillance inspections are used to ensure drugs already on the market are manufactured in compliance with FDA regulations. In recent years, the proportion of foreign surveillance inspections has increased. As figure 2 shows, in fiscal year 2012, 56 percent of foreign inspections were surveillance-only inspections; in contrast, from fiscal year 2016 through 2018, about 70 percent of foreign inspections were surveillance-only, which was comparable to the percentage for domestic inspections during that period. This is a significant increase from the 13 percent of foreign inspections that were surveillance-only when we made our 2008 recommendation that FDA inspect foreign establishments at a comparable frequency to their domestic counterparts (85 percent of which were surveillance-only at that time).²⁴

²³Food and Drug Administration, *Coronavirus (COVID-19) Update: FDA Updates on Surveillance Inspections during COVID-19*, FDA press announcement (May 11, 2020)

²⁴See GAO-08-970, 27.

Figure 2: Percentage of FDA Foreign and Domestic Drug Inspections Conducted for Surveillance Purposes, Fiscal Years 2012 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-626T

Note: FDA conducts surveillance inspections to monitor the ongoing compliance of establishments manufacturing drugs that are already on the market. This figure depicts surveillance-only inspections. FDA conducted additional inspections that had a surveillance component combined with another type of inspection.

In our December 2019 testimony, we also reported that FDA implemented changes to its foreign drug inspection program since our 2008 report that may have contributed to the increase in surveillance inspections. Prior to 2012, FDA was required to inspect domestic establishments that manufacture drugs marketed in the United States every 2 years, but there was no similar requirement for foreign establishments. As a result, and as we reported in 2008, foreign inspections were often preapproval inspections driven by pending applications for new drugs. FDA thus conducted relatively few surveillance-only inspections to monitor the ongoing compliance of establishments manufacturing drugs that were already on the market, with just 13 percent of foreign inspections conducted for surveillance purposes at the time of our 2008 report. However, in 2012, the Food and Drug Administration Safety and Innovation Act eliminated the 2-year requirement for domestic inspections, directing FDA to inspect both domestic and foreign

establishments on a risk-based schedule determined by an establishment's known safety risks, which was consistent with our 2008 recommendation.²⁵

FDA Identified Deficiencies during the Majority of Foreign Inspections

In December 2019, we found that from fiscal year 2012 through 2018, FDA identified deficiencies in approximately 64 percent of foreign drug manufacturing establishment inspections (3,742 of 5,844 inspections). This includes deficiencies necessitating a classification of VAI, or the more serious OAI, as described in the text box.

Inspection Classifications

Based on their inspection findings, FDA investigators make an initial recommendation regarding the classification of each inspection:

- **No action indicated (NAI)** means that insignificant or no deficiencies were identified during the inspection.
- **Voluntary action indicated (VAI)** means that deficiencies were identified during the inspection, but the agency is not prepared to take regulatory action, so any corrective actions are left to the establishment to take voluntarily.
- **Official action indicated (OAI)** means that serious deficiencies were found that warrant regulatory action.

