

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**THE FOOD AND DRUG
ADMINISTRATION'S FOREIGN FOR-CAUSE
DRUG INSPECTION PROGRAM CAN BE
IMPROVED TO PROTECT THE NATION'S
DRUG SUPPLY**

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Office of Inspector General

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Report in Brief

Date: June 2022

Report No. A-01-19-01500

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF INSPECTOR GENERAL



Why OIG Did This Audit

The Food and Drug Administration's (FDA's) oversight responsibility has become increasingly complicated because many drugs used in the United States are manufactured overseas. FDA reported that 74 percent of active pharmaceutical ingredient manufacturers and 54 percent of finished goods manufacturers are located outside the United States. In 2017, FDA began making changes to its foreign inspection program to enhance its ability to protect the public health. Congress has continued to express concerns about FDA's foreign drug inspection process.

Our objective was to determine whether FDA's foreign drug inspection process has improved since programmatic changes were implemented in 2017. Specifically, we determined whether:

- (1) timeframes for the foreign for-cause drug inspection process improved after FDA implemented the 2017 programmatic changes,
- (2) FDA's foreign for-cause drug inspection process followed applicable policies and procedures, and
- (3) lead investigators conducting foreign for-cause drug inspections met FDA's training requirements.

How OIG Did This Audit

We reviewed all 64 foreign for-cause drug inspections that occurred during the period January 1, 2016, through March 31, 2017, and all 68 foreign for-cause drug inspections that occurred during the period January 1, 2018, through March 31, 2019.

The Food and Drug Administration's Foreign For-Cause Drug Inspection Program Can Be Improved To Protect the Nation's Drug Supply

What OIG Found

FDA's timeframes for completing the steps in the foreign for-cause drug inspection process generally improved after it implemented programmatic changes in 2017. However, we found that: (1) FDA did not always follow its policies and procedures for foreign for-cause drug inspections and (2) FDA could not provide documentation to support that all lead investigators completed the required training before they conducted inspections.

According to FDA, it had limited resources and faced unexpected events and complex circumstances. FDA did not ensure that it recorded certain information in the Establishment Inspection Report (EIR), such as whether an inspection was announced. If FDA does not follow its policies and procedures related to timeliness, regulatory deficiencies may not be corrected in an efficient manner. FDA did not ensure that lead investigators completed required training before they conducted inspections because FDA did not have policies and procedures that required investigators' supervisors to verify that lead investigators completed the required training prior to being assigned to an inspection. FDA officials told us that due to multiple location moves, FDA misplaced records indicating that lead investigators completed training requirements. It is a vulnerability to have lead investigators conduct inspections before ensuring that they are qualified.

What OIG Recommends and FDA Comments

We recommend that FDA identify and implement additional ways to improve the timeliness of its foreign for-cause drug inspection process. We also made other procedural recommendations that are listed in the report.

In written comments on our draft report, FDA concurred with our recommendations. FDA stated that it is working to improve the timeliness of the overall foreign for-cause inspection process. Furthermore, pending approval by Congress, FDA stated that it has committed to goals regarding the timing of foreign facility followup inspections. FDA also stated that it is addressing ways to reduce the time spent writing and reviewing EIRs and that it is conducting a workload analysis for individuals responsible for determining final classification, issuing warning letters, and holding regulatory meetings. FDA stated that it will soon begin implementing a new system to better document and track investigators' qualifications and certification.

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INTRODUCTION

WHY WE DID THIS AUDIT

The Food and Drug Administration's (FDA's) oversight responsibility has become increasingly complicated because many drugs used in the United States are manufactured overseas. During a June 2020 congressional hearing, FDA reported in its written testimony that 74 percent of active pharmaceutical ingredient manufacturers and 54 percent of finished goods manufacturers are located outside the United States.¹

Congress has expressed concerns about FDA's foreign drug inspection program since at least 2008 when contaminated Heparin was imported from China.² In 2017, FDA made two programmatic changes to its foreign inspection program to enhance its ability to protect public health. First, FDA restructured the office that is responsible for conducting inspections to better respond to challenges arising from global markets and an increasingly complex legal environment. Second, FDA implemented internal policies to improve collaboration among the FDA offices involved in the foreign inspection process. Despite these programmatic changes, Congress has continued to express concerns about the safety of certain drugs manufactured overseas and the challenges that FDA faces with its foreign drug inspection process. In February 2019, Congress sent a letter to FDA requesting a briefing on FDA's efforts to conduct foreign inspections.³

One type of drug inspection that FDA conducts is a for-cause inspection, which FDA initiates because it has reason to believe that a facility has serious manufacturing quality problems or to evaluate corrections that facilities have made to address previous violations. We decided to review for-cause drug inspections because they involve facilities with suspected quality problems or a history of violations.

OBJECTIVE

Our objective was to determine whether FDA's foreign drug inspection process has improved since programmatic changes were implemented in 2017. Specifically, we determined whether

¹ Statement of Judith McMeekin, Pharm. D., Associate Commissioner for Regulatory Affairs; Mark Abdo, Associate Commissioner for Global Policy and Strategy; and Douglas C. Throckmorton, M.D., Deputy Director for Regulatory Programs, Center for Drug Evaluation And Research (Jun. 2, 2020). Available online at <http://www.finance.senate.gov/imo/media/doc/02JUN2020.FDAJNT.STMNT.pdf>. Accessed on Feb. 28, 2022.

² Heparin is an anticoagulant (blood thinner) that prevents the formation of blood clots. It is used to treat and prevent blood clots caused by certain medical conditions or medical procedures.

³ United States House of Representatives, Committee on Energy and Commerce, a Letter to Scott Gottlieb, M.D., Commissioner, United States Food and Drug Administration (Feb. 13, 2019). Available online at <https://republicans-energycommerce.house.gov/wp-content/uploads/2019/02/02-13-19-Letter-to-Gottlieb-re-foreign-drug-inspections.pdf>. Accessed on Dec. 9, 2021.

timeframes for the foreign for-cause drug inspection process improved after FDA implemented the 2017 programmatic changes. In addition, we determined whether FDA's foreign for-cause drug inspection process followed applicable policies and procedures, and whether lead investigators conducting foreign for-cause drug inspections met FDA's training requirements.

BACKGROUND

FDA's Oversight of Foreign Drug Facilities

The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives FDA the authority to oversee the safety and effectiveness of all drugs distributed in the United States. As part of its oversight activities, FDA conducts inspections of foreign drug facilities in accordance with internal FDA guidance including the Investigations Operations Manual (IOM), Regulatory Procedures Manual (RPM), and various field management directives (FMDs) and agreements. Within FDA, the Office of Regulatory Affairs (ORA) and Center for Drug Evaluation and Research (CDER) collaborate in the inspection process. ORA is responsible for conducting for-cause foreign and domestic inspections of regulated products and facilities. ORA is also responsible for training investigators and ensuring that investigators have the proper knowledge and expertise before they conduct inspections. CDER establishes the policies governing drug quality, aids in planning inspections by assessing risks at foreign facilities, and reviews action recommendations from ORA.⁴

FDA's Foreign Drug Investigators

FDA has three groups of investigators that conduct foreign inspections: (1) U.S.-based investigators who perform both domestic and foreign inspections; (2) U.S.-based investigators who conduct foreign inspections exclusively; and (3) foreign office-based investigators, located in India and China, who inspect drug facilities in those countries. The majority of foreign inspections are performed by U.S.-based investigators who perform both domestic and foreign inspections.

