



January 2022

DRUG SAFETY

FDA Should Take Additional Steps to Improve Its Foreign Inspection Program

Why GAO Did This Study

FDA is responsible for ensuring the safety and effectiveness of all drugs marketed in the U.S., regardless of where they are produced.

Globalization—and the outbreak of COVID-19—have complicated FDA's oversight of the more than 4,000 establishments manufacturing drugs for the U.S. HHS reported that 73 percent of establishments manufacturing active ingredients, and 52 percent of those manufacturing finished drugs for the U.S., were located overseas as of March 2021.

GAO's concerns about FDA's ability to oversee the increasingly global drug supply chain led it to designate the issue as a high risk area in 2009. GAO was asked to update its work on FDA's foreign drug inspection program. This report (1) describes the number of inspections prior to and during the COVID-19 pandemic, (2) examines steps taken to address challenges related to preannouncing foreign inspections and language barriers, and (3) examines efforts to maintain a sufficient inspection workforce, among other objectives. For this work, GAO examined FDA data and documents and interviewed drug investigators and other FDA officials. GAO also visited FDA foreign offices in China and India in fall 2019.

What GAO Recommends

GAO is making three recommendations: that FDA incorporate leading practices into the design of both its unannounced inspection and translation pilot programs and fully develop tailored strategies to ensure it has a sufficient foreign inspection workforce. HHS agreed with GAO's recommendations.

View [GAO-22-103611](#). For more information, contact Mary Denigan-Macauley at (202) 512-7114 or deniganmacauley@gao.gov.

DRUG SAFETY

FDA Should Take Additional Steps to Improve Its Foreign Inspection Program

What GAO Found

In fiscal year 2019, the Food and Drug Administration (FDA) began to increase the number of inspections of foreign drug manufacturing establishments after decreases from fiscal years 2016 through 2018. FDA, an agency within the Department of Health and Human Services (HHS), conducts the largest number of foreign inspections in India and China, where more than one-third of foreign establishments supplying the U.S. market are located. However, beginning in March 2020, FDA postponed most inspections because of the COVID-19 pandemic, conducting three foreign inspections from March to October 1, 2020. In comparison, FDA conducted more than 600 foreign inspections over the same time period in each of the 2 prior years. From October 2020 to April 2021 (the most recent period for which data are available), FDA conducted 18 high priority foreign inspections—primarily in China. In November 2021, FDA announced it was developing plans to potentially resume foreign inspections in February 2022.

GAO has reported that FDA faces unique challenges conducting foreign inspections—including that inspections have generally been preannounced and that investigators may rely on the establishment being inspected to provide translation services. While drugs manufactured overseas for the U.S. market must meet the same requirements as those manufactured in the U.S., these unique challenges raise questions about the equivalence of foreign to domestic inspections. FDA plans on implementing pilot programs focused on evaluating the effect of conducting unannounced inspections and using independent translation services. However, these efforts have been delayed by the COVID-19 pandemic and the agency has not yet finalized the pilots' designs.

As FDA moves forward, the agency could benefit from incorporating leading practices for designing a well-developed and documented pilot program—such as developing a methodology that details the information necessary to evaluate the pilot. This would help ensure the pilots provide FDA with the information it needs to assess the value of unannounced inspections and independent translation services, and to decide whether these approaches should be applied more broadly to other foreign inspections.

While FDA has reduced vacancies among its general drug inspection workforce, FDA data showed that the agency still has persistent vacancies among those who specialize in foreign inspections as of November 2021. Specifically:

- eight of 20 positions were vacant in FDA's cadre of drug investigators that conduct only foreign inspections, and
- five of 15 drug investigator positions were vacant in its foreign offices located in China and India.

These are longstanding challenges that GAO has previously identified. According to FDA officials, foreign inspection work is challenging, requiring the investigator to work independently in a foreign establishment under constrained time frames. In 2020 and 2021, FDA began to take steps to identify new strategies to recruit and retain this workforce, but the agency has not yet detailed implementation steps and time frames. Fully developing such tailored strategies could help ensure FDA has the workforce needed to meet its global mission.

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Abbreviations

API	active pharmaceutical ingredient
CDER	Center for Drug Evaluation and Research
CGMP	current good manufacturing practices
ConOps	Concept of Operations
COVID-19	Coronavirus Disease 2019
FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GDUFA	Generic Drug User Fee Act
GS	General Schedule
HHS	Department of Health and Human Services
NAI	no action indicated
OAI	official action indicated
OGPS	Office of Global Policy and Strategy
OPM	Office of Personnel Management
ORA	Office of Regulatory Affairs
VAI	voluntary action indicated

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January 7, 2022

Congressional Requesters

The Food and Drug Administration (FDA) is responsible for ensuring that drugs marketed in the U.S. are safe and effective.¹ Critical to this oversight are its inspections of the establishments manufacturing those drugs (including brand-name, generic, and over-the-counter finished drugs and their active ingredients). These inspections can identify manufacturing deficiencies, which can lead to serious problems if they are not corrected. However, FDA's inspection responsibilities have been complicated by a manufacturing supply chain that has become increasingly global. According to the Department of Health and Human Services (HHS), as of March 2021, 73 percent of establishments registered with FDA to manufacture active pharmaceutical ingredients, and 52 percent of establishments registered with FDA to manufacture finished drugs, for the U.S. market were located overseas.²

We have reported since 1998 on the ability of FDA, an agency within HHS, to oversee foreign drug manufacturing. Specifically, in 1998, we reported that most FDA inspections identified deficiencies warranting corrective action, though FDA often reclassified the inspection results to a less serious classification during its internal review and was, therefore, less likely to reinspect the establishments to verify that deficiencies had

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 (2020). In this report, we refer both to drug products—drugs in their finished dosage forms—and to active pharmaceutical ingredients as “drugs.”

²The White House, *Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: 100-Day Reviews under Executive Order 14017* (Washington, D.C.: June 2021). 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.

been corrected.³ In addition, we reported that FDA had significant problems managing its foreign inspection data, and in 2008 found that, because of inaccurate information in FDA's databases, the agency did not know how many foreign establishments were subject to inspection.⁴ In 2008, we also found that FDA inspected relatively few foreign drug manufacturing establishments, and, since 2009, the issue has been highlighted in our High Risk Series.⁵ 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 establishment subject to inspection.⁶ We also reported in 2016 that FDA significantly increased the number of foreign establishments it inspected each fiscal year and by 2015 was conducting more inspections of foreign establishments than domestic establishments. In our 2016 report, we also described steps FDA had taken to prioritize establishments for inspection each year using a risk-based approach.

However, in December 2019, we reported that both foreign and domestic inspections decreased from fiscal year 2016 through 2018.⁷ FDA officials attributed this decline, in part, to vacancies among investigators available to conduct foreign inspections, another persistent challenge that we have identified in multiple reports.

³See GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, [GAO/HEHS-98-21](#) (Washington, D.C.: Mar. 17, 1998). FDA classifies inspections based on the severity of the identified deficiencies, as follows: insignificant or no deficiencies identified; deficiencies identified, but corrective action is left to establishment to take voluntarily; and serious deficiencies identified that warrant FDA regulatory action. Inspections may be reclassified—either to a more serious or less serious classification—during FDA's internal review.

⁴See [GAO/HEHS-98-21](#) and 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).

⁵See GAO, *High-Risk Series: Dedicated Leadership Needed to Address Limited Progress in Most High-Risk Areas*, [GAO-21-119SP](#) (Washington, D.C.: Mar. 2, 2021).

⁶See 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 *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).

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

In addition, we have reported on unique challenges to conducting foreign inspections that can raise questions about the equivalence of foreign to domestic inspections.⁸ For example, in our 2019 testimony, we reported that, while domestic inspections have almost always been unannounced, FDA's practice of generally preannouncing foreign inspections up to 12 weeks in advance may have given manufacturers the opportunity to fix problems before the inspection.⁹ According to several investigators we interviewed for our testimony, preannouncing inspections can make it more challenging for investigators to observe the true day-to-day operating environment of an establishment during an inspection. Further, FDA has relied on translators provided by the foreign establishments being inspected, which investigators told us can raise questions about the accuracy of information FDA investigators collect.

The outbreak of Coronavirus Disease 2019 (COVID-19) has further complicated FDA's foreign inspection activities. Citing concern for the safety of its employees, FDA announced in March 2020 that it was postponing most foreign and domestic inspections and any inspections conducted would be preannounced during the COVID-19 pandemic to help ensure the safety of its employees.

You asked us to update our work on FDA's foreign drug inspection program. In this report we do the following:

1. Describe steps FDA has taken to refine its process for identifying and prioritizing foreign drug establishments for inspection since our 2016 report.
2. Describe the number of foreign drug inspections prior to and during the COVID-19 pandemic.
3. Examine FDA's steps to address two unique challenges to conducting foreign drug inspections—preannounced inspections and language barriers.
4. Examine FDA's foreign drug investigator workforce and steps FDA has taken to maintain its sufficiency.
5. Describe the frequency with which FDA identified deficiencies during foreign inspections and classified them as serious enough to warrant regulatory action.

⁸See [GAO-20-262T](#).

⁹See [GAO-20-262T](#).

6. Describe FDA's approach for reclassifying inspection results and ensuring consistency in its decisions.

To describe steps FDA has taken to refine its process for identifying and prioritizing foreign drug establishments for inspection, we reviewed agency documents and interviewed agency officials about the steps FDA has taken to improve the accuracy and completeness of its data on foreign establishments and about improvements to FDA's process for prioritizing establishments for inspection. We also reviewed the list of establishments prioritized for inspection through this process for fiscal years 2019 through 2022.

To describe the number of foreign drug inspections prior to and during the COVID-19 pandemic, we analyzed data from FDA's Field Accomplishments and Compliance Tracking System (FACTS), which contains information on inspections of drug manufacturing establishments. Specifically, we examined FDA data from fiscal year 2016 (the last year of inspections we analyzed when we last issued a full report on this topic) through April 29, 2021, (partial fiscal year 2021) to determine: (1) the number of foreign and domestic inspections conducted by FDA, (2) the type of inspections, and (3) the country in which the inspections took place. Partial fiscal year 2021 data were the most recently available when we conducted our analysis. To provide context for the number of inspections, we also obtained data from FDA on the number of establishments the agency considered to be subject to inspection in each country as of June 2021, which was the most recently available data at the time of our analysis. Finally, we reviewed agency documents and interviewed agency officials about the agency's plans to resume inspections as the COVID-19 pandemic progresses.

To examine FDA's steps to address the challenge of preannounced inspections and language barriers, in the fall of 2019 we visited FDA's foreign offices in China and India, the countries where FDA performs the largest number of foreign drug inspections and has foreign office staff that includes investigators to conduct drug inspections. At these two offices we interviewed the six drug investigators available in the offices at the time of our visits—a nongeneralizable selection—about their inspection efforts. While in those countries, we accompanied investigators to two drug manufacturing establishments to observe inspection procedures. We also interviewed all 12 members of FDA's calendar year 2019 cadre of dedicated drug investigators, who are based in the United States but conduct foreign inspections exclusively. Finally, we reviewed documentation and interviewed officials in FDA headquarters about the

agency's efforts to address preannounced inspections and language barriers. Our review focused on these two challenges because FDA is developing pilot programs specifically to examine these issues. We did not focus on the other two challenges we previously identified—the lack of flexibility in the overseas travel schedule and the post-inspection process—because FDA does not have similar efforts to address them. We compared FDA's plans for designing these pilot programs to leading practices we identified for designing a well-developed and documented pilot program.¹⁰

To examine FDA's foreign drug investigator workforce and steps FDA has taken to maintain its sufficiency, we analyzed FDA data provided during the course of our review on the number of authorized, filled, and vacant investigator positions, as well as data from FACTS on which type of investigators were conducting foreign inspections (e.g., those based in the U.S. or in the foreign offices). We also interviewed officials from the Office of Regulatory Affairs (ORA)—which is responsible for conducting inspections—and the Office of Global Policy and Strategy (OGPS)—which oversees the activities of FDA's foreign offices—about their efforts to maintain a sufficient pool of drug investigators, and we reviewed FDA documents related to workforce planning and investigator recruitment and hiring. We compared FDA's efforts to maintain a sufficient workforce against key principles we identified for strategic workforce planning.¹¹

To describe the frequency with which FDA identified deficiencies serious enough to warrant regulatory action during foreign inspections, we analyzed FACTS data from fiscal year 2018 through fiscal year 2020 (the most recent full fiscal year available at the time of our review). We used these data to determine FDA's initial and final inspection classification of the inspection results and how often FDA's initial classification of inspections were changed for final classification. Our reclassifications analysis focused on inspections conducted for regular surveillance after drugs are marketed in the U.S. and inspections to investigate specific issues. We excluded inspections related to the drug approval process from our reclassifications analysis as policies and procedures for the review of such inspections differ.

¹⁰See GAO, *DATA Act: Section 5 Pilot Design Issues Need to Be Addressed to Meet Goal of Reducing Recipient Reporting Burden*, [GAO-16-438](#) (Washington, D.C.: Apr. 19, 2016).

¹¹See GAO, *Human Capital: Key Principles for Effective Strategic Workforce Planning*, [GAO-04-39](#) (Washington, D.C.: Dec. 11, 2003).

To describe FDA's approach for reclassifying inspection results and ensuring consistency in its decisions, we reviewed FDA procedures and interviewed officials to identify the key procedures and goals related to FDA's inspection classification process, including those related to classification changes that may occur during FDA's process to decide final classifications. We then reviewed FDA's efforts to analyze those classification decisions where there were changes prior to final classification.

To assess the reliability of the data on inspections, the number of establishments subject to inspection, prioritized inspection lists, and investigator staffing we reviewed related documentation, interviewed knowledgeable agency officials, conducted electronic data testing for missing data and outliers, and compared the data to published information from the same database. On the basis of these steps, we found these data sufficiently reliable for the purposes of our reporting objectives.

Our work focused on human drugs regulated by the Center for Drug Evaluation and Research (CDER) and not on most biologics, veterinary medicines, or other items or products for which FDA conducts inspections.¹² Further, our work focused on activities related specifically to the foreign drug inspection program. As part of its oversight of imported drugs, FDA undertakes other activities, such as working toward international harmonization of regulatory requirements, which are beyond the scope of our review.

We conducted this performance audit from June 2019 to January 2022 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.

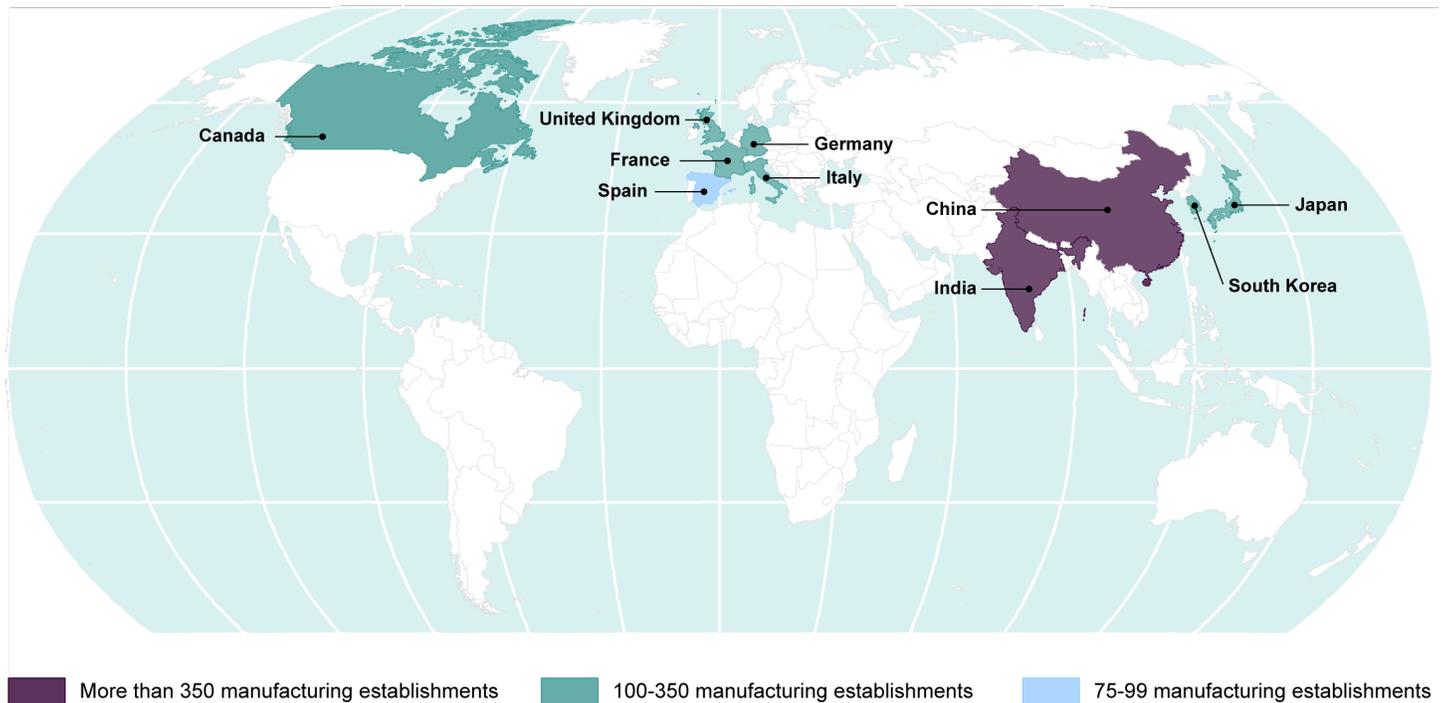
¹²Our analysis focused on inspections related to the drug approval process or inspections conducted to determine an establishment's ongoing compliance with laws and regulations in the manufacture of human drugs already marketed in the United States. FDA conducts additional drug inspections that are beyond the scope of our review, such as to determine whether drug manufacturers are submitting to FDA, as required, complete and accurate data on adverse drug experiences associated with marketed drugs, inspections conducted for the President's Emergency Plan for AIDS Relief, and inspections of clinical trial sites, compounding pharmacies, and medical gas manufacturers.