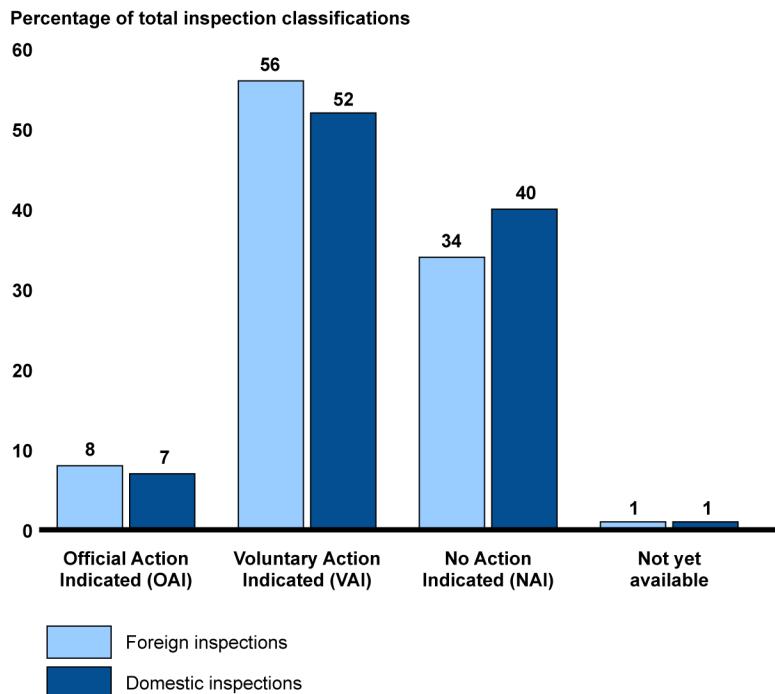
Source: GAO. | GAO-20-626T

About 59 percent of domestic inspections (3,702 out of 6,291) identified deficiencies during this time period. (See fig. 3.) This proportion is similar to what we found when we last looked at this issue in 2008, when FDA identified deficiencies in about 62 percent of foreign inspections and 51 percent of domestic inspections from fiscal years 2002 through 2006.²⁶

²⁵Pub. L. No. 112-144, § 705, 126 Stat. 993, 1066 (2012) (codified at 21 U.S.C. 360(h)). This established a comparable inspection frequency for foreign and domestic establishments with similar characteristics, consistent with our 2008 recommendation.

²⁶In our 2008 report we found that FDA's data did not provide reliable information about the number of foreign inspections with serious deficiencies classified specifically as OAI. Therefore, we reported data on the percentage of inspections classified as either VAI or OAI together. See [GAO-08-970](#), 29. We recommended that FDA correct this issue, and they did so beginning in October 2011, but, for comparison purposes, we continue to report combined VAI and OAI inspection data here.

Figure 3: FDA Inspection Classifications for Foreign and Domestic Drug Establishments by Type of Classification, Fiscal Year 2012 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-626T

Notes: Based on their inspection findings, FDA investigators make an initial recommendation regarding the classification of each inspection: NAI means that insignificant or no deficiencies were identified during the inspection; VAI means that deficiencies were identified during the inspection, but the agency is not prepared to take regulatory action, so any corrective actions are left to the establishment to take voluntarily; and OAI means that serious deficiencies were found that warrant regulatory action, such as issuing a warning letter or import alert.

The analysis presented in this figure is based on 5,844 foreign inspections and 6,291 domestic inspections conducted from fiscal year 2012 through 2018. Totals do not sum to 100 due to rounding. Some classifications were not yet available at the time of our analysis (1 percent of both foreign and domestic inspections). Finally, less than 1 percent of both foreign and domestic inspections received another interim classification, which is not reflected in this figure.

Our December 2019 analysis showed that serious deficiencies identified during foreign drug inspections classified as OAI—which represented 8 percent of inspections from fiscal year 2012 through 2018—include CGMP violations such as those related to production and process

controls, equipment, records and reports, and buildings and facilities.²⁷
For example:

- **Failure to maintain the sanitation of the buildings used in the manufacturing processing, packing, or holding of a drug product (21 C.F.R. § 211.56(a) (2019)).** At an establishment in India producing finished drug products, the investigator reported observing a live moth floating in raw material used in the drug production, and that the facility staff continued to manufacture the drug products using the raw material contaminated by the moth, despite the investigator pointing out its presence.
- **Failure to perform operations relating to the manufacture, processing, and packing of penicillin in facilities separate from those used for other drug products (21 C.F.R. § 211.42 (d) (2019)).** At an establishment in Turkey that manufactured penicillin and other drugs, the investigator reported that the manufacturer had detected penicillin outside the penicillin manufacturing area of the establishment multiple times. According to FDA, penicillin contamination of other drugs presents great risk to patient safety, including potential anaphylaxis (even at extremely low levels of exposure) and death.

Some investigators who conduct foreign inspections expressed concern with instances in which ORA or CDER reviewers reclassified the investigator's initial inspection classification recommendations of OAI to the less serious classification of VAI.