Types of Foreign Drug Inspections

FDA performs several types of foreign drug inspections including preapproval, postapproval, surveillance, and for-cause inspections:

- **Preapproval inspections** are conducted as part of the review of an application seeking approval of a new brand name or generic drug.

⁴ ORA can recommend various actions that FDA can take against inspected facilities, including issuing warning letters and import alerts or holding regulatory meetings.

- **Postapproval inspections** are similar to preapproval inspections in that they are product specific, but they are conducted after applications have been approved. This type of inspection focuses largely on manufacturing changes that may have occurred following approval.
- **Surveillance inspections** focus on systemwide controls to ensure that manufacturing processes produce quality drugs. FDA uses its site selection model to prioritize sites for surveillance inspections.⁵
- **For-cause inspections** are triggered when FDA has reason to believe that a facility has serious manufacturing quality problems or when FDA wants to evaluate corrections that facilities have made to address previous violations.

Foreign Drug Inspection Process

FDA conducts both announced and unannounced foreign drug inspections. According to FDA, an inspection is considered announced when FDA provides a notification to the facility prior to the investigator arriving at the facility. When an inspection is conducted by U.S.-based investigators, FDA's practice is to announce foreign drug inspections 10 to 12 weeks (approximately 70 to 84 days) in advance. When an inspection is conducted by foreign office-based investigators, FDA's practice for announced inspections is to give advanced announcement of the inspection within 5 days of the inspection. FDA defines an unannounced inspection as an inspection that occurs when the investigator arrives at a facility without any prior notification. FDA officials said they consider various factors (including information from an informant or another regulatory agency that drugs may be in violation of requirements) when deciding whether to conduct unannounced inspections.

ORA investigators conduct foreign drug inspections to verify compliance with the FD&C Act and FDA regulations, including current good manufacturing practice (CGMP) regulations.⁶ Investigators document their findings in an Establishment Inspection Report (EIR) and recommend an inspection classification (we refer to this as the initial classification). The EIR is reviewed by the investigators' supervisors and in some cases by other FDA officials, and they determine the final classification. According to FDA's Field Management Directive 86 (FMD-86), inspection results are generally classified as follows:

⁵ FDA's site selection model is a risk-based model that prioritizes manufacturing sites for routine current good manufacturing practice (CGMP) surveillance inspections.

⁶ FDA's CGMP regulations for drugs set out minimum requirements for the methods, facilities, and controls used in the manufacturing, processing, and packaging of a drug product (21 CFR parts 210 and 211).

- Official Action Indicated (OAI): The inspected facility has unacceptable compliance with CGMP regulations. Objectionable conditions were found and regulatory action should be recommended. FDA may take various advisory or administrative actions or seek judicial actions.⁷
- Voluntary Action Indicated (VAI): The inspected facility has minimally acceptable compliance with CGMP regulations. Objectionable conditions were found and documented, but FDA is not prepared to take or recommend regulatory actions. FDA may use an untitled letter, regulatory meeting, or other communication with responsible individuals to inform the establishment of findings that should be corrected.⁸ FDA may request a written response from the establishment, but FMD-86 does not require this. Any corrective action is left to the establishment to take voluntarily.
- No Action Indicated (NAI): The inspected facility has acceptable compliance with CGMP regulations. No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further FDA action).

After FDA determines the final inspection classification, it issues a letter to the inspected facility and provides the facility with a copy of the EIR.⁹

When FDA finds significant objectionable conditions and classifies the inspection as OAI, FDA may take various advisory or administrative actions or seek judicial actions to ensure that facilities take steps to correct those violations and that drugs are removed or prevented from entering the U.S. drug supply chain. These actions include but are not limited to warning letters, import alerts, and regulatory meetings:

⁷ Examples of advisory actions include warning letters and untitled letters. Examples of administrative actions include citations and administrative detentions. Examples of judicial actions include seizure and injunctions.

⁸ An untitled letter cites violations that do not meet the threshold of regulatory significance for a warning letter.

⁹ Prior to FDA's programmatic changes, FDA generally issued a letter (known as an FMD-145 letter) to the facility that informed the inspected facility that the inspection was "closed." After FDA's programmatic changes, FDA generally issued a decisional letter that informed the inspected facility of the inspection classification and in some cases informed the inspected facility that the inspection was "closed."

- **Warning Letters**—A warning letter notifies drug facilities, the public, and other stakeholders about violations that FDA has documented during its inspections. FDA’s policies state that it issues warning letters only for violations of regulatory significance. Violations of regulatory significance are those violations that may lead to enforcement action if not promptly and adequately corrected. A warning letter is FDA’s principal means of achieving prompt voluntary compliance with the FD&C Act and regulatory requirements including CGMP. Warning letters are posted to FDA’s website.
- **Import Alerts**—Import alerts inform the FDA’s field staff and the public that FDA has enough evidence to allow it to detain a product without physically examining it at the time of entry into the United States because the product appears to be in violation of the FDA’s laws and regulatory requirements, including CGMP. These violations could be related to the product, facility, shipper, or other information.
- **Regulatory Meetings**—A regulatory meeting is a meeting requested by FDA management, at its discretion, to inform responsible individuals or facilities about how one or more products, practices, processes, or other activities are considered to be in violation of the law and regulatory requirements, including CGMP regulations. Regulatory meetings can be an effective enforcement tool to obtain prompt compliance and have been used successfully in a variety of situations. FDA is required to keep minutes of each regulatory meeting.

FMD-86 states that FDA is encouraged to conduct timely followup inspections of facilities with significant inspection violations. These followup inspections are conducted to verify that the facility is in compliance with CGMP regulations, and that the facility has corrected the violations found during the initial inspection.

FDA’s Programmatic Changes

In May 2017, FDA began implementing programmatic changes to enhance its ability to protect public health. The first programmatic change was a structural realignment of FDA’s ORA. This realignment involved moving from a geography-based model to a program-based model organized around FDA-regulated products.¹⁰ Under the realignment, management and staff, including investigators, are assigned to inspections based on their specialized knowledge. According to FDA, this realignment was undertaken to respond to challenges arising from more global markets and an increasingly complex legal environment.

¹⁰ Under ORA’s program-based management model, there are seven key programs for operations (Biological Products, Bioresearch Monitoring, Human and Animal Food, Medical Devices and Radiological Health, Pharmaceutical Quality, Tobacco, and Imports). Each program has a unique number of program divisions for a total of 28 operational divisions.