Background

Globalization of Drug Manufacturing

Drugs sold in the United States—including active pharmaceutical ingredients and finished dosage forms—are manufactured throughout the world. As of June 2021, FDA data showed that India and China had the most foreign establishments manufacturing drugs for the U.S. market, with more than one-third of all foreign establishments in these two countries. (See fig. 1.)

Figure 1: The 10 Countries with the Most Foreign Drug Establishments Manufacturing Drugs for the U.S. Market as of June 2021



Source: GAO analysis of Food and Drug Administration data (data); National Atlas (base map). | GAO-22-103611

Note: This figure includes the 10 countries with the most foreign drug establishments manufacturing drugs for the U.S. market and does not include those countries with fewer than 75 establishments. The count of foreign establishments does not include approximately 700 foreign establishments that are only manufacturing alcohol-based hand sanitizers.

Types of Inspections

Drugs manufactured overseas for the U.S. market must meet the same statutory and regulatory requirements as those manufactured in the United States. FDA's CDER establishes standards for the safety, quality, effectiveness of, and manufacturing processes for, over-the-counter and

prescription drugs. CDER requests that 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 practices (CGMP).¹³

Investigators generally conduct three main types of drug manufacturing establishment inspections: preapproval inspections, surveillance inspections, and for-cause inspections, as described in table 1.¹⁴

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) to determine that the establishment is following commitments made in the application and to 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 approval before marketing—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, reports of product quality issues submitted by consumers or health care professionals, 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-22-103611

^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 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. FDA may also conduct post-approval inspections that focus on a specific product and are conducted after applications have been approved. Post-approval inspections largely focus on the process validation lifecycle and any manufacturing changes that may have occurred following approval.

¹³CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. See 21 U.S.C. § 351(a)(2)(b); 21 C.F.R. pts. 210, 211, 212 (2020). FDA considers nearly all drug establishment inspections to include an assessment of CGMPs.

¹⁴At times, FDA may conduct an inspection that combines both preapproval and surveillance inspection components in a single visit to an establishment. Most combined inspections occur when FDA conducts a surveillance inspection at an establishment where a preapproval inspection is also being conducted.

^bCertain drugs, such as some over-the-counter drugs, may not require FDA approval before being marketed in the U.S.

FDA's Process for Prioritizing Establishments for Surveillance Inspection

While preapproval and for-cause inspections occur in response to specific needs, FDA uses a risk-based process to select establishments for surveillance inspections. Initially, FDA uses data from multiple databases to identify foreign and domestic establishments for surveillance inspections, including its registration database and inspection database.

- FDA's registration database contains information on foreign and domestic drug establishments that have registered with FDA. Establishments located in the U.S. that manufacture drugs, as well as establishments located in other countries that manufacture drugs that are imported or offered for import into the U.S., are required to register with FDA.¹⁵ Information in the registration database includes the company's name, address, and the drugs it manufactures for commercial distribution in the U.S., as reported by the establishment.
- FDA's inspection database, FACTS, contains information on domestic and foreign establishment inspections, including the type of inspection conducted and the outcome of those inspections.

Using these and other databases, CDER compiles a catalog of establishments that are subject to inspection. The establishments in the catalog are then prioritized for inspection annually. In our 2008 report we found that, because of inaccurate information in FDA's databases that feed into its catalog of drug establishments subject to inspection, the agency did not know how many foreign drug establishments were subject to inspection.¹⁶ For example, we found that the catalog was inaccurate in that 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 registered with FDA but did not actually manufacture drugs for the U.S. market and thus were not subject to inspection.¹⁷ Further, we found that the catalog was incomplete because some establishments that were

¹⁵Establishments that manufacture, prepare, propagate, compound, or process a drug that are located in the U.S. or that offer drugs for import into the U.S. are required to register annually with FDA. 21 U.S.C. § 360(b), (i), (j).

¹⁶See [GAO-08-970](#).

¹⁷We previously reported that some foreign establishments may register with FDA even if they do not manufacture drugs for the U.S. market because, in foreign markets, registration may erroneously convey "approval" or endorsement of the establishment by FDA, according to FDA officials. See [GAO-08-970](#).

subject to inspection did not register with FDA.¹⁸ In our 2010 and 2016 reports, we found that FDA had taken steps to improve the accuracy and completeness of information in its catalog, such as requiring establishments to provide a unique facility identifier during the annual registration process, which allowed FDA to automatically validate the accuracy of registration information against a commercial database.¹⁹

To prioritize establishments from the catalog for surveillance inspections, CDER applies a risk-based site selection model.²⁰ The Food and Drug Administration Safety and Innovation Act (FDASIA) requires FDA to inspect both domestic and foreign establishments using a risk-based schedule established by the agency and incorporating specific risk factors.²¹ CDER's risk-based model incorporates FDASIA's requirements into its analysis of three major factors—facility score, product score, and time since last inspection—which are in turn scored and weighted based on information about the establishment and the drugs it manufactures. The model helps CDER identify those establishments that, based on the characteristics of the drug being manufactured, pose the greatest potential public health risk should they experience a manufacturing defect. CDER incorporates the results of the model into its site selection process, through which it develops a ranked list of foreign and domestic establishments that FDA considers to be a priority for inspection and submits that list to ORA.²²

¹⁸See [GAO-08-970](#).

¹⁹See [GAO-10-961](#) and [GAO-17-143](#).

²⁰Until 2012, FDA was required to inspect domestic drug manufacturing establishments every 2 years, but there was no comparable requirement for inspecting foreign drug manufacturing establishments. As a result, foreign inspections were often preapproval inspections driven by pending applications for new drugs.

²¹Pub. L. No. 112-144, § 705, 126 Stat. 993, 1066 (2012) (codified in pertinent part at 21 U.S.C. § 360(h)(3) and (4)). FDA is required to incorporate specific risk factors when establishing this schedule: a manufacturing establishment's compliance history, recall history, inherent product risk, inspection frequency and history, and whether the establishment has been inspected by a foreign government or agency recognized by FDA. FDA may consider additional criteria deemed necessary and appropriate.

²²We previously reported that, to use resources efficiently, 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. See [GAO-10-961](#).

FDA Has Improved Its Data for Identifying, and Refined Its Process for Prioritizing, Foreign Establishments for Inspection

Since we last reported in 2016, FDA has taken steps to refine its process for identifying and for prioritizing foreign establishments that are subject to inspection. First, FDA improved the data in the catalog the agency creates to identify establishments subject to inspection, although the agency lacks information on certain establishments manufacturing drugs and their active pharmaceutical ingredients (API) for the U.S. market that are not directly imported. Second, FDA has refined its process for prioritizing establishments for inspection by taking steps to improve its risk-based site selection model and its process for creating a prioritized inspection list.

FDA Continued to Improve the Data It Uses to Identify Establishments for Inspection, although the Agency Lacks Information on Certain Establishments

Catalog of Establishments

Since our 2016 report, FDA has taken additional steps to improve the accuracy and completeness of the catalog of establishments it uses to identify establishments for inspection. These steps included efforts to ensure that FDA's catalog only includes establishments that are actually subject to inspection (i.e., ensure its accuracy) and efforts to identify any establishments that are subject to inspection, but are missing from the catalog (i.e., ensure its completeness).

To improve the accuracy of information that manufacturing establishments submit to the agency through the annual registration process—which is a primary source of data on establishments subject to inspection—in October 2017, FDA held the first of what has become an annual workshop and webinar to help establishments understand and comply with FDA requirements. FDA officials told us that, by helping establishments understand registration requirements, the workshops promote more accurate and complete registration submissions and, accordingly, a more accurate and complete catalog. The 2020 event, for example, was attended by drug industry representatives from 92 countries, including more than 600 attendees from India and more than 70 from China, according to FDA officials.

Once this information has been submitted, FDA took the following steps to confirm its accuracy, FDA officials told us.

-
- FDA contracted with a private group to validate registration information for a selection of drug establishments in China, India, and other countries.²³ Such efforts included both in-person and remote verification of an establishment's address and other information. The contractor conducted these verifications from 2015 to 2017, which helped FDA identify establishments that were registered with FDA but not actually subject to routine inspection, according to FDA officials.
 - Since 2018, FDA has used locally employed staff in FDA's China office to call all Chinese establishments that were newly registered over the previous month to confirm that they were actually shipping drugs to the United States (and therefore required to register and subject to inspection), verify their registration information, and provide any corrections of their information to FDA headquarters. According to FDA officials, this process has helped the agency reduce the number of establishments that were selected for inspection but were later found to not actually be subject to inspection because they were not required to register. For example, an official told us that less than 10 percent of inspections assigned to the China office in fiscal year 2019 were for establishments not subject to inspection, compared to about 40 percent in fiscal years 2017 and 2018. Building on this model, FDA officials told us that, in 2019, staff in the U.S. began reaching out to new foreign registrants in countries other than China and to new domestic registrants to verify registration information and business operations. In addition, the officials told us that the agency's India office began using locally employed staff to contact and verify information from newly registered establishments in India in July 2021.
 - For fiscal year 2019, FDA began verifying the registration and listing, inspection, and shipment information for all establishments in the catalog that were not scheduled for inspection or for oversight through other activities like analyzing drug samples. Officials also told us that, prior to scheduling a foreign inspection, FDA verifies that the establishment is operational, as establishments may stop and then resume manufacturing drugs for the U.S. market over time.

Taken together, FDA officials told us these efforts have greatly reduced the number of instances in which FDA selected an establishment for inspection, but, during the trip planning process, the establishment was later found to not actually be subject to inspection. For example, according to an FDA analysis, there were more than 300 such instances

²³In addition to drug establishments, the contractor also conducted site verifications for manufacturers of other FDA-regulated products, such as foods and medical devices.

Information on Foreign
Establishments Manufacturing
Drugs That Are Indirectly
Imported

each year from fiscal years 2017 through 2019, but less than 100 such instances in fiscal years 2020 and 2021 (through the third quarter of fiscal year 2021).

However, agency officials told us FDA's catalog lacks information about certain foreign establishments manufacturing drugs that are indirectly imported to the U.S., primarily foreign manufacturers of over-the-counter finished dosage forms and their suppliers of API. For example, an establishment manufacturing API in China that ships its API to a finished dosage form manufacturer in Germany, which then ships the finished over-the-counter drug to the United States is still subject to inspection but may not have registered with FDA.

According to FDA officials, this gap exists for manufacturers of API used in certain over-the-counter drugs and in compounded drugs, as well as certain manufacturers of over-the-counter finished dosage form drugs.²⁴ While all foreign establishments manufacturing finished drugs and their active ingredients for the U.S. market are subject to inspection, establishments manufacturing drugs imported indirectly to the United States may not all register with FDA, according to FDA officials. Officials told us that this is because establishments manufacturing drugs that are imported indirectly may not understand their statutory registration responsibilities and therefore may not register with FDA.²⁵ As a result, FDA may not be aware of these establishments and thus may not include

²⁴For drugs that require an FDA approved application before marketing—including all prescription drugs and some over-the-counter drugs—FDA receives information about the location of the API and finished dosage form manufacturers in the application itself. For drugs that do not require an approved application before marketing—including both other over-the-counter drugs regulated through the over-the-counter monograph process and compounded drugs—FDA may not know where the API is manufactured. (Drugs regulated through the over-the-counter monograph process—including aspirin, cough and cold medicine, certain ophthalmic products, and hand sanitizer—do not need individual preapproval from FDA to be marketed, as long as they meet the conditions of the monograph, which outlines active ingredients, indications for use, dosage forms, and product labeling. Inspections related to drug compounding—the process of combining, mixing, or altering ingredients to create a drug tailored to the needs of an individual patient—are outside the scope of this report.) FDA officials told us that in addition to API manufacturers whose drugs are indirectly imported and may not have registered, FDA also lacks information on a small subset of establishments that manufacture finished dosage form drugs in bulk that are then repackaged or relabeled by another establishment before being shipped to the U.S.

²⁵See 21 U.S.C. § 360(i).

them in its catalog.²⁶ Thus, such unregistered establishments would not be prioritized for surveillance inspection, and FDA would be unable to proactively monitor their compliance with CGMPs and other requirements. Officials told us that, based on the agency's experience identifying such unregistered establishments while conducting inspections, they believe that the size of this group of unregistered establishments is substantial.

In our January 2021 CARES Act Drug Supply Chain enclosure, we recommended that FDA ensure the drug manufacturing data it collects—including information on drugs that are indirectly imported and information on the volume of drugs manufactured at each establishment—is complete and accessible to help the agency identify and mitigate supply chain vulnerabilities and, if necessary, to seek authority to obtain complete and accessible information.²⁷ If implemented, this recommendation would help ensure that FDA's catalog provides a more complete list of establishments subject to inspection. HHS neither agreed nor disagreed with our recommendation. In HHS's response, FDA said it would consider the recommendation as it considers options to close these gaps and, since our January 2021 report, the agency took steps to increase its ability to collect more complete drug manufacturing data. For example, as it has for the previous 2 fiscal years, in May 2021 FDA included a legislative proposal in its fiscal year 2022 budget justification to further clarify the agency's ability to require more complete and frequent reporting for finished drug products and in-process material, including API. Agency officials indicated that, among other things, this proposal is intended to clarify the registration responsibilities of establishments that manufacture drugs imported indirectly into the United States. We will continue to monitor such legislation and, if enacted, determine whether it addresses our recommendation.

²⁶FDA officials told us that when inspecting a finished dosage form manufacturer, the investigator conducting the inspection may check the manufacturer's suppliers and can sometimes identify unregistered API manufacturers and contract finished dosage form manufacturers. If this information is discovered, FDA can add them to its establishment inventory at that point.

²⁷See GAO, *COVID-19: Critical Vaccine Distribution, Supply Chain, Program Integrity, and Other Challenges Require Focused Federal Attention*, [GAO-21-265](#) (Washington, D.C.: Jan. 28, 2021).

FDA Continued to Refine Its Process for Prioritizing Establishments for Inspection by Improving Its Site Selection Model

Since our 2016 report, FDA has made additional refinements to the process it uses to prioritize foreign and domestic establishments for surveillance inspections. Our review of FDA documents and interviews with agency officials show that these refinements were focused on (1) improving FDA's risk-based site selection model (hereafter referred to as "the model") and (2) refining how FDA creates its list of establishments prioritized for inspection. Using this process, FDA prioritized approximately 1,500 establishments for surveillance inspection each year from fiscal years 2019 through 2021.

Refinements to the Model

Our review of agency documentation and interviews with officials found that FDA has made a number of improvements to the model since 2016. FDA submitted the model to three peer reviewers in 2017. The reviewers found the model to be reasonable, but they suggested improvements, such as considering whether a different type of mathematical model could be used or whether the methods used for model validation could be modified. In response, FDA conducted research into alternative models, according to FDA officials. Since the peer reviews, the agency has made several changes, including refining the way it calculated facility risk scores and incorporating additional information into the model's calculations.