FDA Continued to Face Challenges Filling Vacancies among Staff Conducting Foreign Inspections

In December 2019, we found that FDA's foreign inspection workforce had staff vacancies, which FDA officials said contributed to the recent decline in inspections. As previously mentioned, FDA used multiple types of staff resources to conduct foreign drug inspections—including ORA investigators based in the United States, members of ORA's dedicated foreign drug cadre based in the United States, and investigators assigned to FDA's foreign offices.²⁸ However, we found that each of these groups had current vacancies. At the time of our December testimony, FDA officials told us that the agency was trying to fill vacancies in each of

²⁷The identification of serious deficiencies is not unique to foreign inspections. For example, at a domestic establishment producing finished drug products, the investigator observed brown stains, white residues, and brown stagnant water in manufacturing equipment.

²⁸In addition to these categories, there are a variety of other FDA staff who, on occasion, may participate in an inspection if certain subject matter expertise is needed.

these groups, but the lower staff numbers may limit FDA's ability to conduct more foreign inspections.

ORA investigators based in the United States. This group of investigators conducted the majority of foreign inspections; about 76 percent of foreign inspections in fiscal year 2018 involved an ORA investigator based in the United States who conducts both foreign and domestic inspections.²⁹ FDA officials said that the more experienced investigators from this group are expected to conduct three to six foreign inspections per year, and investigators hired using generic drug user fees are expected to inspect nine to 12 foreign establishments per year.³⁰ As of June 2019, there were 190 investigators eligible to conduct foreign drug inspections, but officials said that as of November 2019, the agency had an additional 58 vacancies in this group. At the time of our December 2019 testimony, officials said that the agency was in the process of hiring 26 ORA investigators based in the United States to fill these vacancies, with 32 vacancies remaining.³¹

FDA officials attributed the vacancies to multiple factors: investigator retirements, investigator movement to other parts of FDA, and the need to hire to additional investigator positions using generic drug user fees. Officials also said that a reorganization within ORA led to a reduced number of investigators who conduct drug manufacturing establishment inspections. While FDA had recently filled several of the vacancies, officials told us that new investigators are not typically used for foreign inspections until they have been with the agency for 2 to 3 years.

ORA dedicated foreign drug cadre. About 15 percent of foreign inspections in fiscal year 2018 involved an investigator from ORA's dedicated foreign drug cadre—a group of ORA investigators based in the United States who exclusively conduct foreign inspections. FDA officials said that members of the cadre are expected to conduct 16 to 18 foreign inspections each year. According to FDA, the cadre had 20 investigators

²⁹Inspections can be conducted by one investigator or multiple investigators. Therefore, investigators from more than one group could be involved with a single inspection.

³⁰Beginning in 2014, FDA began to use the user fees collected from manufacturers of generic drugs to hire additional investigators focused on inspecting generic drug manufacturers. According to FDA officials, these investigators have primarily been assigned to conduct foreign inspections.

³¹FDA officials indicated that filling these vacancies was a priority for the agency and noted that their recent implementation of direct-hire authority has helped them fill these positions.

in 2012 and 15 investigators in 2016. However, the cadre had only 12 investigators as of November 2019, out of 20 available slots. At the time of our December 2019 testimony, FDA officials told us that the agency was attempting to fill these positions from the current ORA investigator pool, but officials were not confident that all 20 slots would be filled.

Investigators assigned to FDA's foreign offices. Approximately 7 percent of foreign inspections in fiscal year 2018 involved investigators from FDA's foreign offices. The investigators conducting these inspections were those based in the China and India foreign offices—the countries where most drug inspections occur—and also included those investigators on temporary duty assignment to these offices.³² According to FDA officials, these investigators are expected to conduct 15 foreign inspections each year. We have noted high vacancy rates for these foreign offices in past reports.³³ While these vacancy rates have decreased over time, vacancies persist. As of November 2019, FDA's China office had three of 10 drug investigator positions vacant (a 30 percent vacancy rate), while FDA's India office had two of six drug investigator positions vacant (a 33 percent vacancy rate).