In June 2017, FDA implemented the second programmatic change when it issued the Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (ConOps). This internal policy is an agreement between FDA's CDER and ORA regarding the domestic and foreign pre- and postapproval, surveillance, and for-cause inspection processes for human drug facilities. According to FDA, ConOps was implemented to enable CDER and ORA to more effectively manage and oversee the growing complexity of pharmaceutical manufacturing and meet new challenges by:

- ensuring consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision making for marketing applications across FDA;
- advancing strategic alignment across ORA and CDER functional units by clarifying roles and responsibilities;
- improving FDA's operational capacity by enhancing collaboration between various CDER and ORA offices;
- enhancing the quality and accessibility of facility and regulatory decisional information across FDA; and
- meeting user fee commitments and improving the timelines for regulatory and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.¹¹

Investigator Training Requirements

According to FDA's Basic Investigator Training Curriculum and Level 1 Investigator Certification Program (version 3.02, effective August 15, 2018) policies, each newly hired FDA investigator, including investigators who perform foreign drug inspections, is required to complete FDA's training curriculum.¹² The required training includes web-based courses, reading materials, discussion questions, exercises, on-the-job training assignments, and national classroom training courses. According to FDA's Field Management Directive No. 13A, investigators are required to complete courses in Basic Food and Drug Law, Evidence Development, Investigative Interviewing, Basic Drug Manufacturing Quality Control, and Industrial Sterilization. Investigators who successfully complete the required training curriculum are eligible to apply for the Performance Audit. The purpose of the Level 1 Performance Audit is to demonstrate proficiency in various tasks during an actual inspection under the close supervision of an experienced investigator. Level 1 Investigator Certification is conferred upon those who pass

¹¹ *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations* (Sept. 22, 2017). Available online at <https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations>. Accessed on Feb. 24, 2022.

¹² We noted that FDA had multiple versions of the Basic Investigator Training Curriculum and Level 1 Investigator Certification Program document in effect during the audit period including version 2.2 (effective Apr. 13, 2015) and version 3.0 (effective Aug. 1, 2017). Each version of the document contains similar requirements.

the performance audit. Once investigators pass the Level 1 Performance Audit and are certified, they may conduct independent inspections in the role of the lead investigator.

HOW WE CONDUCTED THIS AUDIT

We reviewed all 64 foreign for-cause drug inspections that occurred during the period January 1, 2016, through March 31, 2017, and all 68 foreign for-cause drug inspections that occurred during the period January 1, 2018, through March 31, 2019.^{13, 14} To determine whether inspection efficiency improved following FDA's implementation of programmatic changes in May 2017 for each of the inspections covered by our audit, we calculated the time it took FDA to complete the following steps:

- initiate the inspection;
- conduct the onsite inspection;
- complete the initial and final classifications;
- take further action against the inspected facilities when further action was needed (including issuing warning letters, issuing import alerts, and holding regulatory meetings); and
- conduct followup inspections at facilities previously classified as OAI and not subject to an import alert.

For each step, we reviewed the inspection information provided by FDA, interviewed FDA personnel responsible for foreign for-cause drug inspection oversight, summarized the average and median time to complete the specific steps, and documented deviations from policies and procedures. Furthermore, we reviewed the training records of the 65 lead investigators who conducted the 132 foreign for-cause drug inspections. We limited our review of FDA's internal controls to those related to our audit objective.

We conducted this performance audit 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.

Appendix A contains the details of our audit scope and methodology.

¹³ Of the 64 foreign for-cause drug inspections that occurred during the period Jan. 1, 2016, through Mar. 31, 2017, FDA announced 43 inspections and did not announce 10 inspections; we could not determine whether FDA announced 11 of the inspections. Of 68 foreign for-cause drug inspections that occurred during the period Jan. 1, 2018, through Mar. 31, 2019, FDA announced 54 inspections and did not announce 6 inspections; we could not determine whether FDA announced 8 of the inspections.

¹⁴ We did not review 35 foreign for-cause drug inspections that occurred during the period Apr. 1, 2017, through Dec. 31, 2017, because FDA was implementing its programmatic changes during this period.

FINDINGS

FDA's timeframes for completing the steps in the foreign for-cause drug inspection process generally improved after it implemented the programmatic changes. However, we found that: (1) FDA did not always follow its policies and procedures for foreign for-cause drug inspections and (2) FDA could not provide documentation to support that all lead investigators completed the required training before they conducted inspections.

FDA did not always follow its policies and procedures regarding its foreign for-cause drug inspection process because, according to FDA, it had limited resources and faced unexpected events and complex circumstances. FDA did not ensure that it recorded certain information in the EIR, such as whether an inspection was announced. If FDA does not follow its policies and procedures related to timeliness, regulatory deficiencies may not be corrected in an efficient manner. FDA did not ensure that lead investigators completed required training before they conducted inspections because FDA did not have policies and procedures that required investigators' supervisors to verify that lead investigators completed the required training prior to being assigned to an inspection. Also, FDA officials told us that due to multiple location moves, FDA misplaced records indicating that lead investigators completed training requirements. It is a vulnerability to have lead investigators conduct inspections before ensuring that they are qualified.

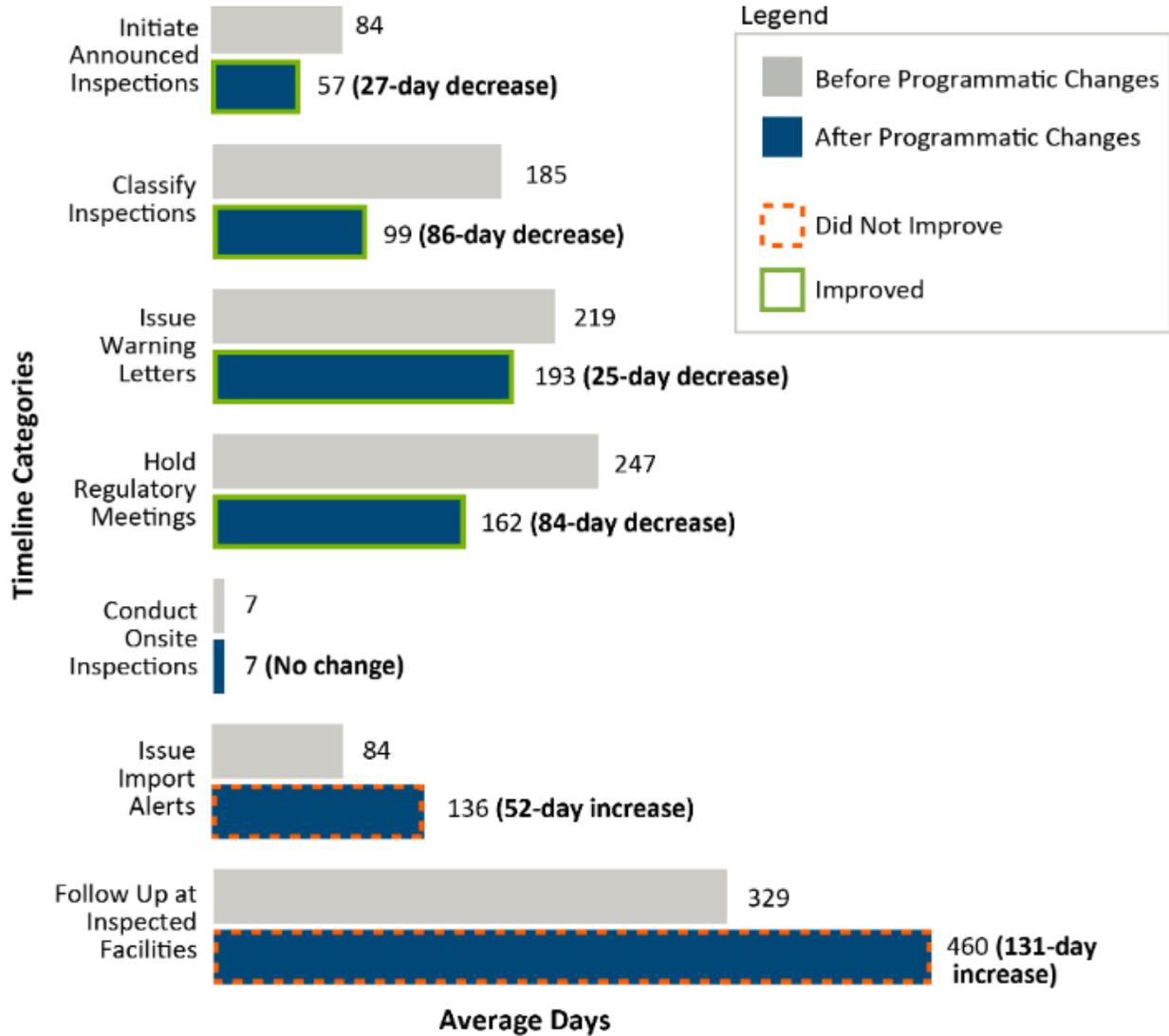
FDA'S TIMEFRAMES RELATED TO THE FOREIGN FOR-CAUSE DRUG INSPECTION PROCESS GENERALLY IMPROVED AFTER IT IMPLEMENTED THE PROGRAMMATIC CHANGES