Overall Risk Score

The Food and Drug Administration's (FDA) risk-based site selection model analyzes three major factors to create an overall risk score. This risk score identifies those establishments that pose the greatest potential public health risk should they not comply with manufacturing quality standards. The three major factors, and associated subfactors, that underlie the overall risk score are:

- Facility score;
- Product score; and
- Time since last inspection.

Source: GAO analysis of FDA information. | GAO-22-103611

Refining risk scores. FDA made refinements to how the model calculates risk scores for each establishment in its catalog, including the following. (See sidebar.)

- First, FDA officials told us that, in response to the peer reviewers, FDA made changes to better discriminate between different types of facilities when calculating the facility score.²⁸ For example, whereas previously the “facility type” risk factor differentiated between six higher-level facility types (e.g., manufacturer, control laboratory), it now has 11 more precise facility type options (e.g., sterile drug manufacturer, non-sterile finished dosage form manufacturer, non-sterile API manufacturer) to better differentiate between the relative risk of different types of facilities.²⁹
- Second, beginning in fiscal year 2021, FDA incorporated a risk score adjustment for establishments located in countries that—according to an FDA analysis—had higher compliance rates.

Incorporating additional information. FDA also refined the model by incorporating additional information into the facility score calculations.

- First, for fiscal year 2022, FDA began incorporating information from its assessment of records and other information that it requested from establishments into the calculations of the facility score.³⁰ FDA substantially increased the use of these assessments during the COVID-19 pandemic.³¹ FDA officials told us that the agency now

²⁸The facility score includes information about various subfactors related to the facility and its history, such as the type of establishment (for example, a manufacturer or a laboratory), number of products manufactured, and inspection history. The product score, meanwhile, captures information about a product itself, such as its therapeutic category (for example, an anti-fungal), its dosage form, and whether it is sterile.

²⁹For example, maintaining sterility throughout the production process is challenging, yet it is particularly important for sterile injectable drugs as serious injury can occur if contaminated drugs are injected into patients. Thus, all other factors being equal, establishments manufacturing sterile drugs may be considered to be a relatively higher priority for inspection than establishments manufacturing other drugs.

³⁰FDA may request that establishments provide records and other information in advance of or in lieu of an inspection. 21 U.S.C. § 374(a)(4).

³¹We previously reported that, prior to the COVID-19 pandemic, FDA used this authority in a more limited capacity to obtain information from 10 establishments that the agency would not routinely inspect because of travel warnings. See [GAO-21-265](#).

includes this information in the model's facility score calculation, along with information from prior inspections of the establishment.

- Second, FDA began systematically including the results of inspections conducted by foreign regulators into the model, the only risk factor required by FDASIA that the agency had not fully incorporated at the time of our 2016 report. FDA has a mutual recognition agreement with certain European regulators.³² Beginning with fiscal year 2019 inspection planning, FDA has been incorporating into the facility score information from reports of inspections these regulators conduct within their own country.³³ In response to the global pandemic FDA assessed and, in the first quarter of fiscal year 2021 also began incorporating, information from inspections that certain of these European regulators conducted in other countries, including India, according to FDA officials.

Refinements to FDA's Final Prioritized List

In interviews and planning documents, FDA officials outlined the changes the agency has made in its process for developing a final prioritized list of domestic and foreign establishments for inspection. Following the application of the model to the catalog, FDA first uses the model's output to develop a preliminary prioritized list of establishments subject to inspection—comprising both establishments that FDA deems mandatory for inspection and the remaining list of establishments in the catalog ranked by risk score (see sidebar). FDA then creates a final, smaller prioritized list of those establishments that it actually intends to inspect in that year.

³²For the purposes of this report, when we refer to European regulators, we are referring to the 27 European regulators that are part of the mutual recognition agreement with FDA, plus the United Kingdom, which has a separate mutual recognition agreement.

³³FDA officials told us that, when an establishment in a country with which FDA has a mutual recognition agreement is prioritized for inspection by the model, FDA staff request, review, and may classify the most recent inspection report from that regulator. Reports that lack sufficient information to be classified will not be used in determining an establishment's compliance status. If a report for that establishment is not available, FDA may request that the European regulator conduct an inspection on FDA's behalf, or FDA may conduct its own inspection. FDA incorporates information from European regulator inspection reports it reviews into its own inspection database, and thus this information is considered by the model in future years, providing more data and insight into the compliance history of establishments.

Creation of Preliminary Prioritized List

To create a preliminary list of establishments prioritized for inspection, the Food and Drug Administration (FDA) first identifies establishments for inspection that it considers to be “mandatory”—those establishments in its catalog that have never had a surveillance inspection or haven’t had a surveillance inspection in 5 years—regardless of their assigned risk score. According to FDA, officials deem such establishments to represent significant risks to drug quality, though the extent of the risk is uncertain. Thus, FDA considers inspections of such establishments to be “mandatory,” even if the overall risk scores assigned by the risk-based site selection model are lower for these establishments than other establishments in the catalog that may have been inspected more recently.

FDA then ranks all of the remaining establishments in its catalog by overall risk score.

Source: GAO analysis of FDA information. | GAO-22-103611

FDA has made refinements to how it determines the final list of establishments prioritized for surveillance inspections by considering whether methods of oversight other than an FDA inspection could be appropriate for any establishments. This has allowed FDA to remove certain establishments from the list of those needing an FDA inspection.

- **Over-the-counter manufacturers with no recent shipping history.** First, FDA no longer prioritizes for routine inspection those foreign over-the-counter manufacturers that have not shipped to the U.S. within the last 3 years. Instead, FDA gathers other information to determine whether and when to perform an inspection at such establishments in the future. FDA officials told us that this change allowed FDA to use inspection resources for higher priority sites, rather than sending investigators to establishments that did not pose a risk to the U.S. public, as they were not actively shipping products to the U.S.
- **Establishments in countries with which FDA has a mutual recognition agreement.** Second, when an establishment in a country with which FDA has a mutual recognition agreement is prioritized for inspection, FDA staff first request and review the most recent inspection report from that country’s regulator to see if FDA can substitute the report for its own inspection.³⁴ This allows the agency to focus its inspection resources on higher-risk establishments, FDA officials told us. According to FDA, in fiscal year 2018 the agency substituted European regulator reports for 29 FDA inspections; this grew to over 160 inspections in fiscal year 2020.

After incorporating the improvements to the model and overall selection process noted above, FDA creates the final prioritized list of establishments to be inspected in a given year. The number and order of establishments on this final list is driven by risk and resource availability, FDA officials told us. Specifically, FDA determines the total number of surveillance inspections it has the resources to conduct that year and determines how many of these resources are needed to conduct the inspections it considers to be mandatory. FDA then prioritizes as many of

³⁴According to FDA officials, the agency is unable to substitute a report from a regulator with which FDA has a mutual recognition agreement for its own inspection in all situations (e.g., if the foreign regulator’s inspection report did not include key products of interest). Thus, FDA staff review each inspection report and determine whether it can be accepted and classified in FDA’s own inspection database and thus be substituted for an FDA inspection. Officials further noted that when reviewing an inspection report from a foreign regulator, FDA does not accept the outcome assigned by the regulator, but instead reviews and assigns an FDA classification to the inspection.

the remaining establishments in the catalog for inspection as it can according to their overall risk scores (see text box).

Example of How the Food and Drug Administration (FDA) Creates Its Final Prioritized Inspection List

FDA's fiscal year 2020 catalog was made up of about 4,200 foreign and domestic drug manufacturing establishments. In planning inspections for fiscal year 2020, FDA determined that it had the resources to conduct 1,500 surveillance inspections, of which 450 inspections were for establishments that FDA considered to be mandatory for inspection. Therefore, for the remaining surveillance inspections in that year, it prioritized the 1,050 establishments with the highest risk scores to complete the list of 1,500 prioritized for inspection. The roughly 2,700 establishments not prioritized for inspection in fiscal year 2020—which may have had risk scores higher or lower than the establishments on the final prioritized list—would be considered for inspection in future years.

Source: GAO analysis of FDA information. | GAO-22-103611

According to FDA officials, in the recent years prior to the pandemic, FDA had been able to inspect both the mandatory establishments and most of the remaining highest risk establishments on its prioritized inspection list.³⁵ Officials told us FDA's risk-based process thus ensures that all establishments are inspected at least once, and, because any establishment not otherwise inspected in 5 years will eventually show up as mandatory, at least every 5 years thereafter. Officials said that there was capacity to inspect relatively higher risk establishments more frequently and relatively lower risk establishments less frequently, though the model itself does not provide for a specific inspection frequency or schedule for any given establishment.

³⁵If any establishments identified as mandatory for inspection are not inspected in a given year, they will carry over as mandatory inspections in the following year.

FDA Foreign Drug Inspections Increased Prior to the COVID-19 Pandemic after Several Years of Decreases, but Most Have Since Been Postponed

Prior to the COVID-19 Pandemic, FDA Foreign Drug Inspections Had Begun to Increase and the Largest Increase Was in India

Our review of FDA data shows that, after several years of decreases, FDA foreign drug inspections had begun to increase in fiscal year 2019, as we reported in March 2021.³⁶ Further, FDA continued to conduct more foreign than domestic inspections in each fiscal year from 2016 through 2019. In fiscal year 2019, FDA continued to conduct the largest number of foreign inspections in India and China, as we reported in March 2021, with an increasing number of inspections conducted in India, where about 20 percent of foreign establishments subject to inspection were located in recent years. (See table 2.)

Table 2: Drug Manufacturing Inspections by Country, Fiscal Years 2016 through 2019

Country	2016	2017	2018	2019	Number of establishments subject to inspection, as of June 2021 ^a
India	207	219	252	305	496
China	173	165	153	167	397
Canada	56	72	48	70	148
Germany	72	69	68	69	170
Japan	65	46	43	51	130
All other foreign countries	462	422	371	315	1,193
Total foreign	1,035	993	935	977	2,534
Total domestic	882	772	742	694	1,792
Total	1,917	1,765	1,677	1,671	4,326

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-22-103611

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

³⁶See [GAO-21-409T](#).

^aThe counts in this column represent the number of establishments FDA considered to be subject to inspection when applying the risk-based site selection model to its catalog for fiscal year 2022 inspection planning.

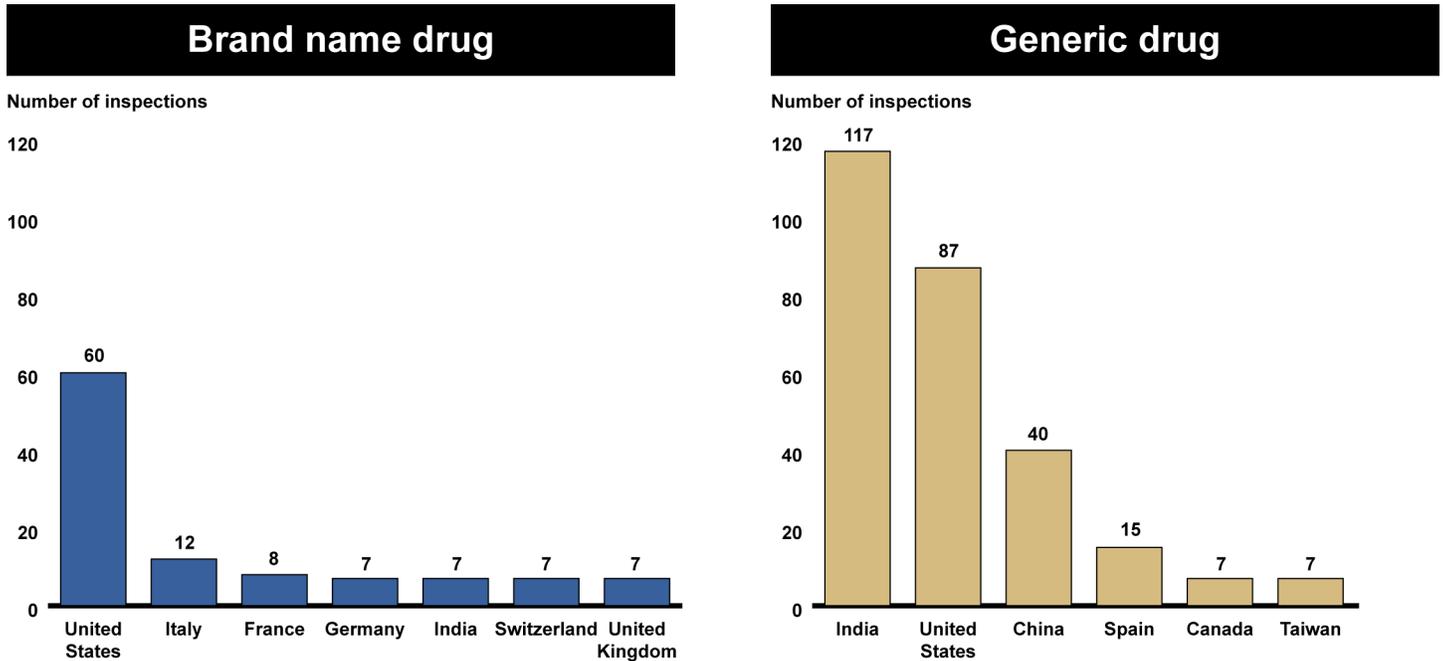
The majority of foreign inspections from fiscal year 2016 through 2019 continued to be routine surveillance inspections conducted after drugs are marketed. This remains a significant change from when we first reported on FDA's foreign drug inspection program in 1998 and found that foreign establishments were typically only inspected when they were listed in new drug applications.³⁷ For fiscal years 2016 through 2019, between 60 and 75 percent of FDA's foreign inspections were conducted for surveillance purposes, compared to about 20 percent at the time of our 1998 report.

FDA conducted more preapproval inspections in foreign countries than in the United States from fiscal year 2016 through fiscal year 2019, although most foreign inspections were for surveillance purposes. For example, in fiscal year 2019, FDA conducted about 300 preapproval inspections in foreign countries compared to about 150 in the United States. The largest number of inspections related to brand drug applications were conducted in the United States and the largest number of inspections related to generic drug applications were conducted in India (see fig. 2).³⁸

³⁷See [GAO/HEHS-98-21](#).

³⁸Preapproval inspections are not always required as part of FDA's review of new brand-name or generic drug applications. According to FDA, the agency may consider such factors as the novelty of the product, the complexity of the manufacturing process, and the compliance history of the manufacturing establishment in determining whether a preapproval inspection is necessary to support an application decision. Because preapproval inspections are not always required as part of FDA's review of a drug application and because subsequent FDA inspections of an establishment after the initial preapproval inspection would be classified as surveillance inspections, data on the number of preapproval inspections does not provide a complete picture of where manufacturing associated with brand and generic drugs is located.

Figure 2: Countries with the Most Brand and Generic Preapproval Inspections, Fiscal Year 2019



Source: GAO analysis of Food and Drug Administration data. | GAO-22-103611

Notes: In fiscal year 2019 the Food and Drug Administration (FDA) conducted six additional inspections that had both brand and generic preapproval components, with two inspections in the United States and one inspection each in Germany, Hungary, India, and Spain.

Data on the number of preapproval inspections does not provide a complete picture of where manufacturing associated with brand and generic drugs is located because preapproval inspections are not always required as part of FDA's review of a drug application, and subsequent FDA inspections of an establishment after the initial preapproval inspection would be classified as surveillance inspections.

FDA's Postponement of Most Foreign Inspections Due to the COVID-19 Pandemic Continued through Fiscal Year 2021, Increasing the Size of the Surveillance Inspection Backlog

Our review of FDA data shows that FDA postponed most foreign and domestic drug inspections starting in March 2020, due to risks and travel restrictions related to the COVID-19 pandemic, and this postponement

continued in fiscal year 2021.³⁹ In January 2021, we reported that from March 2020 through October 1, 2020, FDA conducted three foreign mission-critical inspections, in contrast to the more than 600 foreign inspections the agency conducted from March to September of each of the prior 2 years.⁴⁰ Our analysis of FDA data for October 2020 through April 2021—the data most recently available at the time we conducted our analysis—shows that FDA conducted 18 foreign inspections, primarily in China.⁴¹ According to FDA officials, while the agency began to resume routine domestic inspections in July 2021, it was continuing to primarily conduct only mission-critical inspections in most foreign countries. Officials told us that staff in the agency’s China and India offices resumed conducting prioritized inspections beyond mission-critical ones in fiscal year 2021—including both pre-approval inspections and inspections to follow-up on previous inspections at which serious deficiencies had been identified—but such staff were still not conducting routine surveillance inspections in China and India.⁴² In November 2021, FDA reported that it was developing a plan for resuming prioritized foreign inspections, including surveillance and preapproval inspections, starting in February 2022 for all commodities, subject to the dynamics of the global pandemic.⁴³

Although FDA conducts preapproval inspections of manufacturing establishments prior to making some drug approval decisions, we reported in January 2021, that the agency relied on alternative tools during the temporary postponement of most inspections due to the

³⁹As we reported in January 2021, FDA announced in March 2020 that, in light of the COVID-19 pandemic and citing the safety of its employees, the agency would temporarily not conduct any foreign or domestic inspections other than those deemed mission-critical. FDA identifies mission-critical inspections on a case-by-case basis by considering many factors related to the public health benefit of patients having access to the product subject to inspection, as well as considering the safety of its inspection staff and employees of the establishment to be inspected. See [GAO-21-265](#).