In our December 2019 testimony, we reported that FDA had taken steps to address vacancies in the foreign offices but continued to face challenges. In our 2010 report, we recommended that FDA develop a strategic workforce plan to help recruit and retain foreign office staff.³⁴ FDA agreed with our recommendation and released such a plan in March 2016, but the long-standing vacancies in the foreign offices raise questions about its implementation. FDA officials told us that one challenge in recruiting investigators for the foreign offices is that well-qualified investigators for those positions need foreign inspection experience. For example, an official in FDA's India office told us that foreign inspections can be challenging, and the India office does not have the resources to develop or train new investigators. Therefore, it is important to recruit investigators who have experience conducting foreign inspections, and such investigators are recruited from ORA. Thus,

³²The percentage of inspections involving these groups of investigators do not equal 100 percent because some inspections may involve only non-investigator staff, such as CDER drug application reviewers.

³³See 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.: Sep. 30, 2010), and GAO-17-143.

³⁴GAO-10-960.

vacancies in the other two groups of investigators can influence the number of staff available to apply for positions in the foreign offices.

Further, according to FDA officials, after employees have accepted an in-country position, the agency can experience significant delays before they are staffed in the office due to delays in processing assignments. For example, an official in FDA's India office said that investigators need to complete a week-long security training program and must obtain the security clearance needed to work at the U.S. Embassy, which is where FDA's foreign office is located. However, the official told us that there are limited availabilities for that training, and background checks for security clearances can take time.³⁵ According to this official, FDA investigators did not usually receive first priority for the training. FDA estimated that it can take as little as 1 month to over 2 years for an investigator to clear background and medical checks and arrive at a foreign office. For example, an investigator in FDA's China office told us that as a result of these requirements and other issues, it took nearly 2 years for the investigator to arrive at the office after FDA had accepted the investigator's application. According to FDA's own strategic workforce plan for the foreign offices, these types of delays have resulted in staff changing their decision after accepting a position in the foreign offices.

Persistent Challenges Unique to Foreign Inspections Raised Questions about Their Equivalence to Domestic Inspections

In December 2019, we found that FDA continues to face unique challenges when inspecting foreign drug establishments that raise questions about whether these inspections are equivalent to domestic inspections. Specifically, based on our interviews with drug investigators in the dedicated foreign drug cadre and in FDA's foreign offices in China and India, we identified four challenge areas related to conducting foreign inspections, which are described below. Of the four challenge areas identified, three areas—preannouncing inspections, language barriers, and lack of flexibility—were also raised in our 2008 report.³⁶

Preannouncing Inspections. As we reported in 2008, the amount of notice FDA generally gives to foreign drug establishments in advance of an inspection is different than for domestic establishments.³⁷ Drug establishment inspections performed in the United States are almost always unannounced, whereas foreign establishments generally receive

³⁵We have highlighted timeliness concerns with the government-wide personnel security clearance process in our High Risk series. See [GAO-19-157SP](#).

³⁶[GAO-08-970](#).

³⁷[GAO-08-970](#).

advance notice of an FDA inspection. According to FDA officials, FDA is not required to preannounce foreign inspections. However, they said the agency generally does so to avoid wasting agency resources, obtain the establishment's assistance to make travel arrangements, and ensure the safety of investigators when traveling in country.

In our December 2019 testimony, we found that FDA does conduct some unannounced foreign inspections, particularly if the investigators conducting the inspection are based in FDA's foreign offices. However, FDA officials told us that FDA does not have data on the frequency with which foreign drug inspections are unannounced, nor the extent to which the amount of notice provided to foreign establishments varies. According to FDA officials, this is because FDA does not have a data field in its database to systematically track this information.³⁸ However, the officials estimated that the agency generally gives 12 weeks of notice to establishments that investigators are coming when investigators are traveling from the United States. While investigators in FDA's China and India offices do conduct unannounced or short-notice inspections, these staff do not perform most of the inspections in these countries. (See table 3.)

³⁸According to FDA officials, FDA planned to add a new variable to its data to identify preannounced and unannounced inspections.