FDA implemented its programmatic changes to respond to challenges arising from more global markets, an increasingly complex legal environment, and to enable CDER and ORA to more effectively manage and oversee the growing complexity of pharmaceutical manufacturing. For example, ConOps was implemented to meet new challenges by ensuring efficiency, consistency, and transparency in inspections. To determine whether timeframes for the foreign for-cause drug inspection process generally improved after FDA implemented the 2017 programmatic changes, we compared the calculated timeframes before and after the programmatic changes.

Based on this comparative analysis, we found that the times to: (1) initiate inspections, (2) classify inspections, (3) issue warning letters, and (4) hold regulatory meetings improved after implementing the programmatic changes. However, the time to conduct the onsite inspection did not change after programmatic changes, and the times to: (1) issue import alerts and (2) follow up at inspected facilities previously classified as OAI did not improve after programmatic changes (Figure 1 on next page).¹⁵

¹⁵ The facilities previously classified as OAI that FDA followed up at where not subject to an import alert.

Figure 1: Timeframes Before and After Programmatic Changes by Category



Initiate Announced Inspections—Before programmatic changes, FDA announced 67 percent (43 of the 64) of inspections an average of 84 days (median of 80 days and ranging from 3 to 543 days) prior to arriving at the facility to conduct the onsite inspection. After the programmatic changes, FDA announced 79 percent (54 of the 68) of inspections an average of 57 days (median of 41 days and ranging from 0 to 531 days) prior to arriving at the facility to conduct the onsite inspection.

Classify Inspection—Before the programmatic changes, it took FDA an average of 185 days (median of 155 days and ranging from 42 to 611 days) to determine the final classification. After the programmatic changes, it took FDA an average of 99 days (median of 87 days and ranging from 21 to 532 days) to determine the final classification.

Issue Warning Letters—Before the programmatic changes, it took FDA an average of 219 days (median of 198 days and ranging from 144 to 360 days) from the end of a foreign for-cause drug inspection to issue the 12 warning letters. After the programmatic changes, it took FDA an average of 193 days (median of 165 days and ranging from 131 to 335 days) from the end of the foreign for-cause drug inspection to issue the nine warning letters.

Hold Regulatory Meetings—Before the programmatic changes, FDA held 12 regulatory meetings related to 13 inspected facilities an average of 247 days (median of 218 days and ranging from 104 to 545 days) after the end of a foreign for-cause drug inspection. After the programmatic changes, FDA held 16 regulatory meetings related to 20 inspected facilities an average of 162 days (median of 166 days and ranging from 102 to 222 days) after the end of the foreign for-cause drug inspection.

Conduct Onsite Inspections—Before the programmatic changes, FDA took an average of 7 days (median of 5 days and ranging from 1 to 15 days) to conduct an onsite inspection. After the programmatic changes, it took FDA an average of 7 days (median of 7 days and ranging from 1 to 17 days) to conduct an onsite inspection.

Issue Import Alerts—Before the programmatic changes, FDA issued nine import alerts an average of 84 days (median of 102 days and ranging from 6 to 182 days) after the end of a foreign for-cause drug inspection. After the programmatic changes, FDA issued eight import alerts an average of 136 days (median of 119 days and ranging from 102 to 248 days) after the end of the foreign for-cause drug inspection.

Follow Up at Inspected Facilities—Before the programmatic changes, FDA conducted followup inspections at 11 facilities an average of 329 days (a median of 321 days ranging from a minimum of 142 days to 476 days) after FDA classified the prior inspection as OAI and after FDA finalized any subsequent actions. After the programmatic changes, as of September 14, 2021, FDA conducted followup inspections at six facilities an average of 460 days (a median of 427 days ranging from 240 days to 843 days) after OAI classification had been finalized and any actions taken.

More specifically, after it implemented programmatic changes, FDA’s timeframe to initiate announced foreign for-cause drug inspections decreased by an average of 27 days (median of 39 days). Although FDA’s timeframe for initiating announced foreign for-cause drug inspections decreased after FDA implemented its programmatic changes, the data we reviewed suggests that FDA may have performed fewer unannounced inspections after it implemented the programmatic changes in 2017 than it had performed before it implemented the programmatic changes.^{16, 17} A decline in the proportion of foreign for-cause drug inspections that were unannounced would raise questions because, according to a Government Accountability Office report, multiple FDA investigators have indicated that unannounced inspections are generally preferable to announced inspections.¹⁸

During a Congressional hearing on December 10, 2019, FDA was asked if it felt that “unannounced or short-notice inspections could help [FDA] better discover manufacturing issues or even data quality issues when they are occurring.” An FDA official stated, “Certainly.

¹⁶ FDA could not provide documentation indicating whether 11 inspections prior to programmatic changes and 8 inspection after the programmatic were announced or unannounced.

¹⁷ Prior to the programmatic changes, 16 percent (10 of the 64) of foreign for-cause drug inspections were unannounced. After the programmatic changes, 9 percent (6 of the 68) of foreign for-cause drug inspections were unannounced.

¹⁸ *COVID-19 Complicates Already Challenged FDA Foreign Inspection Program*, GAO-20-626T (Washington, D.C.: Jun. 2, 2020). Available online at <https://www.gao.gov/assets/gao-20-626t.pdf>. Accessed on Dec. 9, 2021.