⁴⁰See [GAO-21-265](#).

⁴¹Over this same time period, FDA conducted 78 domestic inspections. In November 2021, FDA reported that it conducted 37 foreign drug inspections from April through September 2021. U.S. Food and Drug Administration, *An Update to the Resiliency Roadmap for FDA Inspectional Oversight* (November 2021).

⁴²Officials told us that FDA was temporarily detailing additional investigators to its China and India offices in order to conduct more inspections in those countries without having to account for quarantine restrictions placed on staff coming directly from the U.S.

⁴³U.S. Food and Drug Administration, *An Update*.

COVID-19 pandemic (see sidebar).⁴⁴ Through the use of alternative tools, such as information from inspections conducted by foreign regulators, FDA reduced the need for the agency to conduct its own preapproval inspection about 50 to 60 percent of the time from mid-fiscal year 2020 through mid-fiscal year 2021, according to FDA. According to an FDA statement, the combination of mission-critical FDA inspections and alternative tools allowed FDA to complete its review of at least 90 percent of brand and generic drug applications and supplements on or before their user fee goal date, as of the second quarter of 2021.⁴⁵

Alternative Tools

During the Coronavirus Disease 2019 pandemic, the Food and Drug Administration (FDA) largely paused drug inspections, instead relying on alternative tools to maintain oversight of drug manufacturing quality, including

- relying on inspections conducted by foreign regulators;
- requesting and reviewing records and other information;
- sampling and testing drugs; and
- using teleconferences, livestream video, and screen sharing of data and documents as part of a remote interactive evaluation.

Source: GAO and review of FDA documentation. | GAO-22-103611

While FDA has been able to substitute alternative tools for a preapproval inspection, such tools are generally not a substitute for routine surveillance inspections, resulting in an increasing backlog of such inspections.⁴⁶ In our January 2021 report, we noted that if routine surveillance inspections continued to be postponed, a backlog of establishments never inspected or not inspected within 5 years could develop—categories for which FDA considers inspections mandatory.⁴⁷ We reported that this backlog could both extend the interval between inspections and reduce the resources FDA has available for inspecting the other highest-priority establishments identified by FDA’s model. We recommended that FDA ensure that inspection plans for future fiscal years identify, analyze, and respond to the issues presented by the backlog. FDA concurred with our recommendation and in response, FDA officials told us that they are tracking the inspection status of establishments on a quarterly basis. They noted that the backlog is unavoidable and will be resolved over time, and they also reiterated the role of alternative inspection tools in providing oversight of these establishments between routine inspections.

Since we last reported, FDA issued its fiscal year 2022 inspection plan, which documents the increasing size of the backlog as we predicted.

⁴⁴See [GAO-21-265](#).

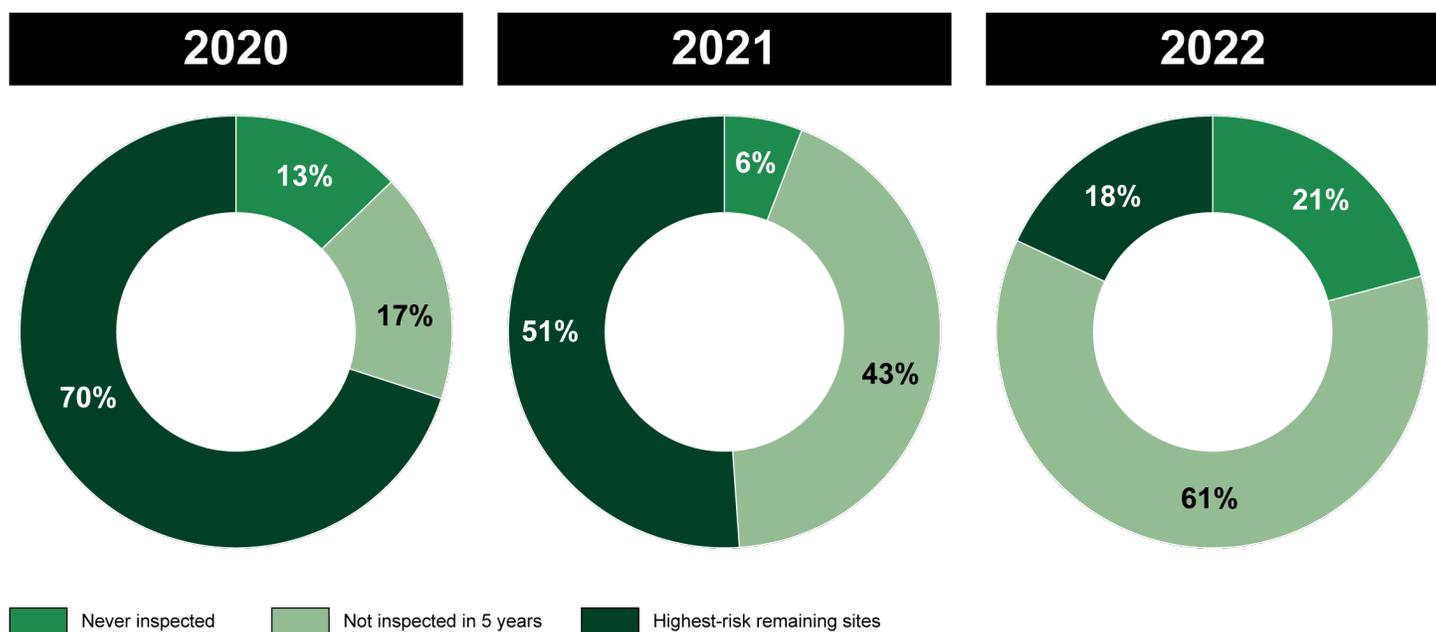
⁴⁵FDA receives user fees from the drug industry under congressionally authorized user fee programs to supplement agency resources available for review of drug applications and related activities. In exchange for receiving user fees, FDA commits to meeting certain performance goals, such as reviewing applications within a specified time frame.

⁴⁶FDA can substitute certain foreign regulator inspection reports for its own inspection. While alternative tools like requesting and reviewing records and other information allow the agency to assess aspects of quality assurance and CGMP conformance, they are not substitutes for a surveillance inspection.

⁴⁷See [GAO-21-265](#).

More than 80 percent of FDA’s planned fiscal year 2022 surveillance inspections are of establishments never inspected or not inspected within 5 years—compared to 30 percent in fiscal year 2020 and 49 percent in fiscal year 2021—leaving fewer resources to be devoted to inspecting the other highest-priority establishments identified by the model (see fig. 3).

Figure 3: Effect of COVID-19 Backlog on Distribution of FDA’s Risk-Based Surveillance Inspections over Time



Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-22-103611

In an August 2021 response to recommendations from our January 2021 report, HHS noted that FDA’s *Resiliency Roadmap for FDA Inspectional Oversight* outlined the agency’s inspection-related activities during the COVID-19 pandemic, including its inspection priorities going forward.⁴⁸ In particular, the response stated that FDA will prioritize preapproval inspections over surveillance inspections. Because the backlog we identified is made up of surveillance inspections, the response that such inspections would be a relatively lower priority suggests that the size of the backlog could continue to grow. In November 2021, FDA updated that it had completed twice as many domestic surveillance oversight activities

⁴⁸U.S. Food and Drug Administration, *Resiliency Roadmap for FDA Inspectional Oversight* (May 2021).

than had been projected in its *Resiliency Roadmap for FDA Inspectional Oversight*.⁴⁹ While foreign inspections largely continue to be postponed, FDA also reported that it was developing a plan for resuming prioritized foreign inspections, including surveillance inspections, starting in February 2022 for all commodities, subject to the dynamics of the global pandemic. While the November 2021 update states that surveillance inspections will be considered under established risk models, the agency's inspection plan does not document how FDA will respond to the issues the backlog presents to the agency's goal of shifting toward exclusively risk-driven surveillance inspections. Given that the majority of establishments manufacturing drugs for the U.S. market are located overseas, it will be important for FDA to continue to account for, and respond to, the backlog in its inspection plans for future fiscal years. We will continue to monitor FDA's inspection plans and progress toward addressing the backlog.

FDA Plans on Implementing Pilot Programs to Address Preannounced Inspections and Language Barrier Challenges but Has Not Yet Finalized Pilots' Design

FDA plans to implement two pilot programs to help it address challenges related to preannounced inspections and language barriers. However, the agency has not yet finalized the design of these two pilot programs because its efforts have been delayed by the COVID-19 pandemic.

Preannounced inspections. As a first step to addressing challenges related to preannounced inspections, FDA established procedures to track whether an inspection is preannounced or unannounced. We have previously reported that preannouncing inspections to foreign establishments raises concerns about their equivalence to domestic inspections, which have typically been unannounced. In December 2019, we found that FDA did not systemically track which foreign inspections were unannounced.⁵⁰ In June 2020, FDA added a new data field in its inspections database to identify whether an inspection is preannounced or unannounced, which will be populated by investigators after an inspection. FDA officials told us that the information collected by this data field could be used in a pilot program to evaluate differences in preannounced and unannounced inspections. However, FDA's collection of data on unannounced inspections has been delayed in light of the pandemic. Since July 2020, the agency has been preannouncing all

⁴⁹FDA's November 2021 update did not specify how many of the domestic surveillance activities were human drug inspections. U.S. Food and Drug Administration, *An Update*.

⁵⁰See [GAO-20-262T](#).

inspections, both domestic and foreign, and will do so for the foreseeable future due to COVID-19 safety concerns.

India Preannounced Initiative

Between January 2014 and August 2015, the Food and Drug Administration (FDA) conducted an initiative to reduce the notification time for a drug inspection in India to one business day or less. This initiative allowed for the utilization of in-country FDA and State Department resources for logistics (e.g., visa invitation letters, hotel reservations).

In August 2015, FDA decided not to extend the initiative due to the following: (1) the lack of a sufficient protocol and evaluation criteria for such an initiative limited to a single country, and (2) the need to analyze the dataset generated during the initiative up until that point in order to consider its impact on agency resources, on industry operating within India, and on other aspects of FDA's foreign inspection program.

Despite deciding not to extend the initiative, FDA officials told us that the agency did implement some best practices from the initiative that it determined were useful. First, FDA stopped involving establishments in its process to make travel arrangements, including obtaining visas and hotel reservations. Next, FDA began a program where the investigator receives a pre-inspection briefing from colleagues to improve the efficiency and effectiveness of the inspection, according to FDA officials.

Source: GAO analysis of FDA information. | GAO-22-103611

FDA has plans to use data on unannounced inspections in a pilot program it intends to implement to evaluate the effectiveness and efficiency of unannounced foreign inspections. According to FDA documentation, it decided to conduct the unannounced pilot program in part to gain a better understanding of whether announced, unannounced, or short-notice inspections provide any relative advantage or result in a difference in compliance findings. According to this documentation, this pilot program would examine the costs and effects of unannounced or short-notice surveillance inspections in China and India—the countries where FDA typically performs the largest number of foreign drug inspections and has foreign office staff that includes investigators to conduct drug inspections. Specifically, our review of FDA documentation found that the agency plans to utilize its foreign office staff in China and India to help maximize efficiencies of inspection planning and resources and to minimize the need to reschedule inspections, and that its evaluation of inspections conducted under this pilot would include an assessment of the effect that these inspections have on compliance and public health outcomes. FDA indicated it will use this information to determine whether and how best to expand the pilot program to normal operating procedures and help support the agency's ability to respond to inquiries about parity of foreign and domestic inspections as it relates to preannounced inspections. As we reported in January 2021, Congress directed FDA to use \$3.5 million of its fiscal year 2021 appropriation to establish pilot programs to increase the agency's use of unannounced and short-notice foreign inspections.⁵¹ Congress also directed FDA to use these funds to build on the work done in the unannounced inspection initiative begun in India in 2014 and to establish unannounced inspection pilots in India and in China to improve workforce development activities and include unannounced and short-notice inspections.⁵² (See sidebar.)

⁵¹See [GAO-21-265](#). Explanatory Statement, 166 Cong. Rec. H7891 (daily ed. Dec. 21, 2020) (statement of Rep. Lowey) (stipulates that the language set forth in House Report 116-446 “carries the same weight as language included in this explanatory statement and should be complied with unless specifically addressed to the contrary in this explanatory statement”); Pub. L. No. 16-260, § 4, 134 Stat. 1182, 1185 (2020) (clarifying that the explanatory statement regarding this act shall have the same effect as a joint explanatory statement with respect to the allocation of funds and implementation of certain divisions).

⁵²H. Rept. No. 116-446, 116th Cong. 2d. Sess. 86 (2020).

FDA has identified the steps it will take to design the unannounced inspection pilot program; however, as of September 2021, FDA had not yet finalized its plans for how the pilot will be designed. According to ORA's statement of work we reviewed, ORA intends to work with a contractor to develop key metrics for evaluating both the efficiency and effectiveness of inspections performed under the pilot. Additionally, the contractor will develop an assessment methodology for collecting and analyzing the information FDA needs to demonstrate that unannounced or short-notice inspections are either equivalent, inferior, or superior to preannounced foreign inspections, both in terms of costs of implementation as well as the ultimate public health impact. In July 2021, FDA officials told us that ORA was in the process of selecting a contractor to help it finalize the design of its pilot program. According to FDA officials, efforts to finalize the design of the pilot program have been delayed because of the public health concerns and operational changes arising from the COVID-19 pandemic. However, officials said ORA expected to finalize its plans in March 2022 and begin the pilot in early 2022, as long as it is safe to do so given the conditions of the COVID-19 pandemic. FDA officials told us that the expected duration of the pilot depends on several factors, such as when travel can resume and a sufficient sample size can be collected for review.

Language barriers. FDA also plans to implement a pilot program to evaluate the costs and effects of using different types of translation services during foreign inspections. Specifically, under the pilot proposal, FDA would use an interagency agreement with the Department of State to provide independent translators for certain inspections in China and Hong Kong, rather than relying on the drug establishment being inspected to provide translation services to facilitate the inspection, as FDA typically does.⁵³ These inspections would then be compared to other FDA inspections in China and Hong Kong that use either the translation services provided by the establishment being inspected or locally employed staff who work in FDA's China office to determine whether the use of State Department translators should be expanded to other countries. According to FDA documentation, since December 2019, ORA has been interested in using generic drug user fee funds to support the

⁵³The State Department provides foreign language services to other federal agencies on a fee-reimbursable basis.

provision of independent translators on foreign inspections.⁵⁴ ORA documentation noted that this is because relying on the translation services provided by the inspected establishments may present risks to the agency, given that FDA is unable to evaluate the competency of the translator used by the establishment to facilitate the inspection and does not have independent verification that the information being translated is accurate and complete. However, before obligating the user fee funds to support the provision of independent translators on foreign inspections, FDA first wanted to fund a pilot program to evaluate the reliability, costs, and effects of using different types of translators.