Table 3: FDA Estimates of the Amount of Notice It Provides to Foreign Drug Establishments Prior to Inspection, by Investigator Type, and the Percentage of Inspections in Which These Investigator Types Are Involved, Fiscal Year 2018

Type of investigator	Amount of notice provided	Percentage of inspections involving this investigator type in fiscal year 2018 ^a
China office investigator	Announcement: 0-5 days FDA officials stated that investigators based in FDA's China office will announce surveillance inspections (those related to drugs already on the U.S. market) to drug establishments 5 business days in advance of an inspection. According to FDA officials, for-cause inspections (those conducted in response to specific issues or concerns) conducted by investigators based in the China office are unannounced, meaning that they are not preannounced to the drug establishments in advance.	Involved in 27 percent of total number of inspections in China
India office investigator	Announcement: 0-5 days FDA officials stated that investigators based in FDA's India office will announce inspections to drug establishments 3 to 5 days in advance of an inspection and can conduct short-notice inspections that are announced 30 minutes before the inspection.	Involved in 10 percent of total number of inspections in India
U.S.-based investigator (Including dedicated foreign drug cadre)	Announcement: generally 12 weeks FDA officials said that the agency generally announces foreign inspections conducted by domestically based investigators about 12 weeks in advance.	Involved in: <ul style="list-style-type: none">• 73 percent of total number of inspections in China• 90 percent of total number of inspections in India• 100 percent of total number of inspections in other foreign countries

Source: Interviews with Food and Drug Administration (FDA) officials and GAO analysis of FDA data. | GAO-20-626T

^aThese percentages add up to over 100 percent as some inspections may involve more than one type of investigator.

Our work indicated that preannouncing foreign inspections can create challenges and raises questions about the equivalence to domestic inspections. Of the 18 investigators we interviewed, 14 said that there are downsides to preannouncing foreign inspections, particularly that providing advance notice gives foreign establishments the opportunity to fix problems before the investigator arrives. For example, when an inspection is preannounced, it gives establishments time to clean up their facility and update or generate new operating procedures ahead of the inspection. However, establishments are expected to be in a constant state of compliance and always ready for an FDA inspection, and several investigators told us seeing the true day-to-day operating environment for an establishment is more likely during an unannounced inspection.

Of the 18 investigators we interviewed for our December 2019 testimony, 12 said that unannounced inspections are generally preferable to

preannounced inspections. One investigator told us that, although they believed the best way to ensure industry compliance to CGMPs was for establishments to not know when FDA is coming for an inspection, there was no data that would allow the agency to evaluate whether unannounced inspections were better than preannounced inspections. In addition, some investigators told us that it was still possible to identify serious deficiencies during preannounced inspections. For example, investigators could still identify issues by looking at the firm's electronic records, including time-stamped data relating to the creation, modification, or deletion of a record. Three investigators also told us that in some cases there could be benefits to announcing inspections in advance. For example, for preapproval inspections, announcing the inspection in advance gives the establishment time to organize the documentation and staff needed to conduct the inspection.

Language Barriers. Work for our December 2019 testimony indicated that language barriers—which we first reported as a challenge to conducting foreign inspections in our 2008 report—can add time to inspections and raise questions about the accuracy of information FDA investigators collect and thus about the equivalence to domestic inspections.³⁹ FDA generally does not send translators on inspections in foreign countries. Rather, investigators rely on the drug establishment to provide translation services, which can be an English-speaking employee of the establishment being inspected, an external translator hired by the establishment, or an English-speaking consultant hired by the establishment.

Of the 18 investigators that we interviewed, 14 said that language barriers can be a challenge to conducting foreign inspections and were especially challenging in parts of Asia, including China and Japan. Seven investigators told us this issue was less of a challenge for inspections conducted in other foreign countries, including India and countries in Europe, because workers at establishments in these countries were more likely to speak English, and documentation was also more likely to be in English. Investigators told us that compared to domestic inspections, it can be more challenging and take longer to complete typical inspection-related activities, such as reviewing documentation or interviewing employees, if the investigator needed to rely on translation.