Those are desirable. You just have to think about the tradeoffs in doing that. But no—no one is opposed to those, and we do them routinely for for-cause inspections.”¹⁹

The timeframe to complete some steps did not improve. For example, the timeframe to issue import alerts resulting from foreign for-cause drug inspections increased by 52 days after the programmatic changes. For seven of the eight inspections reviewed during our audit, FDA issued an import alert but did not issue a warning letter or hold a regulatory meeting. For the remaining inspection, FDA held a regulatory meeting then issued an import alert. In this specific instance, FDA classified the inspection as OAI and held a regulatory meeting 136 days after the inspection end date.²⁰ FDA received the facility’s response to the regulatory meeting 8 days after the regulatory meeting and determined that the response was inadequate. FDA issued an import alert 104 days after it received the facility’s response to the regulatory meeting (a total of more than 8 months (248 days) after the inspection end date). During the 248 days after the inspection, drugs from the inspected facility entered the United States and were released into the drug supply.²¹ According to FDA, the import alert was not a direct result of the inspection, but it was also based on the facility’s inadequate response to the regulatory meeting.²²

FDA DID NOT ALWAYS FOLLOW ITS POLICIES AND PROCEDURES THROUGHOUT THE FOREIGN FOR-CAUSE DRUG INSPECTION PROCESS AFTER THE PROGRAMMATIC CHANGES

FDA did not always follow its policies and procedures for foreign for-cause drug inspections after it implemented the programmatic changes. Specifically, we found FDA:

- did not follow its policies and procedures related to the timeliness of inspection classification for 40 percent of foreign for-cause drug inspections,

¹⁹ House Committee on Energy and Commerce, *Securing the U.S. Drug Supply Chain: Oversight of FDA’s Foreign Inspection Program* (Dec. 10, 2019). Available online at https://www.youtube.com/watch?app=desktop&v=miVge_e2kQc. (YouTube, 1:11:49). Accessed on Dec. 9, 2021.

²⁰ During the inspection, FDA noted eight observations, including complaints and unplanned deviations that were not investigated and fully documented, unapproved labeling found on materials, and inadequate standard operating procedures.

²¹ After the import alert, drugs from this facility were no longer allowed to enter the United States.

²² FDA officials told us that one of the eight inspections was an outlier because the import alert was not solely the result of the inspection. We did not exclude this inspection from our analysis and note that in doing so would only have a minimal impact on the results of our analysis. Specifically, when excluding this inspection from our calculation, the average and median time to issue import alerts for the 2018–2019 period would drop to 120 days and 118 days, respectively. Including this inspection in our calculation, the average and median time to issue import alerts for the 2018–2019 period is 136 days and 119 days, respectively.

- did not follow its policies and procedures related to the timeliness of warning letters for 33 percent of warning letters issued as a result of foreign for-cause drug inspections,
- generally followed its policies and procedures related to the timeliness of regulatory meetings for 90 percent of regulatory meetings resulting from foreign for-cause drug inspections, and
- did not indicate in the establishment inspection reports whether an inspection was announced in accordance with its policies and procedures for eight foreign for-cause drug inspections.

FDA Did Not Follow Its Policies and Procedures Related to the Timeliness of Inspection Classification for 40 Percent of Foreign For-Cause Drug Inspections

FDA's Policies and Procedures

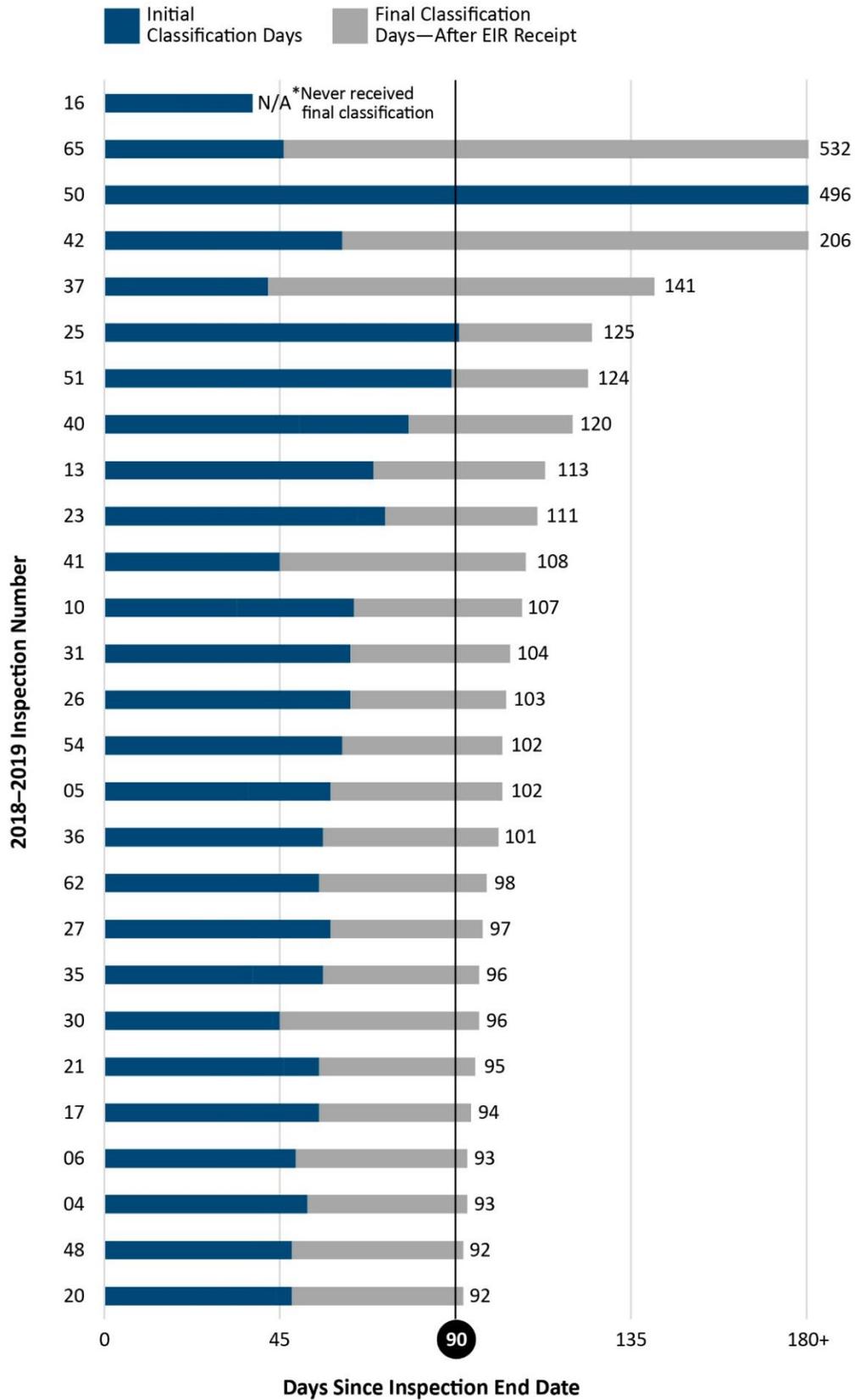
According to section 5.3 of ConOps, within 45 days of the close of a foreign for-cause drug inspection, ORA should complete an EIR, which it sends to the office that initiated the for-cause assignment with a package of evidence collected during the inspection.²³ In addition to the EIR, ORA recommends an inspection classification (generally OAI, VAI, or NAI). The office that initiated the for-cause assignment should complete a final classification within 45 days of receiving the completed EIR from ORA. The entire classification process should be completed within 90 days.

FDA's Foreign For-Cause Drug Inspection Classification

FDA did not always classify foreign for-cause drug inspections in accordance with the timeframe outlined in its policies and procedures. After FDA's programmatic changes, FDA did not complete the final classification within 90 days of the inspection end date for 27 of the 68 (40 percent) foreign for-cause inspections (Figure 2 on the next page).

²³ We used the "Inspection End Date" to determine whether an inspection was closed after the programmatic changes.

Figure 2: After the Programmatic Change: Timing of Final Classification Greater Than 90 Days



According to FDA officials, writing and reviewing the EIR and the initial classifications were delayed by unexpected events such as family emergencies, competing inspectional priorities, computer issues, and Government shutdowns. Delays in final classification were due to the lead investigator being furloughed and resource constraints. Delays in the inspection classification process that extend the time for regulatory action could result in facilities continuing to produce drugs in violation of CGMP for extended periods of time, potentially making them unsafe for use.