While FDA has proposed a pilot to examine its use of translation services, the agency has not fully developed its plans for how the pilot will be designed. In the preliminary documentation we reviewed related to this pilot, FDA noted that the pilot may include both an assessment of the actual costs of using different types of translation services during foreign inspections and their benefits—as identified by investigators, the FDA staff responsible for planning and handling the logistics of foreign travel, and the FDA staff reviewing inspection findings. However, FDA has not yet identified specific evaluation criteria. FDA noted that ORA would need to collaborate with CDER and OGPS to develop the evaluation criteria, an assessment methodology for the pilot program, and to provide training for FDA staff on the pilot. According to the preliminary documentation we reviewed, the agency had initially planned to implement the pilot program in May 2020. However, officials told us that its efforts to design the pilot program were then postponed because FDA had to pull staff from its China office in February 2020 as a result of the COVID-19 pandemic. While FDA staff in the agency’s China office resumed conducting

⁵⁴Generic Drug User Fee Amendments Act (GDUFA) authorized FDA to assess and collect user fees from manufacturers of generic drugs, which supplement funding available through annual appropriations to support FDA oversight activities relating to generic drugs. See the Generic Drug User Fee Amendments of 2012, Pub. L. No. 112-144, § 302, 126 Stat. at 1011 and the Generic Drug User Fee Amendments of 2017, Pub. L. No. 115-52, § 303, 131 Stat. 1005, 1020 (both laws, in pertinent part, adding and amending FDCA § 744B, codified at 21 U.S.C. § 379j-42). Pursuant to commitment letters reflecting agreements with industry representatives, FDA generally applies user fees collected from the generic drug industry to reduce the time necessary to review and make decisions on drug applications. This may involve applying fees to specific activities, such as inspections, to facilitate meeting specified performance commitments, such as reviewing generic drug applications within specified time frames. Generally, GDUFA user fees may be collected and obligated only to the extent and in the amount provided for in advance in appropriation acts. Once appropriated, GDUFA user fees are available for obligation by FDA until expended—user fees collected and not obligated at the end of the fiscal year (referred to as carryover funds) are available for obligation in future fiscal years.

prioritized inspections in October 2020, they were not conducting routine foreign inspections, according to FDA officials.⁵⁵

As FDA finalizes the design of its two pilot programs, it has the opportunity to ensure its plans incorporate leading practices we identified for designing a well-developed and documented pilot program. Specifically, in 2016, we identified five leading practices for designing a pilot program: 1) establish well defined, appropriate, clear, and measurable objectives; 2) articulate an assessment methodology that details the type and source of the information necessary to evaluate the pilot and the methods for collecting that information; 3) develop an evaluation strategy that defines how the information collected will be analyzed to evaluate the pilot's implementation and performance; 4) assess the scalability of the pilot design to inform whether and how to implement a new approach in a broader context; and 5) ensure appropriate stakeholder communication at all stages of the pilot.⁵⁶ These practices can enhance the quality, credibility, and usefulness of pilot program evaluations and help ensure that time and resources are used effectively. While each of the five practices serves a purpose on its own, taken together they form a framework for effective pilot design.

FDA's plans to implement each of these pilot programs are a positive step toward addressing the challenges related to preannounced inspections and language barriers. FDA could benefit from incorporating leading practices as it develops and documents these pilot programs to help ensure that the agency collects the information needed to evaluate these efforts, and that FDA time and resources are used effectively. As FDA begins to develop the details of how it will conduct these pilot programs, using these practices would better position FDA to assess whether unannounced or short-notice inspections and independent translation services benefit inspections under the pilot program and whether such practices can and should be expanded to other foreign inspections.

⁵⁵In November 2021, FDA reported that it was developing a plan for resuming prioritized foreign inspections, including surveillance and preapproval inspections, starting in February 2022 for all commodities, subject to the dynamics of the global pandemic. U.S. Food and Drug Administration, *An Update*.

⁵⁶See [GAO-16-438](#).

FDA Has Undertaken Initiatives to Reduce Persistent Vacancies in Its Foreign Drug Investigator Workforce, Though Some Strategies for Doing So Are Not Fully Developed

FDA's Foreign Investigator Workforce Depends on FDA Maintaining Both U.S.-Based and Overseas Personnel

FDA relies on a foreign drug inspection workforce primarily composed of three groups of investigators based both in the U.S. and overseas, and the agency has faced challenges maintaining each of these groups. In addition to a general pool of investigators who primarily conduct domestic inspections, but who also conduct foreign inspections, FDA created two groups of investigators who specialize in conducting foreign inspections—a U.S.-based dedicated foreign drug cadre and investigators assigned to foreign offices.⁵⁷ All investigators are initially hired by ORA and begin their careers in the general pool based in the U.S., conducting only domestic inspections. Investigators may become eligible to conduct foreign inspections, join the cadre, or move to a foreign office after gaining experience and training. FDA officials told us that new investigators are typically with the agency for 2 to 3 years before they can conduct foreign inspections independently. Experience conducting foreign inspections is required to move to a foreign post. Experienced investigators are needed to conduct foreign inspections, as, according to FDA officials, this work is challenging, requiring the investigator to work independently in a foreign establishment under constrained time frames.

ORA investigators based in the U.S. The majority of foreign inspections are conducted by investigators in the general pool of U.S.-based investigators who conduct both domestic and foreign inspections. FDA officials said that the more experienced investigators from this group are expected to conduct three to six foreign inspections per year, which would

⁵⁷In 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.

generally occur over one or two foreign trips.⁵⁸ Some investigators in this general pool were hired using generic drug user fees and are expected to conduct nine to 12 foreign inspections per year, which would generally occur over three or four foreign trips.⁵⁹ These investigators are assigned to conduct foreign inspections in a different manner than their other U.S.-based counterparts, which allows the agency to assign inspections about 3 weeks faster, according to FDA officials.⁶⁰

FDA data shows that about 72 percent of foreign inspections in fiscal year 2019, and about 70 percent in fiscal year 2020, were conducted by ORA investigators in the general pool.⁶¹ We have previously reported on vacancies among this group. For example, FDA officials have said that vacancies among this group had contributed to the decline in inspections from fiscal year 2016 through fiscal year 2018.

Dedicated foreign drug cadre. ORA's dedicated foreign drug cadre is a group of U.S.-based investigators who exclusively conduct foreign inspections.⁶² Overall, this cadre conducted about 18 percent of all foreign inspections in fiscal year 2019 and about 19 percent in fiscal year 2020. Individual cadre members conduct significantly more foreign inspections than other investigators based in the U.S.—16 to 18 foreign inspections each year over six foreign trips—and thus have valuable experience overcoming the challenges of inspections in a foreign environment, which makes them well-suited for conducting high-priority, complex foreign inspections, according to FDA officials. Cadre members are also assigned foreign inspections in a similar manner as investigators

⁵⁸According to FDA officials, overseas inspections are typically conducted in 3-week trips.

⁵⁹Beginning 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.

⁶⁰According to FDA officials, foreign inspections typically are assigned to individual investigators through a process where each week FDA announces upcoming foreign inspection trips and asks for volunteers to conduct the inspections. If no staff volunteer, then FDA can direct specific staff to conduct the trip in question. In contrast, FDA can directly assign foreign inspection trips to investigators hired using generic drug user fees, without FDA having to take the time to first seek volunteers.

⁶¹Inspections can be conducted by one investigator or multiple investigators. Therefore, investigators from more than one group could be involved with a single inspection.

⁶²According to FDA officials, U.S.-based investigators apply to the cadre for 1-year assignments, which can be renewed, or they can be hired as permanent cadre members.

hired using generic drug user fees, which allows the agency to assign inspections about 3 weeks faster than for foreign inspections conducted by most other investigators based in the U.S., according to FDA officials.

However, we have reported that FDA has struggled to keep the cadre fully staffed in recent years.⁶³ FDA officials largely attributed long-standing cadre vacancies to the challenges of conducting foreign inspections and hardships related to the frequent travel overseas. Cadre members generally take six, 3-week, foreign trips each year, often to countries such as India and China that require flights of 14 hours or more from the U.S. (see fig. 4). FDA officials told us that federal travel regulations place restrictions on air travel options that can exacerbate the effects of this challenging schedule, which is one of several reasons, according to investigators we interviewed, that made foreign trips particularly grueling. (See text box for other challenges related to foreign trips.) In addition, FDA officials told us that some vacancies can be attributed to investigators transferring to other parts of FDA where they do not have to travel as much and receive the same or higher pay.

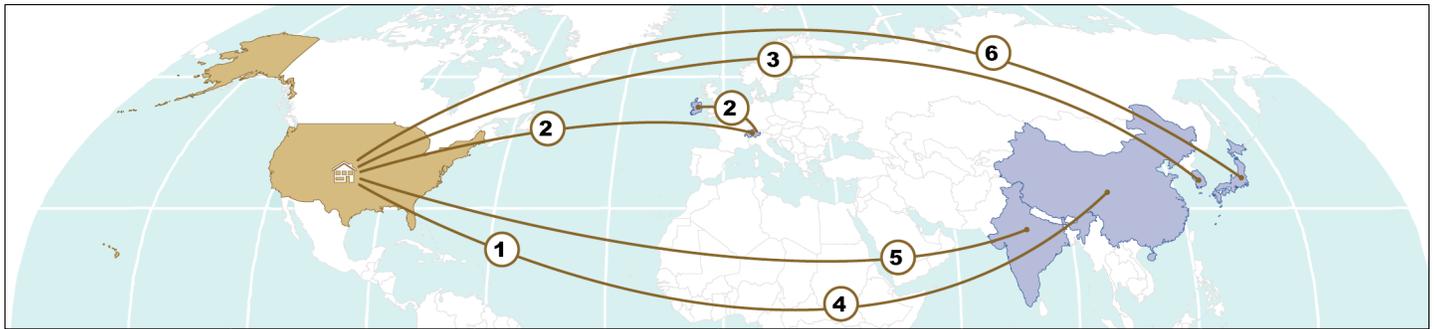
Foreign Inspection Challenges Related to Lack of Flexibility and Reporting Time Frames

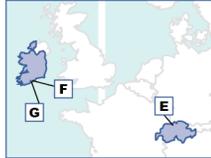
Eight of the 12 dedicated foreign drug cadre investigators we interviewed told us that there is little flexibility to extend foreign inspections because overseas inspections are scheduled back-to-back in 3-week trips that may involve travel between different countries. As a result, investigators may work long hours, including spending long days onsite and reviewing data and documentation when they return to their hotel at night. In addition, the time frame for writing inspection reports and having them reviewed can also create challenges. For example, given reporting and review time frames, if an investigator on a 3-week inspection trip finds serious deficiencies on the first inspection, the investigator needs to write the inspection report and send it for review before returning home from the 3-week overseas trip.

Source: GAO analysis of interviews with foreign drug cadre investigators. | GAO-22-103611

⁶³See [GAO-20-262T](#).

Figure 4: Schedule for a Member of the FDA’s Dedicated Foreign Drug Cadre in Fiscal Year 2018



TRIP 1	TRIP 2	TRIP 3	TRIP 4	TRIP 5	TRIP 6
<p>China</p> 	<p>Switzerland/Ireland</p> 	<p>South Korea</p> 	<p>China</p> 	<p>India</p> 	<p>Japan</p> 
<p>Estimated total days^a on trip 1 with travel time: 29 days</p>	<p>Estimated total days^a on trip 2 with travel time: 23 days</p>	<p>Estimated total days^a on trip 3 with travel time: 6 days</p>	<p>Estimated total days^a on trip 4 with travel time: 23 days</p>	<p>Estimated total days^a on trip 5 with travel time: 23 days</p>	<p>Estimated total days^a on trip 6 with travel time: 22 days</p>
<ul style="list-style-type: none"> Oct. 9-13: Establishment A inspection Oct. 16-20: Establishment B inspection Oct. 23-26: Establishment C inspection Oct. 30-Nov. 2: Establishment D inspection <p>Return to home in United States. Write inspection reports and prepare for next trip^b in about 27 days.^a</p>	<ul style="list-style-type: none"> Dec. 4-8: Establishment E inspection in Switzerland Dec. 11-14: Establishment F inspection in Ireland Dec. 18-22: Establishment G inspection in Ireland <p>Return to home in United States. Write inspection reports and prepare for next trip^b in about 43 days.^a</p>	<ul style="list-style-type: none"> Feb. 8-9: Establishment H inspection <p>Return to home in United States. Write inspection reports and prepare for next trip^b in about 40 days.^a</p>	<ul style="list-style-type: none"> Mar. 26-30: Establishment I inspection Apr. 2-6: Establishment J inspection Apr. 9-12: Establishment K inspection <p>Return to home in United States. Write inspection reports and prepare for next trip^b in about 40 days.^a</p>	<ul style="list-style-type: none"> May 28-June 5: Establishment L inspection June 7-15: Establishment M inspection <p>Return to home in United States. Write inspection reports and prepare for next trip^b in about 33 days.^a</p>	<ul style="list-style-type: none"> July 23-27: Establishment N inspection July 30-Aug. 3: Establishment O inspection Aug. 6-9: Establishment P inspection <p>Return to home in United States. Write inspection reports and prepare for next trip^b in about 55 days.^a</p>

Source: GAO analysis of Food and Drug Administration (FDA) data and interviews with foreign drug cadre members. | GAO-22-103611

^aThese time frames are estimated due to airline travel schedules, rest days, and other factors. In calculating total days on trip and time between trips, we made the assumption that the investigator left the U.S. 3 days before the first day of the first inspection of the trip (generally the Friday before an

inspection that began on a Monday) and returned to the U.S. on the day after the last day of the last inspection of the trip.

^bAccording to our interviews with foreign drug cadre investigators, in addition to writing inspection reports and preparing for their next trip, investigators perform administrative duties (such as completing their travel vouchers) and may attend trainings between inspection trips.

Investigators assigned to foreign offices. FDA's foreign offices in China and India include both full-time investigators and those on temporary duty assignment.⁶⁴ These investigators are expected to conduct 15 foreign inspections each year, according to FDA officials. They conducted about 11 percent of all foreign inspections in fiscal year 2019 and about 9 percent in fiscal year 2020.⁶⁵

In addition to having experience overcoming the unique challenges of working in a foreign environment, investigators assigned full-time to FDA's foreign offices in China and India provide the agency with the ability to conduct more timely inspections with greater flexibility. For example, investigators can conduct short-notice or unannounced inspections, whereas U.S.-based investigators may need several months to obtain visas and make travel arrangements. Officials noted that foreign office investigators have more flexibility to remain at an inspection site longer, if necessary, as they are not limited by travel arrangements to return to the U.S. Further, during the COVID-19 pandemic, foreign office investigators have conducted the majority of inspections in India and China in light of international travel restrictions.⁶⁶

However, the agency has faced long-standing vacancies within the foreign offices. We have previously reported on challenges FDA faces in

⁶⁴FDA began opening offices around the world in 2008 to obtain better information on the increasing number of products coming into the U.S. from overseas, to build relationships with foreign stakeholders, and to perform inspections. 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.

FDA also relies on locally employed staff—non-U.S. citizens employed by the foreign office—to work on administrative issues or provide technical expertise, as needed.

⁶⁵The percentage of inspections conducted by each of these groups of investigators does not equal 100 percent because some inspections may involve only non-investigator staff, such as CDER drug application reviewers.

⁶⁶In addition to the benefits noted of having investigators based in-country, we also previously reported that former foreign office staff said it is valuable for investigators to be able to focus on their host country's manufacturers and to better understand how the manufacturers satisfy CGMPs or their difficulties with doing so. See [GAO-17-143](#).

filling these positions related to the length of time needed for staff to be cleared for deployment and on other investigator concerns, including: staff reintegration into FDA's domestic offices after a foreign tour, financial concerns, and environmental and security concerns.⁶⁷ Officials also stated that additional challenges, including a lengthy process of obtaining security and medical clearances and other prerequisites, can take 9 to 12 months for selected candidates to complete. Further, as we also previously reported, FDA officials told us that an additional challenge recruiting investigators for the foreign offices is that well-qualified investigators for these positions need foreign inspection experience before joining a foreign office.⁶⁸ Thus, vacancies in the other two groups of investigators can influence the number of staff available to apply for positions in the foreign offices.

FDA Has Undertaken a Number of Initiatives to Recruit New Investigators, Reducing Its Vacancies

FDA has undertaken a number of initiatives to recruit new investigators to the general pool of investigators in the U.S. and has reduced its vacancies. According to FDA officials, this general pool of investigators initially conducts only domestic inspections, but are later required to conduct foreign inspections, and may also fill vacancies in FDA's specialized foreign inspection groups. In an attempt to fill its vacancies, FDA has undertaken the following investigator recruitment initiatives.

- According to FDA officials, as of October 2019, FDA began hiring at a higher General Schedule (GS) level for its U.S.-based investigator positions, hiring at a GS-9 level rather than a GS-7. FDA requires that investigators conducting foreign inspections be at least a GS-12 and, according to FDA officials, recruiting new investigators at the higher GS level—for which prospective hires would need more experience to qualify—helps decrease the amount of time before they are able to conduct foreign inspections. FDA officials also said they offered monetary incentives, including recruitment incentives, retention incentives, and the Student Loan Repayment Program.⁶⁹
- FDA also used direct-hire authority and other initiatives—including a program for recent graduates—that provide additional pathways for

⁶⁷See [GAO-17-143](#).