³⁹[GAO-08-970](#).

Fourteen of the 18 investigators we interviewed said that there can be concerns related to relying on establishment staff and independent translators. Specifically, 11 investigators told us there can be uncertainties regarding the accuracy of the information being translated, particularly when investigators rely on the translation provided by an employee of the establishment being inspected. For instance, one investigator said that there was more risk of conflict of interest if the establishment used its own employees to translate. Another investigator said that they went to a drug establishment in China that told FDA it had English-speaking employees to translate the inspection, but that was not the case, and the investigator had to use an application on their phone to translate the interviews. In addition, the firm representative providing the translation may be someone who does not have the technical language needed, which can make it harder to communicate with firm staff and facilitate the inspection. One investigator told us that the independent translators hired by firms were sometimes consultants and, in those instances, it can seem like the consultants are coaching the firm during the inspection.

FDA officials told us that when they conduct unannounced for-cause inspections in China, investigators bring locally employed staff who work in FDA's China office to act as translators. The investigators we interviewed said that in such instances, they valued knowing that the translation they were getting was accurate. However, FDA does not have the resources to provide locally employed staff on every inspection, according to an FDA official.

Lack of Flexibility. Work for our December 2019 testimony indicated that, as we first reported in 2008, the overseas travel schedule can present unique challenges for FDA's domestically based investigators—including both ORA investigators and members of the dedicated foreign drug cadre—who conduct the majority of foreign inspections.⁴⁰ Eight of the 12 dedicated foreign drug cadre investigators that we interviewed for our December 2019 testimony told us that there is little flexibility to extend foreign inspections conducted by domestically based investigators, because the inspections they conduct on an overseas trip are scheduled

⁴⁰GAO-08-970.

back-to-back in 3-week trips that may involve three different countries.⁴¹ This raises questions about their equivalence to domestic inspections. For instance, extending one inspection would limit the amount of time the investigator has to complete their other scheduled inspections, some investigators told us.

In addition, eight investigators told us that domestically based staff are generally unable to extend the total amount of time spent on an overseas trip—one investigator told us that an investigator would have to find something really bad to justify an extension. In contrast, FDA officials told us that inspections conducted by in-country investigators in China or India, and domestic inspections in the United States, are generally scheduled one at a time and can thus more easily be extended if the investigator needs additional time to pursue potential deficiencies. However, in-country investigators are not involved in the majority of inspections conducted in China or India.

Three investigators from the dedicated foreign drug cadre told us that when they travel overseas, they adjust their inspection approach to help ensure they finish foreign inspections on time. For example, one investigator told us that an investigator may start the inspection in an area of the establishment that was noted as having issues during the last inspection. However, one investigator said that sometimes it is not possible to cover everything in depth during a foreign inspection. Another investigator told us that they focus on identifying the most serious issues during a foreign inspection, and that less serious issues can be identified in the establishment inspection report for reference in the next inspection. Five investigators also noted that they work long hours during their inspection to ensure they can complete the needed work.⁴² While FDA may assign more than one investigator to an inspection to complete needed work, one investigator said that FDA does not usually assign more than one person to an inspection because investigators are expected to have the experience to conduct inspections by themselves.

⁴¹According to FDA officials, investigators in the dedicated foreign drug cadre are expected to conduct 16 to 18 foreign inspections per year. To meet this expectation, cadre members travel overseas six times a year, with each trip lasting 3 weeks, and conduct two or three back-to-back inspections per trip.

⁴²According to FDA officials, members of the dedicated foreign drug cadre can receive up to 15 hours of overtime per week during an overseas week to complete inspection-related work. For example, investigators may use overtime hours to extend the amount of time on site or to review relevant data and documentation when they return to their hotel at night.