FDA Did Not Follow Its Policies and Procedures Related to the Timeliness of Warning Letters for 33 Percent of Warning Letters Issued as a Result of Foreign For-Cause Drug Inspections

FDA's Policies and Procedures

According to section 4-1-1 of the RPM, when it is consistent with the public protection responsibilities of the agency and depending on the nature of the violation, it is the FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning letters are issued to achieve voluntary compliance. Warning letters are issued only for those violations that may lead to enforcement action if not promptly and adequately corrected. A warning letter is FDA's principal means of achieving prompt voluntary compliance with the FD&C Act.

Any followup actions, which can include warning letters, should be issued within 6 months after the inspection end date (ConOps § 5.3).

Warning Letters

FDA did not always follow its policies and procedures for issuing warning letters. After FDA's programmatic changes, FDA conducted nine foreign for-cause drug inspections that resulted in warning letters. Three of the nine warning letters (33 percent) were issued more than 6 months after the inspection end date (Figure 3 on the next page).

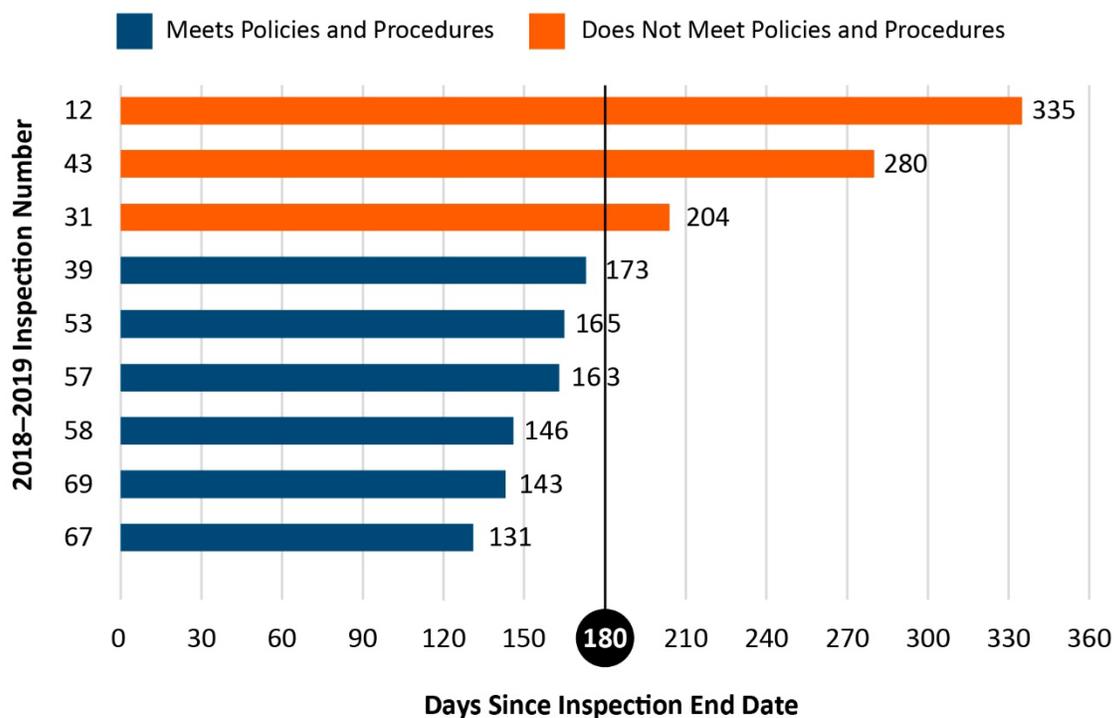
For example, FDA issued a warning letter to a foreign drug facility it inspected during the 2018 through 2019 timeframe that was not issued within 6 months of the inspection end date. Specifically, the warning letter, which cited three violations, was issued more than 9 months after the inspection end date.²⁴ During the 9 months, buyers and consumers were unaware of

²⁴ The warning letter cited three violations related to the facility's failure to: (1) thoroughly investigate any unexplained discrepancy or failure of a batch (or the batch's components) to meet any of its specifications; (2) establish adequate written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess; and (3) clean, maintain, and, as appropriate for the nature of the drug, sanitize or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official, or other established, requirements.

the violations identified by FDA at the facility while drugs from the facility were available in the U.S. market.

According to FDA, warning letters were not always issued in a timely manner due to limited resources. Delays in issuing warning letters could lead to untimely notifications to consumers and other stakeholders about a facility’s compliance with CGMP.

Figure 3: After the Programmatic Changes: Timing of Warning Letters



FDA Generally Followed Its Policies and Procedures Related to the Timeliness of Regulatory Meetings for 90 Percent of Regulatory Meetings Resulting From Foreign For-Cause Drug Inspections