⁶⁸See [GAO-20-262T](#).

⁶⁹The federal student loan repayment program permits agencies to repay federally insured student loans as a recruitment or retention incentive for candidates or current employees of the agency. See 5 U.S.C. § 5379.

recruiting new investigators.⁷⁰ For example, according to FDA officials, through the use of hiring authorities and other initiatives, FDA was able to hire 53 new drug investigators from September 2019 through September 2021.

- FDA began cohort hiring in 2019, which according to FDA officials, combines medical product and human and animal food investigator announcements to maximize the number of applicants in a certain location. The officials explained that hiring managers come together across programs on interview panels and decide which program is the best fit for the most highly qualified candidates. Interview questions are standardized so all candidates have the same interview experience, which includes a clear explanation of job requirements and travel expectations.

Since our December 2019 testimony, FDA has hired new investigators for its general pool of investigators based in the U.S. using the above strategies and others, decreasing the number of vacancies among this group.⁷¹ FDA data show that vacancies decreased from 32 vacant positions in November 2019 to 4 vacant positions in November 2021, out of about 230 total authorized investigator positions.

FDA Has Not Fully Developed Specific Strategies for Ensuring It Has the Investigators It Needs to Maintain Its Workforce of Foreign Drug Inspection Specialists

FDA has also made efforts to increase recruitment into its two groups of investigators that specialize in foreign drug inspections—the dedicated foreign cadre and foreign office investigators—though vacancies persist. These groups rely on recruitment from ORA’s general pool of experienced investigators based in the U.S. In addition to the efforts to increase recruitment of investigators into the general pool outlined above, in recent years FDA has also made efforts to increase recruitment of investigators from the general pool into these specialized foreign inspection groups.

⁷⁰Under direct-hire authority, FDA may be authorized by the Office of Personnel Management (OPM) to expedite the typical hiring process associated with traditional hiring to fill certain positions for which a critical need exists or for which there is a severe shortage of candidates. See 5 U.S.C. § 3304(a)(3); 5 C.F.R. pt. 337, subpt. B (2021). According to FDA officials, direct-hire authority has provided flexibility that has been used to address vacancies resulting from departing staff, among other purposes. Although FDA direct-hire authorization was expiring in October 2021, the agency was seeking to extend it. FDA may also provide developmental opportunities designed to lead to a career in federal service to individuals who have recently graduated from qualifying educational institutions or programs. See 5 C.F.R § 362.301 et seq. (2021).

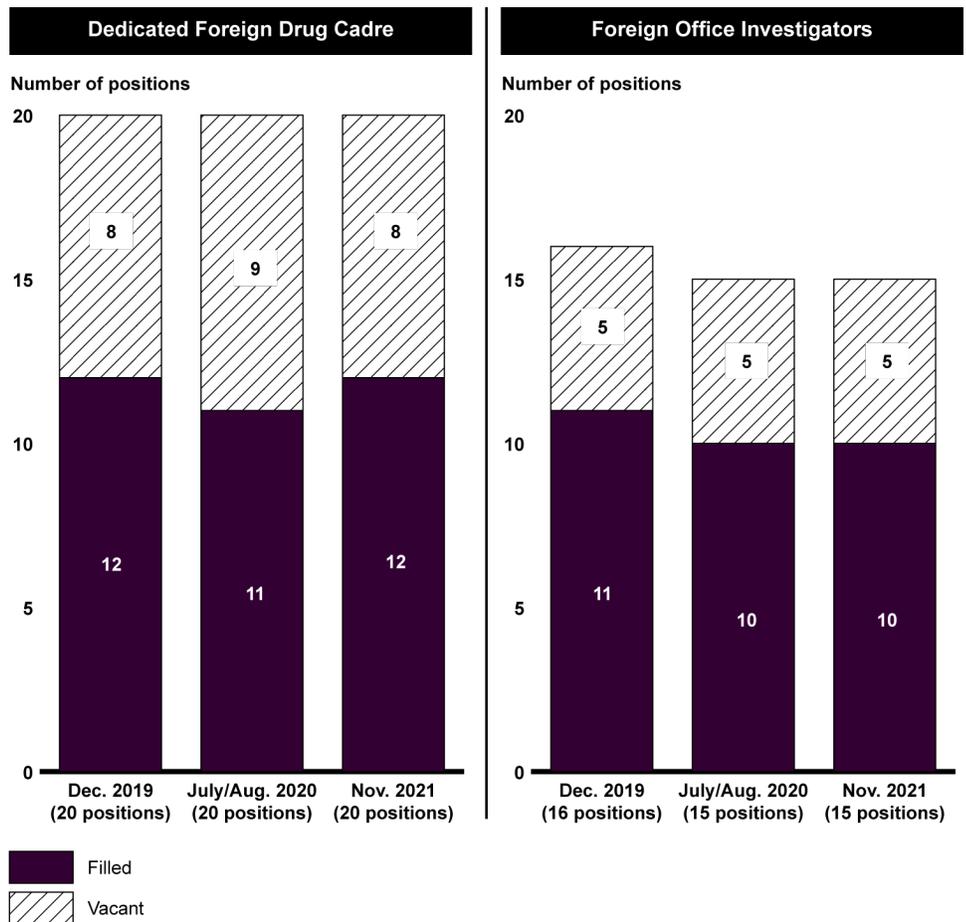
⁷¹See [GAO-20-262T](#).

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- In an effort to increase recruitment into the foreign cadre, according to officials, ORA posted job announcements twice per year, rather than once per year, in 2019. However, FDA data show that as of November 2021, ORA's dedicated foreign drug cadre had eight of 20 positions vacant—a 40 percent vacancy rate—and according to officials, there have been persistent vacancies in this group in recent years.
 - In an effort to recruit investigators assigned to FDA's foreign offices, OGPS instituted an open continuous job announcement from May 2020 through November 2020 and from January 2021 through June 2021, which, according to agency officials, removed administrative inefficiencies and allowed candidates to apply at any time of year, rather than only when FDA issued a time-limited job announcement.⁷² OGPS also instituted the Student Loan Repayment Program in October 2019, categorical retention incentives in October 2017, and overseas comparability pay in July 2017.⁷³ However, as of November 2021, FDA data show that foreign office drug investigators had four of nine positions vacant in China (a 44 percent vacancy rate) and one of six positions vacant in India (a 17 percent vacancy rate), and according to officials, there have been persistent vacancies in this group since 2016. (See fig. 5.) According to FDA officials, the challenge of recruiting for positions in China is not unique to FDA, as other agencies with a presence in China also have vacancies.

⁷²During the time that ORA investigators are posted full-time overseas, they are detailed to OGPS, which manages the foreign offices, among other duties.

⁷³OPM may authorize an agency to pay a retention incentive to a current employee if the agency determines that the unusually high or unique qualifications of the employee or a special need of the agency for the employee's services makes it essential to retain the employee and that the employee would be likely to leave the federal service in the absence of a retention incentive. Retention incentives may be authorized for a group of employees if there is a high risk that a significant portion of employees in a particular group may be likely to leave in the absence of such incentives. See 5 U.S.C. § 5754; 5 C.F.R. pt. 575, subpt. C (2021).

Figure 5: Number of Vacancies for FDA Foreign Drug Inspection Specialists



Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-22-103611

Given these persistent vacancies, FDA recently began several efforts to improve workforce planning for these two specialized foreign investigator groups. According to OGPS officials, in June 2020, OGPS began working with the Office of Personnel Management (OPM) under an Interagency Agreement to improve its workforce planning for all staff, including drug investigators based in foreign offices. In the fall of 2020, OPM recommended that OGPS explore the possibility of co-developing a recruitment program with ORA that would market the potential to transition to a career in international locations to applicants for ORA positions. In response, OGPS began an effort to develop new strategies for recruiting and retaining staff to ensure it will have a pool of staff who

can apply to the foreign offices. According to OGPS officials, these strategies are targeted to be completed in September 2022.

OGPS and ORA described additional efforts to increase coordination and planning for the foreign offices. In July 2020, OGPS and ORA began holding quarterly leadership meetings to discuss recruitment and reintegration of foreign office staff. In July 2021, OGPS officials told us that they had recently begun discussions with ORA related to overseas staff challenges and opportunities, with the goal of identifying and implementing potential solutions. Further, in August 2021, ORA officials also told us that they had created and filled a new position intended to foster coordination between OGPS and ORA operations in order to be productive and efficient in hiring, recruiting, and reintegration.

In August 2021, ORA officials also told us that they are in the beginning stages of determining how to re-envision the foreign drug cadre.

- First, ORA is considering offering 6-month details to the cadre so investigators can consider the position prior to applying for a full year, while accomplishing FDA program goals. As of September 2021, this new option was being reviewed by FDA officials.
- Second, ORA has provided some highly skilled cadre applicants with a permanent promotion to GS-13 or GS-14, whereas previously the promotion had been temporary while an investigator was a member of the cadre. ORA is also in the process of extending cash bonuses to permanent cadre investigators.
- Finally, ORA is considering developing a career pathway for newly hired investigators to directly convert them to dedicated foreign drug cadre investigators or foreign office staff after their initial training.

These efforts are promising; however, they are still in early stages and not yet fully developed to include detailed proposals and implementation time frames. For example, while ORA officials told us they have had multiple meetings at which they discussed developing a career pathway for newly hired investigators to directly convert them to cadre investigators, they have not yet documented a formal proposal for such a pathway or developed any time frames for developing such a proposal. In addition, OPGS has identified broad steps and initial time frames related to exploring a partnership with ORA for marketing job postings and other recruitment and retention initiatives. For example, OGPS has broadly stated it will “collaborate with ORA leadership on international opportunities” and “determine how to return employees back to HQ with

useful skills learned overseas.” However, OGPS has not yet documented how these broad steps will be carried out and in what time frame. As it finalizes its recruitment plans, FDA could benefit from including key elements of strategic workforce planning into its efforts to help ensure success. By fully developing strategies—including detailing implementation steps and time frames—specifically tailored for recruiting new investigators and for preparing and retaining current investigators to specialize in foreign drug inspections, the agency would be better able to ensure that it is recruiting investigators with an interest in foreign work and providing a pathway to cultivate its current investigators to gain the skills necessary to join the foreign cadre or foreign offices. GAO’s *Key Principles for Effective Strategic Workforce Planning* states that agencies should determine the critical skills and competencies that will be needed to achieve the future programmatic results, and that agencies should develop strategies tailored to address gaps and human capital conditions in critical skills and competencies that need attention, among other things.⁷⁴ Including detailed proposals and time frames is consistent with these criteria.

FDA Determined Most Deficiencies Identified during Foreign Inspections Did Not Warrant Regulatory Action

Our review of FDA data shows that, from fiscal years 2018 through 2020, FDA identified deficiencies in the majority of foreign inspections it conducted but, in most cases, the agency determined that the deficiencies did not warrant regulatory action.⁷⁵ During an inspection, investigators are responsible for identifying any significant objectionable conditions and practices and reporting these to the establishment’s management on a list-of-observations form, commonly referred to as FDA

⁷⁴See [GAO-04-39](#), Principle 2 and Principle 3.

⁷⁵FDA may take a number of different regulatory actions in response to deficiencies it identifies during a foreign drug inspection. For instance, FDA may issue warning letters to establishments manufacturing drugs for the U.S. market that are in violation of applicable U.S. laws and regulations and thus may be subject to enforcement action if violations are not promptly and adequately corrected. In addition, if FDA identifies serious deficiencies during a foreign drug inspection, the agency may place the drug products or establishment on an import alert, which informs FDA staff and the public that the agency has enough evidence to detain an establishment’s products that have been offered for entry into the U.S.

Inspection Classifications

Based on inspection findings and the Food and Drug Administration's (FDA) review, each inspection is classified into one of the following categories:

- **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-22-103611

Form 483.⁷⁶ After each inspection, FDA classifies the inspection into one of three categories based on its determination of whether any deficiencies identified during the inspection are serious enough to warrant regulatory action. The three categories are: no action indicated (NAI), voluntary action indicated (VAI), or official action indicated (OAI), as described in the sidebar.

Our analysis of FDA's final classification data shows that, from fiscal years 2018 through 2020, FDA determined the following.

- Approximately 66 percent of all foreign inspections (1,502 of 2,286 inspections) identified deficiencies at the establishment (as identified by the percentage of inspections it classified as VAI or the more serious OAI), of which 16 percent (244 of 1,502 inspections) had deficiencies serious enough to warrant regulatory action (an OAI classification). For example, based on our review of a warning letter FDA issued during this time, at an establishment in China manufacturing finished drug products the investigator learned, upon questioning the establishment staff on the validity of some of the documentation provided during the inspection, that multiple documents had been falsified for the purpose of the inspection. These falsified documents included cleaning validation reports, batch records for multiple products, and annual product reviews. Further, the investigator was told that the establishment could not provide basic records related to CGMP requirements for the manufacture of drugs.⁷⁷
- Similarly, FDA data showed that the agency determined that 64 percent of domestic inspections (1,167 of 1,812 inspections) it conducted during this same time period identified deficiencies, of which 17 percent (203 of 1,167 inspections) had deficiencies serious

⁷⁶An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator observes conditions during the inspection that, in their judgement, may constitute violations of applicable U.S. laws. Observations are made when, in the investigator's judgement, the conditions or practices observed would indicate that a drug has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health. Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.

⁷⁷FDA CGMP regulations require that establishments have a quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products. Additionally, the quality control unit should have the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated and documented in writing. See 21 C.F.R. §§ 211.22, 211.192 (2020).

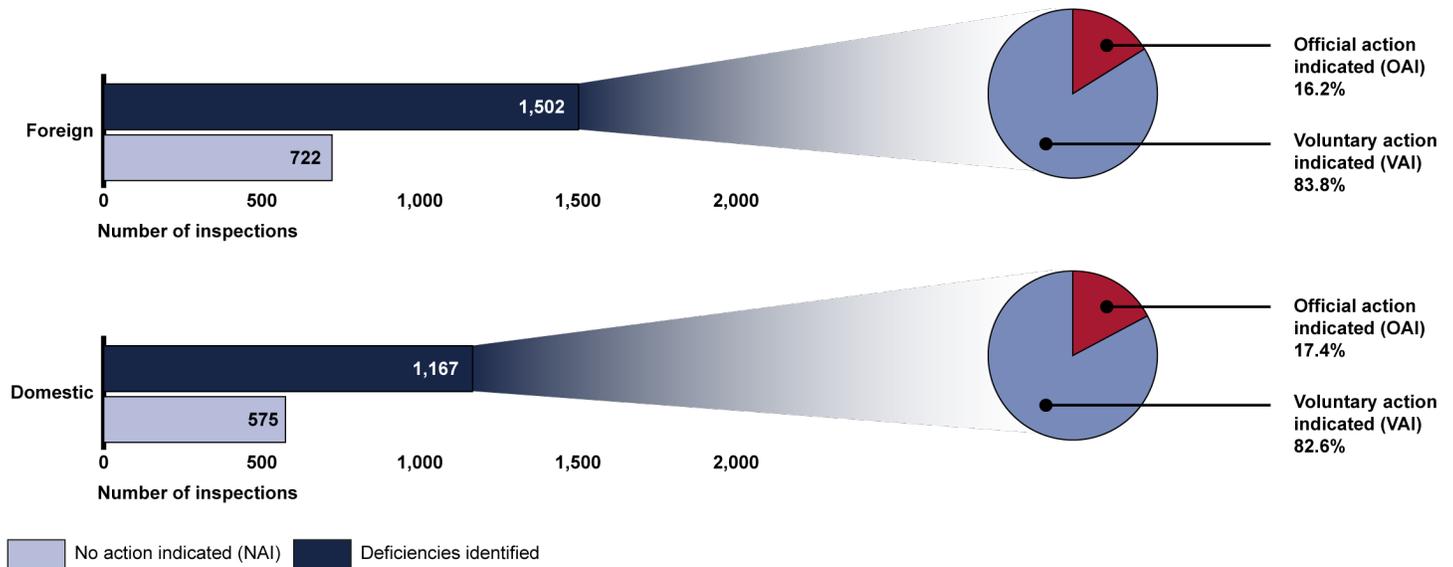
enough to warrant regulatory action. (See fig. 6.) For example, based on our review of a warning letter FDA issued during the time of our review, at a domestic establishment producing finished drug products the investigator reported that the establishment did not test for diethylene glycol on incoming drug manufacturing components that contain glycerin despite the serious hazard associated with diethylene glycol contamination.⁷⁸

This proportion is similar to what we reported in our December 2019 testimony for fiscal years 2012 through 2018.⁷⁹

⁷⁸FDA CGMP regulations require testing of each lot of components, that a representative sample of each shipment of each lot be collected for testing, and that the number of containers to be sampled shall be based upon appropriate criteria. See 21 C.F.R. §§ 211.22(a), 211.84 (2020). Under CGMP regulations, “component” means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product. See 21 C.F.R. § 210.3(3) (incorporated by reference into pt. 211 by 21 C.F.R. § 211.3). In 2007, FDA issued a guidance document for testing of glycerin for diethylene glycol contamination to alert manufacturers to a potential public health hazard. FDA’s guidance states that FDA had received reports of poisoning of consumers who ingested medicinal syrups, such as cough syrup, that were manufactured with diethylene glycol-contaminated glycerin. To avoid the use of contaminated glycerin, certain analytical testing procedures are recommended for all lots of glycerin. See Food and Drug Administration, *Guidance for Industry on Testing of Glycerin for Diethylene Glycol: Availability*, FDA Notice, 84 Fed. Reg. 24316 (May 2, 2007).