FDA data show that from fiscal years 2012 through 2018, the majority of both foreign and domestic inspections were conducted by one person—77 percent and 66 percent, respectively.⁴³

Post-Inspection Classification Process. According to FDA officials, starting in fiscal year 2018, FDA implemented a new post-inspection classification process: when an ORA investigator recommends an OAI classification following an inspection, ORA compliance is required to send that inspection report to CDER for review within 45 calendar days from the inspection closeout. Among other things, the process was intended to help ensure FDA can communicate inspection results to domestic and foreign establishments within 90 days of the inspection closeout, as committed to under the Generic Drug User Fee Amendments of 2017(GDUFA II).⁴⁴ FDA officials told us that the changes also required an additional ORA review for foreign inspection reports to align that process with the process for domestic inspection reports.⁴⁵ Although the 45-day reporting time frame for potential OAI classifications is a requirement for both domestic and foreign inspections, adding the additional level of review within ORA effectively shortened the amount of time investigators have to document findings for foreign inspections.

Our work indicated that the post-inspection reporting time frames can create challenges for domestic investigators who conduct foreign inspections and raise questions about the equivalence to domestic inspections. Eight of the 18 investigators we interviewed for our December 2019 testimony said shortening the time for completing reports and adding a level of review has made it more challenging to meet reporting requirements, especially if serious deficiencies are identified during the inspection. Investigators told us that for a potential OAI

⁴³In addition to the time pressures associated with sending only one investigator on a foreign inspection, two of the investigators we interviewed from the dedicated foreign drug cadre expressed a preference for conducting team inspections as it helps reduce risks to their personal safety.

⁴⁴Pub. L. No. 115-52, § 301(b), 131 Stat. 1005, 1020 (codified in pertinent part at 21 U.S.C. § 379j-41 note). Prior to each user fee program reauthorization, FDA negotiates with representatives of the generic drug industry to identify goals for how FDA should spend those user fees over the next 5-year authorization period.

⁴⁵Prior to this change, officials told us that all foreign inspection reports, regardless of classification type, were sent to CDER for review after being endorsed by ORA supervisors. Under the new process, all foreign inspections are reviewed by ORA compliance after being endorsed by ORA supervisors. Foreign inspection reports now only go to CDER compliance for review in certain circumstances, such as if there is an OAI recommended, which had been the process for domestic inspections.

inspection, they now need to send the inspection report to their supervisor for endorsement within 10 days of the closeout of a foreign inspection, regardless of when the investigator's next inspection is scheduled for, or whether the investigator has to travel from overseas back to the United States after the inspection. For example, if a domestic investigator finds serious deficiencies on the first inspection of an overseas trip—thus indicating an initial OAI classification—the investigator needs to write and send the related inspection report to the ORA supervisor for endorsement before returning home from the 3-week overseas trip to meet the required time frame. One investigator told us that, as a result of the time pressures, post-inspection reports may be less thorough, and that some inspection observations could be better supported if investigators had more time to write the reports.

In conclusion, foreign manufacturing establishments continue to be a critical source of drugs for millions of Americans, and FDA inspections are a key tool to ensure the quality of these drugs. Over the years since we first examined this issue, FDA has made significant changes to adapt to the globalization of the pharmaceutical supply chain and has greatly increased the number of inspections it conducts of foreign establishments. However, we found in December 2019 that the agency faced many of the same challenges overseeing foreign establishments that we identified over the last two decades. These included inspector vacancies and unique challenges when inspecting foreign drug establishments that raised questions about the equivalence of those inspections to domestic inspections. Since then, the outbreak of COVID-19 has added a layer of complexity. It also further highlights the global nature of our pharmaceutical supply chain.

Chairman Grassley, Ranking Member Wyden, and Members of the Committee, this completes my prepared statement. I would be pleased to respond to any questions that you may have at this time.

GAO Contact and Staff Acknowledgments

If you or your staff have any questions about this testimony, please contact Mary Denigan-Macauley, Director, Health Care at (202) 512-7114 or DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this statement. GAO staff who made key contributions to this testimony are William Hadley (Assistant Director); Derry Henrick (Analyst-in-Charge); Katherine L. Amoroso; George Bogart; Zhi Boon; Rebecca Hendrickson; John Lalomio; Gail-Lynn Michel; Laurie Pachter; and Vikki Porter.

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