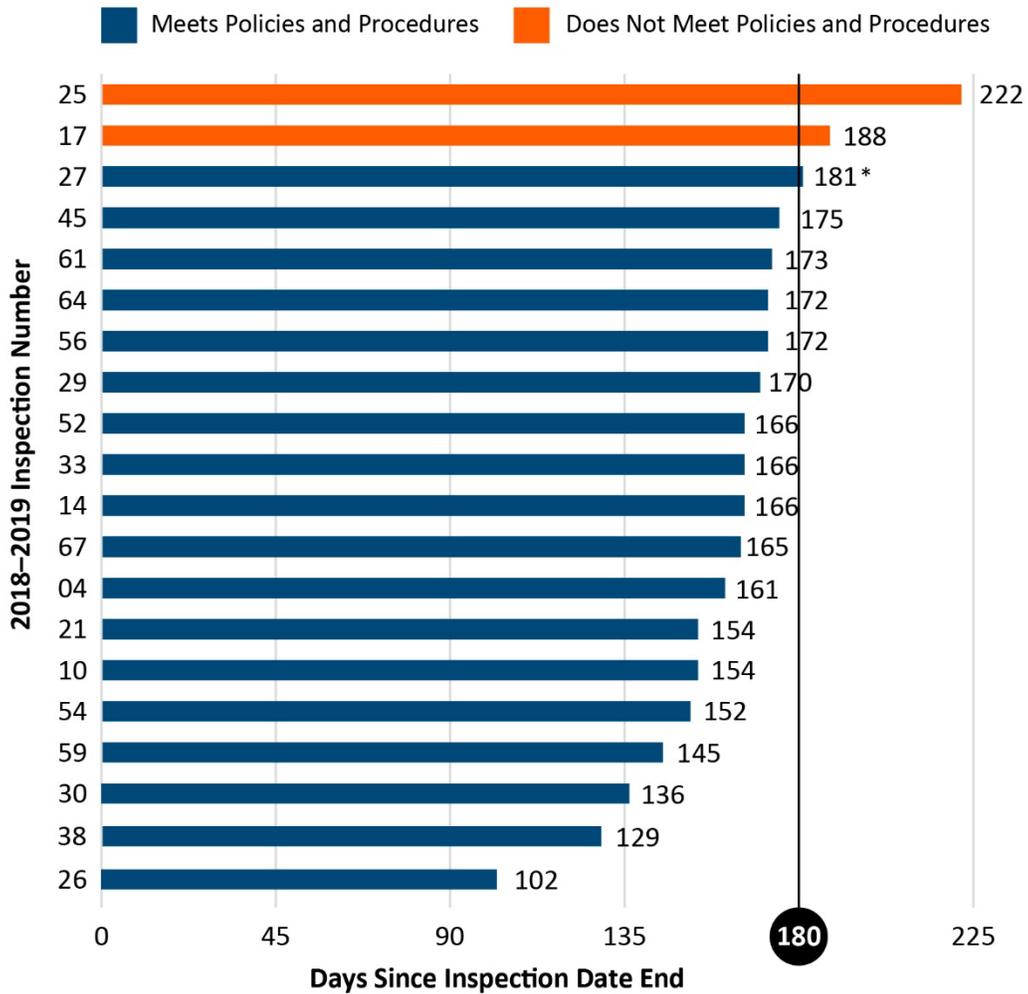
FDA’s Policies and Procedures

A regulatory meeting is requested by FDA management at its discretion to inform responsible individuals or firms about how one or more products, practices, processes, or other activities are considered to be in violation of the law. Regulatory meetings can be an effective enforcement tool to obtain prompt voluntary compliance and have been used successfully in various ways, including as followup to a warning letter and to communicate documented violations that do not warrant the issuance of a warning letter. Summary minutes must be prepared for all regulatory meetings (RPM § 10-3). According to ConOps, regulatory meetings should be held within 6 months postinspection (ConOps § 5.3).

Regulatory Meetings

FDA generally followed its policies and procedures for holding regulatory meetings. After FDA’s programmatic changes, FDA conducted 20 foreign for-cause drug inspections that resulted in 16 regulatory meetings.²⁵ However, for 2 of the 20 inspections, the regulatory meeting was held more than 6 months postinspection (Figure 4).

Figure 4: After the Programmatic Changes: Timing of Regulatory Meetings



*Inspection was within 6 months per the ConOps requirement.

For example, during this period, FDA conducted an inspection and then held a regulatory meeting with a foreign drug facility more than 6 months (188 days) after the inspection end

²⁵ Three regulatory meetings covered multiple facilities. Each facility received its own inspection.

date.²⁶ During the meeting, the facility indicated that its quality system was “sufficiently robust.” However, FDA did not agree and stated that the inspection of the facility will remain OAI. Had the regulatory meeting been held sooner, FDA and the facility could have potentially begun actions to get the facility into compliance with CGMP sooner.

According to FDA, the two regulatory meetings were not held in accordance with FDA policies and procedures because: (1) FDA needed to consult with microbiological experts in preparation of the regulatory meeting and (2) the regulatory meeting covered multiple facilities that resulted in a longer amount of time needed to prepare for the regulatory meeting. Delays in holding regulatory meetings could result in facilities not correcting deficiencies at their facilities in a timely manner.

FDA Did Not Indicate in the Establishment Inspection Reports Whether an Inspection Was Announced in Accordance With Its Policies and Procedures for Eight Foreign For-Cause Drug Inspections

FDA’s Policies and Procedures

During the audit period, FDA procedures specify that FDA should include in an EIR whether the inspection was announced (IOM § 5.2.1.1.3).

Key Inspection Information

Despite the IOM’s requirement to include in an EIR whether an inspection was announced, FDA did not always include in the EIRs whether the inspection was announced. We determined that for 8 of the 68 inspections after FDA’s programmatic changes FDA did not include in the EIR whether the inspection was announced, and FDA could not locate documentation that indicated whether the inspections were announced.

FDA did not ensure that it recorded certain information in the EIR, such as whether an inspection was announced. However, in June 2020 after we started our audit, FDA added a required field to its inspection reporting and tracking system to track whether an inspection was announced. Because FDA took this action during our audit, there is no need for a recommendation. Without recording certain information in the EIR and tracking the number of announced and unannounced inspections, FDA was unable to provide the data to evaluate if there was an association between facility performance and whether an inspection was announced or unannounced.

²⁶ During the inspection, FDA noted eight observations, including the failure to timely recall batches that had confirmed out-of-specification results, a lack of adequate oversight for document destruction, and deficient procedures for the sampling and handling of reserve samples.

FDA COULD NOT PROVIDE DOCUMENTATION TO SUPPORT THAT LEAD INVESTIGATORS COMPLETED REQUIRED TRAINING BEFORE THEY CONDUCTED INSPECTIONS

FDA could not provide documentation to support that all lead investigators completed the required training before they conducted inspections. Specifically:

- two lead investigators did not complete required training before they conducted inspections and
- six lead investigators' training records did not include documentation showing that required training was completed.

Two Lead Investigators Did Not Complete Required Training Before They Conducted Inspections

FDA Policies and Procedures

FMD-13A outlines the qualifications and capabilities of FDA personnel who will be expected to lead international inspection activities, including foreign drug inspections. According to FMD-13A, to work in the role of lead investigator, FDA investigators are required to, among other requirements, complete several training courses.²⁷ Once the required training courses are completed, the investigator must pass the Level 1 Investigator Certification performance audit. After investigators complete required training courses and pass the performance audit, they are eligible for Level 1 Investigator Certification. According to FDA, investigators who received Level 1 Investigator Certification may conduct independent inspections in the role of lead investigator.²⁸

Lead Investigators Did Not Complete Training Before They Conducted Inspections

FDA did not ensure that all lead investigators completed the training requirements before they conducted inspections. Specifically, two investigators, who each conducted one inspection, did not complete the required training before they conducted the inspections as lead investigators.²⁹ We found the following:

²⁷ FDA investigators are required to complete training courses, including basic food and drug law, evidence development courses, an investigative interviewing course, a basic drug manufacturing quality control course, and an industrial sterilization course.

²⁸ According to FDA, investigators can conduct an inspection as a lead investigator prior to being certified if there is a certified investigator as part of the inspection.

²⁹ According to FDA, although the two employees did not have the proper documentation at the time of the inspection, FDA is "very confident in the investigators abilities to conduct inspections."

- One lead investigator who completed an inspection on August 28, 2018, did not complete the Level 1 Performance Audit and receive Level 1 Investigator Certification until June 14, 2019.³⁰
- One lead investigator completed an inspection on May 20, 2016, but did not complete the Level 1 Audit and Certification Program until 2017. According to FDA officials, this investigator had been conducting independent inspections prior to the Level 1 Performance Audit requirement, and FDA did not know why the employee did not complete the Level 1 Audit and Certification Program until 2017. FDA did not provide evidence that this employee would qualify as an experienced investigator.³¹

According to FDA, the investigators' supervisors are responsible for ensuring that the investigators are qualified to conduct inspections. FDA did not have written policies and procedures that require supervisors to verify that investigators assigned as lead investigators met training requirements to conduct foreign drug inspections. It is a vulnerability to have lead investigators conduct inspections before ensuring that they are qualified.

Six Lead Investigators' Training Records Did Not Include Documentation Showing That Required Training Was Completed

FDA Policies and Procedures

FDA policies state that the FDA Office of Training, Education, and Development tracks the completion for many training requirements through a system known as Pathlore. An FDA employee inputs information into Pathlore when an investigator completes required training courses, the Level 1 Performance Audit, and Level 1 Investigator Certification.³² FDA stated that its document retention policies require training documentation to be retained for 5 years after employees leave FDA.