⁷⁹We found that, from fiscal years 2012 through 2018, FDA identified deficiencies in 64 percent of foreign inspections and 59 percent of domestic inspections and identified deficiencies serious enough to warrant regulatory action in approximately 8 percent of foreign inspections and 7 percent of domestic inspections during that time period. See [GAO-20-262T](#).

Figure 6: FDA Inspection Results for Foreign and Domestic Drug Manufacturing Establishments, Fiscal Years 2018 through 2020



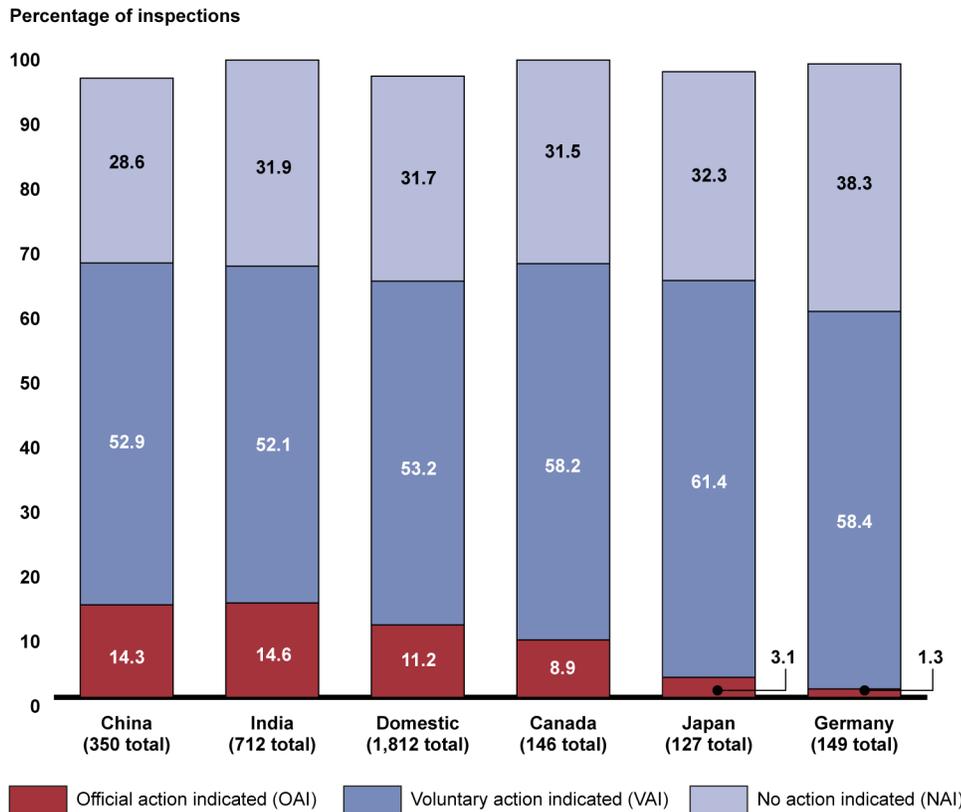
Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-22-103611

Notes: After each inspection, FDA classifies the inspection into one of three categories based on its determination of whether any deficiencies identified during the inspection are serious enough to warrant regulatory action: 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.

The analysis presented in this figure is based on 2,286 foreign inspections and 1,812 domestic inspections conducted from fiscal year 2018 through 2020. The percentage of foreign and domestic inspections with deficiencies identified include both inspections that FDA classified as VAI and OAI. Totals do not sum to 100 due to rounding and because some inspections had not yet received a final classification as of the date that FDA pulled these classification data.

While FDA identified serious deficiencies warranting regulatory action in relatively few inspections, such deficiencies were identified more frequently during inspections in China and India than during domestic inspections in the U.S. or during foreign inspections in the other countries FDA inspected most frequently during this time period. (See fig. 7.)

Figure 7: Percentage of FDA Inspection Classifications in the U.S. and in the Five Foreign Countries with the Most Inspections, Fiscal Years 2018 through 2020



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-22-103611

Notes: After each inspection, FDA classifies the inspection into one of three categories based on its determination of whether any deficiencies identified during the inspection are serious enough to warrant regulatory action: 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.

The analysis presented in this figure is based on the total number of inspections FDA conducted in each country from fiscal year 2018 through 2020. Totals do not sum to 100 due to rounding and because some inspections had not yet received a final classification as of the date that FDA pulled these classification data.

FDA Reclassified Some Inspections and Has Taken Steps to Ensure Consistency and Transparency in Its Classification Process

From Fiscal Years 2018 through 2020, FDA Reclassified Approximately 40 Percent of Foreign Inspections Recommended for Regulatory Action

During its process to classify inspections of marketed drugs, FDA evaluates and may decide to reclassify inspections. FDA may reclassify an inspection recommended for OAI classification to a less serious classification if it determines that the deficiencies do not meet the threshold for regulatory action or that the establishment has taken action to address the deficiencies. This type of reclassification is referred to as a downgrade. FDA may also reclassify inspections recommended for a less serious to a more serious classification (i.e., from NAI to VAI or OAI or from VAI to OAI). This type of reclassification is referred to as an upgrade. Since fiscal year 2018, FDA has used a redesigned process to classify foreign inspections. As part of its redesign, FDA aligned its foreign inspection classification process with its process for domestic inspections to help ensure consistency in its inspection classification decisions across geographic locations.⁸⁰ Under the redesigned process, reclassifications may occur first during ORA's review of the inspection findings or later during CDER's review, depending on the type of

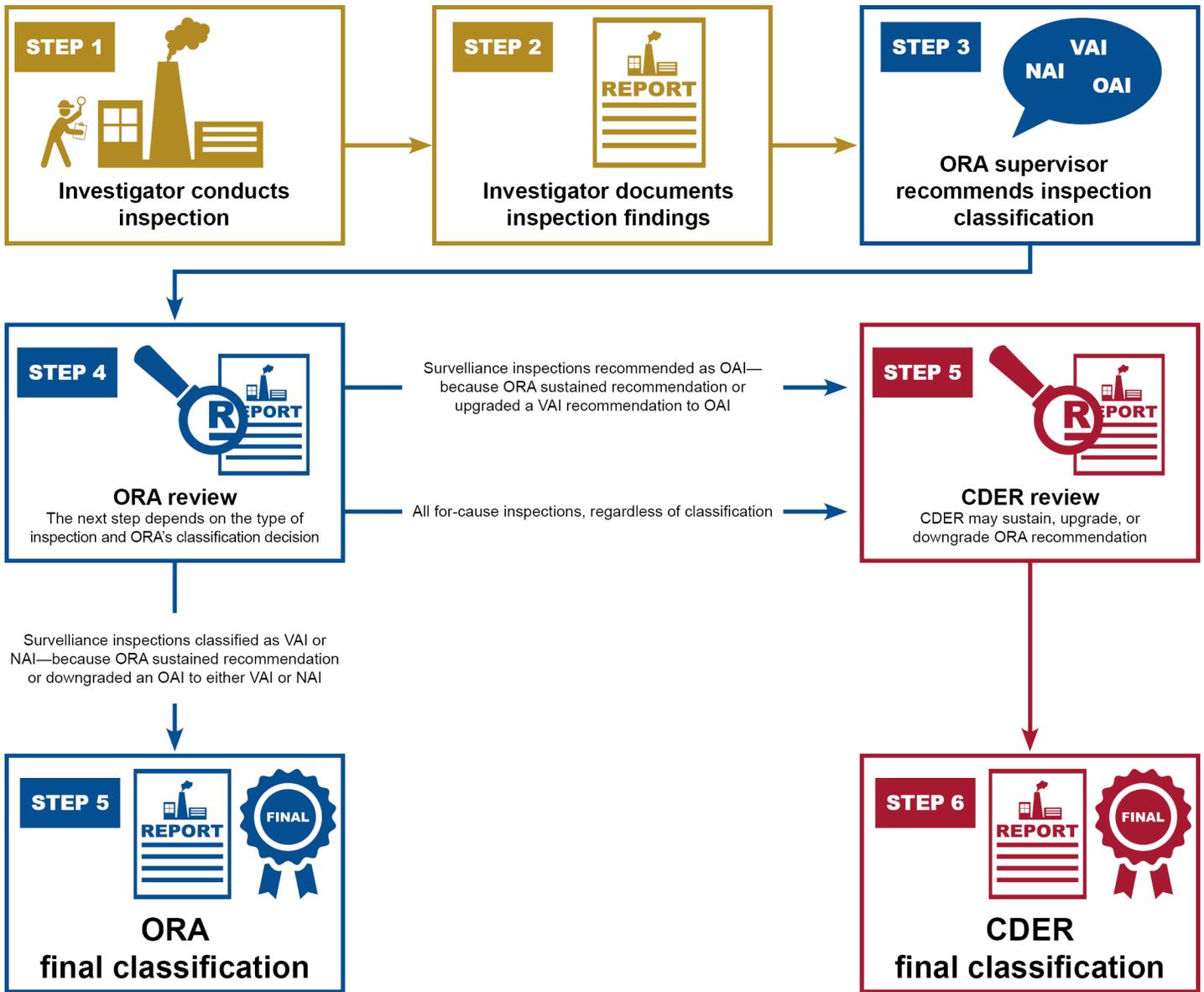
⁸⁰In June 2017, FDA instituted a *Concept of Operations* (ConOps) agreement to help streamline human drug facility evaluations, inspections, and communication. This agreement outlines the redesigned responsibilities of ORA and CDER staff and workflow for pre-approval, surveillance, and for-cause inspections at domestic and foreign establishments. See Food and Drug Administration, Center For Drug Evaluation and Research, Office of Regulatory Affairs, *Integration of FDA Facility Evaluation and Inspection Program For Human Drugs: A Concept of Operations* (Washington, D.C.: 2017).

Among other things, under ConOps, the redesigned classification process for foreign inspections included an additional level of review within ORA, according to FDA officials. Prior 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, foreign for-cause inspections issued by CDER and OAI recommendations are reviewed by ORA after being endorsed by ORA supervisors. Foreign inspection reports now only go to CDER for review in certain circumstances, such as if there is an OAI recommended, which had been the process for domestic inspections.

inspection. (See fig. 8.) FDA documentation shows that ORA and CDER base their classification decisions on their review of the inspection findings and other information.⁸¹ For example, ORA or CDER may downgrade an inspection recommended for OAI classification if they determine the inspection findings lack the evidence needed to support regulatory action, or if the immediate corrective actions undertaken or promised by the establishment following the inspection are adequate to address the identified deficiencies.

⁸¹According to FDA officials, ORA and CDER may use a compliance analysis tool to support their review of inspections. Specifically, FDA officials told us that this tool was developed to help ensure that review staff consider consistent factors in their process to determine an establishment's compliance status and whether and what regulatory action may be warranted.

Figure 8: FDA's Process for Classifying Surveillance and For-Cause Inspections of Drug Manufacturers



Legend: ORA=Office of Regulatory Affairs; CDER=Center for Drug Evaluation and Research; NAI=No action indicated; VAI=Voluntary action indicated; OAI=Official action indicated.

Source: GAO summary of Food and Drug Administration (FDA) classification procedures. | GAO-22-103611

Notes: After each inspection, FDA classifies the inspection into one of three categories based on its determination of whether any deficiencies identified during the inspection are serious enough to warrant regulatory action: 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.

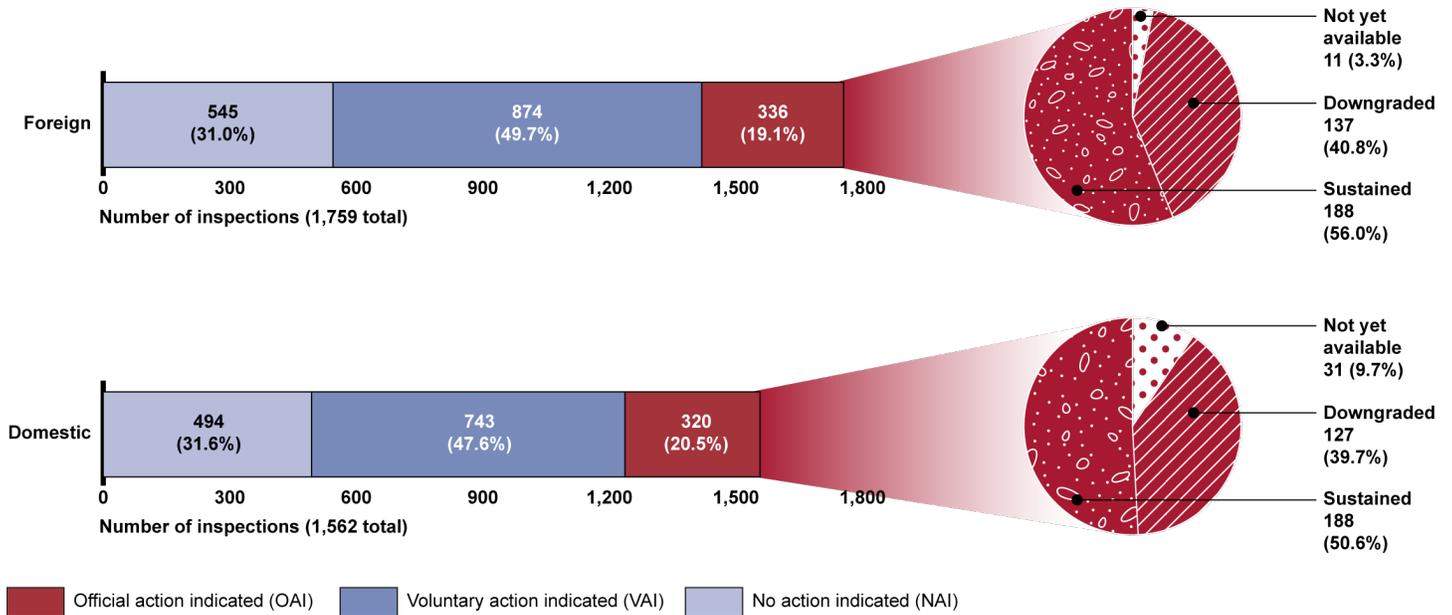
Our review of FDA surveillance and for-cause inspection data shows that, from fiscal years 2018 through 2020, ORA or CDER reclassified 9.4 percent of foreign inspections (165 of 1,759 inspections) and 9.6 percent of domestic inspections (150 of 1,562 inspections) during its process to classify inspections.⁸² About 82 percent of the foreign inspections ORA or CDER reclassified during this time (136 out of 165 inspections) were downgraded from a recommendation for the more serious OAI classification to a less serious final classification of VAI.⁸³ About 12 percent of the foreign inspections ORA or CDER reclassified during this time (20 out of 165) were upgraded from a less serious to a more serious classification (i.e., from NAI to VAI or OAI or from VAI to OAI). FDA officials told us that they were not surprised that most of the reclassifications were downgrades because, they said, under the classification process, inspections recommended as OAI go through more reviews than other inspections. Additionally, according to FDA policy, an inspection should be classified as OAI or VAI if an FDA Form 483, which is used to list any conditions or practices observed during the inspection that may violate applicable regulations, was issued to the establishment. Thus, inspections for which no Form 483 was issued would rarely be upgraded to VAI or OAI, according to FDA officials.

Given the larger proportion of downgrades among all reclassifications, we also analyzed the downgrade data further and found that, from fiscal years 2018 through 2020, 40.8 percent of the foreign inspections recommended for OAI classification were downgraded by ORA or CDER for final classification (137 of 336 inspections). (See fig. 9.)

⁸²FDA's policies and procedures for preapproval inspections differ from its policies and procedures for surveillance and for-cause inspections; thus, preapproval-only inspections are excluded from our analysis of reclassifications.

⁸³Inspections recommended for OAI may also be downgraded to NAI, but FDA officials told us that such changes are rare. From fiscal years 2018 through 2020, we found that one foreign and seven domestic surveillance and for-cause inspections recommended for OAI classification were downgraded to NAI. Inspections can also be downgraded from VAI to NAI. From fiscal years 2018 through 2020, we found that eight foreign and three domestic surveillance and for-cause inspections recommended for VAI classification were downgraded to NAI.

Figure 9: Total FDA Foreign and Domestic Surveillance and For-Cause Inspection Classification Recommendations and Percent of Official Action Indicated Recommendations Sustained and Downgraded, Fiscal Years 2018 through 2020



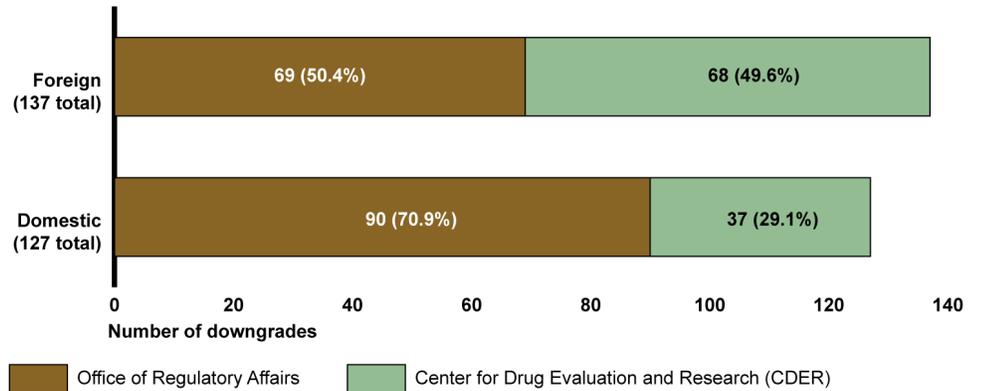
Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-22-103611

Notes: After each inspection, FDA classifies the inspection into one of three categories based on its determination of whether any deficiencies identified during the inspection are serious enough to warrant regulatory action: 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.

During FDA's process to classify inspections, inspection classification recommendations may be changed and such changes are referred to as reclassifications. Reclassifications include upgrades (changing to a more serious classification, from VAI to OAI for example) and downgrades (changing to a less serious classification, from OAI to VAI for example).

Of those foreign inspections that were downgraded from an OAI to VAI or NAI, we found that 50.4 percent (69 of 137 inspections) were downgraded during ORA's review, and the other 49.6 percent (68 of 137 inspections) were downgraded during CDER's review. In comparison, for domestic inspections, decisions to downgrade inspections were made more frequently during ORA's review. (See fig. 10 and notes section.)

Figure 10: Official Action Indicated Recommendations Downgraded by ORA or CDER for Surveillance and For-Cause Inspections of Foreign and Domestic Drug Manufacturing Establishment Inspections, Fiscal Years 2018 through 2020



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-22-103611

Notes: After each inspection, FDA classifies the inspection into one of three categories based on its determination of whether any deficiencies identified during the inspection are serious enough to warrant regulatory action: 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; and official action indicated (OAI) means that serious deficiencies were found that warrant regulatory action.

During FDA’s process to classify inspections, inspection classification recommendations may be changed and such changes are referred to as reclassifications. Reclassifications include upgrades (changing to a more serious classification, from VAI to OAI for example) and downgrades (changing to a less serious classification, from OAI to VAI for example). Inspections that identify serious deficiencies and are thus recommended for OAI classification may be downgraded by FDA’s Office of Regulatory Affairs (ORA) or the Center for Drug Evaluation and Research (CDER) if they determine, based on their review of the inspection findings and other information, that the deficiencies do not meet the threshold for regulatory action or that the establishment has taken action to address the deficiencies.

This analysis is based on a total of 137 foreign and 127 domestic surveillance and for-cause inspections that, from fiscal years 2018 through 2020, were recommended for OAI classification and downgraded to VAI or NAI for final classification.

FDA Has Recently Taken Steps to Ensure Consistency and Transparency In Its Process Classifying Drug Inspections

FDA has taken steps to help ensure consistency and transparency in its process to classify foreign and domestic drug inspections, some of which it initiated late in our review. In June 2017, FDA instituted its *Concept of Operations* (ConOps) agreement, which, among other things, redesigned its classification process.⁸⁴ Our review of FDA documentation found that the ConOps agreement outlines the roles and responsibilities of ORA and CDER in FDA’s processes to conduct and classify inspections and includes goals to enhance the agency’s ability to manage the growing

⁸⁴Food and Drug Administration, *Integration of FDA Facility Evaluation and Inspection Program For Human Drugs*.

complexity of drug manufacturing and to meet new challenges by: 1) ensuring consistency, efficiency, and transparency in FDA's inspections of drug establishments across the agency and 2) improving the quality of and increasing access to information on drug manufacturing establishments and FDA's regulatory decisions across the agency. According to FDA documentation related to the goals of the ConOps agreement, tracking both the rate at which inspection recommendations were downgraded from OAI to VAI and the reasons why are important for measuring the agency's performance in meeting the ConOps objectives.

ConOps has helped the agency ensure consistency in its process to classify individual inspections, according to FDA officials. Since implementing its redesigned classification process in fiscal year 2018, FDA has used a standard approach to classify each inspection. According to FDA officials, using the same process to classify individual foreign and domestic inspections better ensures consistency in their classification decisions, regardless of geographic location.

To help ensure transparency in their process to classify individual inspections, FDA requires ORA and CDER to document their decisions to downgrade individual inspections. Specifically, if ORA or CDER downgrade an inspection that has been recommended for OAI classification, FDA requires the office responsible for the downgrade (ORA or CDER) to document the reasons for the downgrade in a memo that is then saved in the inspection record for that establishment. According to FDA officials, CDER and ORA staff (including investigators and supervisory investigators) both have access to these inspection records and thus can review the reasons why an inspection recommended for OAI classification was downgraded.

ORA recently began analyzing the information in the memos drafted by ORA and CDER to identify trends in the reasons each office reclassified inspections.

- In 2019, ORA began to analyze trends in all reclassifications made by ORA in an effort to measure consistency in its classification decisions. In its analysis of fiscal years 2019 and 2020 reclassification decisions, ORA found that reclassifications were generally due to two factors for most of the foreign inspections that ORA reclassified. Specifically, ORA found that 54 percent of foreign reclassifications were because ORA determined that the establishment had implemented or proposed adequate corrective actions to address the deficiencies identified during the inspection, and 23 percent were because ORA determined

there was a lack of evidence to support that the identified deficiencies were related to products for the U.S. market or had a negative effect on product quality and patient safety. Starting in January 2020, ORA incorporated this trend analysis into its annual management review process, which, ORA officials told us, is designed to promote quality and to identify and prevent negative trends. According to ORA officials, the annual analysis of trends in ORA's reclassification decisions will help it determine whether opportunities exist to provide its staff with additional training.

- ORA also analyzed CDER's reclassification decisions for fiscal years 2019 and 2020 to identify trends. Based on this analysis, ORA determined that the trends in CDER's decisions were similar to ORA's decisions during this time. Specifically, ORA found that 65 percent of inspections were reclassified by CDER because of an adequate establishment response, and 15 percent of inspections were reclassified because CDER determined there was a lack of support that the identified deficiencies were related to products for the U.S. market or had a negative effect on product quality and patient safety. According to ORA, monitoring CDER trends better enables ORA to sufficiently identify and react to potentially adverse trends and identify potential changes, and it plans to include this analysis in its annual management review process.

CDER also began analyzing the information in its downgrade memos, and expanded this effort during the course of our review. Specifically, in fiscal year 2019, CDER analyzed inspections recommended for OAI classification by ORA that it reviewed between December 20, 2017, and January 31, 2019, and found that most downgrades were due to CDER's determination that the inspection observations lacked adequate evidentiary support, the observed deficiencies pose a low risk to patient safety, or adequate corrective actions had been proposed by the inspected establishments. CDER shared its analysis findings with ORA staff as part of a June 2019 case analysis and risk management workshop. ORA officials told us that, after the June 2019 workshop, ORA provided additional training for all investigators and their supervisors on what should be included to support a regulatory action and how to evaluate risk. According to FDA officials, CDER did not initially have specific plans to analyze downgrade trends again because the number of inspections it reclassified since its 2019 analysis was small given the limited number of inspections conducted in light of the COVID-19 pandemic, making it difficult to see a statistical difference. However, in September 2021, officials told us that CDER determined it would begin analyzing downgrade trends on an annual basis and finalized its standard

operating procedures for conducting and sharing the results of this analysis.

Conclusions

Foreign manufacturing establishments continue to be critical sources of drugs for millions of Americans, and FDA inspections are a key tool to ensure the quality of these drugs. While drugs manufactured overseas for the U.S. market must meet the same statutory and regulatory requirements as those manufactured in the U.S., the unique foreign inspection challenges the agency faces related to preannounced foreign inspections and language barriers has called this into question. FDA is in the process of developing plans to conduct pilot programs intended to examine these issues. As it does so, FDA has the opportunity to incorporate leading practices we identified for pilot design. By incorporating such practices, FDA would be better positioned to assess whether unannounced or short-notice inspections and independent translation services have benefits and should be expanded to other foreign inspections.

Maintaining its investigator workforce to carry out foreign inspections has been a persistent challenge for FDA. Recent efforts to identify strategies for recruiting new investigators, as well as developing and retaining current investigators to specialize in foreign drug inspections, are promising. By developing tailored strategies—including detailing implementation steps and time frames—the agency would better ensure that it is recruiting new investigators with an interest in foreign work and providing a pathway to develop and retain its current investigators to gain the skills necessary to join the foreign cadre or foreign offices. Maintaining a robust investigator workforce is particularly important as FDA will likely continue to face a backlog of surveillance inspections in future years in light of the COVID-19 pandemic.

Recommendations for Executive Action

We are making a total of three recommendations to FDA.

The Commissioner of FDA should ensure that the agency incorporates leading practices we identified for designing a well-developed and documented pilot program as it finalizes its plans for implementing a pilot program to evaluate the effectiveness and efficiency of unannounced foreign inspections. (Recommendation 1)

The Commissioner of FDA should ensure that the agency incorporates leading practices we identified for designing a well-developed and documented pilot program as it finalizes its plans for implementing a pilot

program to evaluate the costs and effects of using different types of translation services during foreign inspections. (Recommendation 2)

The Commissioner of FDA should ensure the agency fully develops tailored strategies—including detailing implementation steps and time frames—focused on recruiting new and developing and retaining current investigators to specialize in conducting foreign drug inspections. (Recommendation 3)

Agency Comments

We provided a draft of this report to HHS for comment. In its written comments, reproduced in appendix I, HHS concurred with our three recommendations. For the two recommendations related to the pilot programs to examine unannounced inspections and translation services, HHS said that FDA will incorporate our identified leading practices into their designs. HHS noted that the unannounced inspection pilot is scheduled to begin in early 2022, as our report states. However, concerns over the COVID-19 outbreaks and associated travel restrictions to protect public health may impact the timing of conducting the translation services pilot. For the workforce recommendation, HHS stated that FDA is reviewing its current hiring and retention processes and considering our key principles for effective strategic workforce planning in order to develop detailed strategies focused on recruiting new and retaining the current foreign drug investigator workforce. It also outlined additional steps the agency is taking, such as announcing a recruitment effort focused on bilingual drug investigators. HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the appropriate congressional committees, the Secretary of Health and Human Services, and other interested parties. In addition, the report will be available at no charge on GAO's website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at deniganmacauleym@gao.gov. Contact points for our Office of Congressional Relations and Office of Public Affairs can be found on the last page of this report. Other major contributors to this report are listed in appendix II.

A handwritten signature in black ink that reads "Mary Denigan-Macauley". The signature is written in a cursive style with a long horizontal flourish at the end.

Mary Denigan-Macauley
Director, Health Care

List of Requesters

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Cathy McMorris Rodgers
Republican Leader
Committee on Energy and Commerce
House of Representatives

The Honorable Brett Guthrie
Republican Leader
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives

The Honorable Diana DeGette
Chair
The Honorable H. Morgan Griffith
Republican Leader
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Honorable Michael C. Burgess, M.D.
House of Representatives

Appendix I: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

December 10, 2021

Mary Denigan-Macauley
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Denigan-Macauley:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, **"Drug Safety: FDA Should Take Additional Steps to Improve its Foreign Inspection Program"** (GAO-22-103611).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED – DRUG SAFETY: FDA SHOULD TAKE ADDITIONAL STEPS TO IMPROVE ITS FOREIGN INSPECTION PROGRAM (GAO-22-103611)

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

Recommendation 1

The Commissioner of FDA should ensure that the agency incorporates leading practices we identified for designing a well-developed and documented pilot program as it finalizes its plans for implementing a pilot program to evaluate the effectiveness and efficiency of unannounced foreign inspections (Recommendation 1).

HHS Response

HHS concurs with GAO's recommendation. The Food and Drug Administration recognizes the need to assess differences in conducting unannounced compared to announced inspections to ensure that any differences do not lead to inconsistent outcomes or impact FDA's public health mission. FDA also recognizes the need to evaluate the impact unannounced inspections will have on foreign operations, including any changes to FDA's inspectional processes and procedures. The FDA is in the process of developing and implementing a pilot in India and China focused on evaluating the impact of notification type (e.g., announced or unannounced) on length of inspection, investigator safety, inspectional outcomes and where possible public health outcomes. This pilot will be designed, and results documented, using GAO-identified leading practices and is scheduled to begin in early 2022.

Recommendation 2

The Commissioner of FDA should ensure that the agency incorporates leading practices we identified for designing a well-developed and documented pilot program as it finalizes its plans for implementing a pilot program to evaluate the costs and effects of using a different types of translations services during foreign inspections (Recommendation 2).

HHS Response

HHS concurs with GAO's recommendation.

FDA will initiate a pilot to evaluate the use of U.S. Department of State-provided translators for drug inspections in Hong Kong and China. The pilot will utilize the agency's current Inter Agency Agreement with the Department of State to provide independent translators for a select number of drug inspections in China. The pilot will incorporate GAO-identified leading practices for designing a pilot program, and the foreign drug inspections using the independent translators will be evaluated against other drug inspections in the same region that use firm-provided translators or locally employed staff who work in FDA's China office.

The timeline for the pilot will include planning portions such as developing strong evaluation criteria and an implementation strategy for the translation pilot. Concerns over the COVID-19 outbreaks and associated travel restrictions to protect public health may impact the timing of conducting the pilot.

**GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN
SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT
REPORT ENTITLED – DRUG SAFETY: FDA SHOULD TAKE ADDITIONAL STEPS
TO IMPROVE ITS FOREIGN INSPECTION PROGRAM (GAO-22-103611)**

Recommendation 3

The Commissioner of FDA should ensure the agency fully develops tailored strategies – including detailing implementation steps and time frames — focused on recruiting new and developing and retaining current investigators to specialize in conducting foreign drug inspections (Recommendation 3).

HHS Response

HHS concurs with GAO's recommendation.

The Food and Drug Administration is reviewing current hiring and retention processes and considering key elements of GAO's Key Principles for Effective Strategic Workforce Planning to develop detailed proposals and timelines focused on recruiting new and developing and retaining the current foreign drug investigator workforce. Additional steps, beyond FDA efforts outlined in the report and already under way, include exploring alternate hiring authorities and compensation methodologies and announcing a recruitment effort focused on bilingual drug investigators. FDA will also continue to look for ways to optimize use of available retention incentives, such as the Student Loan Repayment Program, monetary recruitment and retention incentives, as well as cash and time-off incentive awards.

Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

Mary Denigan-Macauley, Director, Health Care, (202) 512-7114 or deniganmacauleym@gao.gov

Staff Acknowledgments

In addition to the contact named above, William Hadley (Assistant Director), Katherine L. Amoroso (Analyst-in-Charge); George Bogart; Derry Henrick; John Lalomio; Laurie Pachter; Vikki Porter; and Dan Ries made key contributions to this report.

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