³⁰ There were no other investigators or FDA employees who participated in the inspection.

³¹ The investigator was the only investigator who participated in the inspection. There was also a chemist who participated in the inspection.

³² When investigators' Pathlore records were missing evidence of a Level 1 Performance Audit or Level 1 Investigator Certification, we asked FDA to provide hardcopy evidence that the investigator passed the audit and obtained the certification.

Missing Investigator Training Documentation

FDA could not provide documentation to support that 6 of the 65 lead investigators for the inspections we reviewed completed the required training, passed a Level 1 Performance Audit, which is needed to obtain a Level 1 Investigator Certification.³³ Specifically, for:

- three investigators who each conducted one inspection, FDA could not provide documentation to support that the investigators completed all the required training courses; and
- three investigators who each conducted one inspection, FDA could not provide documentation that the employees completed the Level 1 Performance Audit and Level 1 Investigator Certification.³⁴

Of these six investigators, FDA stated that five qualify as experienced investigators, but FDA could not provide evidence to support that these investigators completed courses equivalent to the required training courses, completed the Level 1 Performance Audit, Level 1 Investigator Certification, or were recommended as experienced investigators by their supervisors.^{35, 36} Regarding the sixth investigator, FDA stated that the investigator qualified as a Generic Drug User Fee Amendments (GDUFA) investigator.³⁷ However, this investigator was not included on the listing of GDUFA investigators that FDA provided to us.

³³ The six lead investigators conducted six inspections: four inspections from 2016 through 2017 and two inspections from 2018 through 2019.

³⁴ For five of the six inspections, the lead investigator was the only investigator conducting the inspection (two of these inspections had an FDA microbiologist or chemist present at the inspection). For the remaining inspection, there were two investigators present. The second investigator was Level 1 certified at the time of the inspection.

³⁵ According to FDA, experienced investigators are investigators hired prior to January 1, 2002, who were not required to demonstrate competence through a Level 1 Performance Audit. Instead these investigators have to be recommended as experienced investigators by their supervisors. Although these investigators were not subject to a Level 1 Performance Audit, they are required to receive training courses equivalent to the current required training courses.

³⁶ We requested training records on March 17, 2020. If a lead investigator on an inspection covered by this audit left FDA after 2016, all training records requested fall within the 5-year documentation retention period and, therefore, should be available.

³⁷ In response to GDUFA, FDA hired four “cohorts” of individuals with prior experience in the pharmaceutical industry. GDUFA investigators hired in the first two cohorts went through a different training program and were not required to take the Level 1 Performance Audit. Later, FDA changed the GDUFA training requirements to align with the current requirement, and the third and fourth GDUFA investigator cohorts hired were required to take the Level 1 Performance Audit.

According to FDA, training records for these individuals could not be located. FDA officials informed us that since 2002 it has physically moved hardcopy records several times and made changes to its electronic training systems; therefore, some of these records have become misplaced in the process. FDA also noted that all six investigators were qualified to conduct and lead inspections because of their preceding years of experience. Without adequate documentation of investigator training or a recommendation by their supervisor, FDA could not accurately determine which investigators have the qualifications necessary to conduct inspections.

RECOMMENDATIONS

We recommend that the Food and Drug Administration:

- identify and implement additional ways to improve the timeliness of its foreign for-cause drug inspection process;
- consider streamlining the process for writing and reviewing EIRs to minimize potential delays due to unexpected events;
- conduct an analysis of the workloads of individuals responsible for: (1) determining final classification, (2) issuing warning letters, and (3) holding regulatory meetings, and address any potential issues identified by this analysis;
- implement policies and procedures to ensure that lead investigators assigned to inspections have completed the Level 1 Investigator Certification Process;
- ensure that supervisors review investigators' qualifications and document that they meet applicable training requirements when the investigator training records do not exist; and
- review the training records of the lead investigators that were outside the scope of the audit to verify that documentation supports either:
 - that the investigators completed the required training courses, Level 1 Performance Audit, and Level 1 Investigator Certification, or
 - that investigators are recommended as "experienced investigators" by supervisors and have completed training courses equivalent to the current required training courses.

FOOD AND DRUG ADMINISTRATION COMMENTS

In written comments on our draft report, FDA concurred with our recommendations. FDA stated that it is working to improve the timeliness of the overall foreign for-cause inspection process. Furthermore, pending approval by Congress, FDA stated that it has committed to goals regarding the timing of foreign facility followup inspections. FDA also stated that it is addressing ways to reduce the time spent writing and reviewing EIRs and that it is conducting a workload analysis for individuals responsible for determining final classification, issuing warning letters, and holding regulatory meetings. FDA stated that it will soon begin implementing a new system to better document and track the qualifications and Level 1 Certification status of investigators.

FDA also provided us written technical comments that we addressed, as appropriate. FDA's comments, excluding its technical comments, are included as Appendix B.

OTHER MATTERS

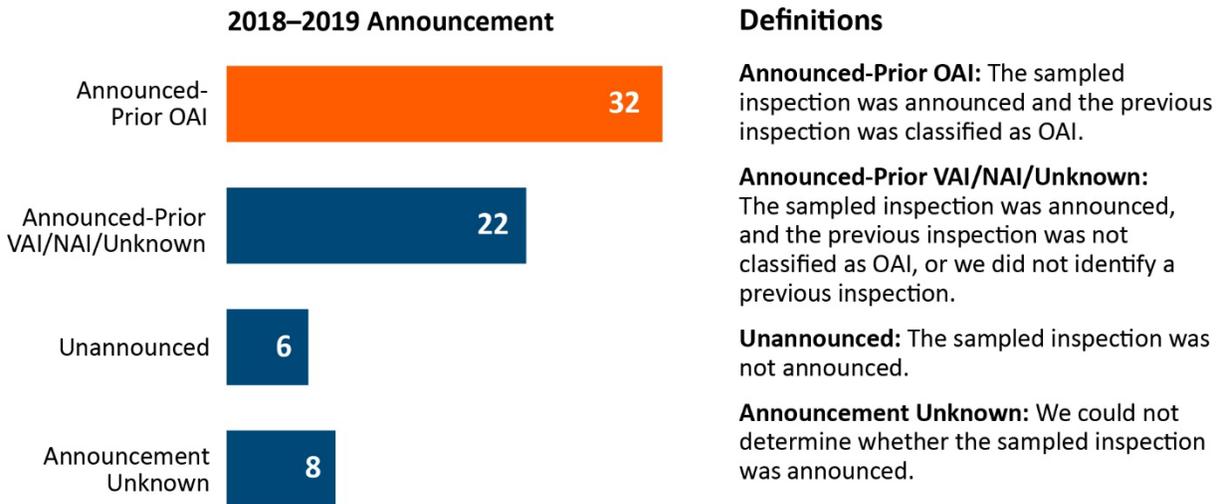
FDA ANNOUNCED FOREIGN FOR-CAUSE DRUG INSPECTIONS AT FACILITIES WITH A HISTORY OF CGMP VIOLATIONS 59 PERCENT OF THE TIME

FDA is not required to announce foreign for-cause drug inspections, but inspections may be announced at the discretion of the program division. If the program division believes announcing a facility inspection will facilitate the inspection process, then the program division should follow the procedures for announcing inspections under section 5.2.1.1 of the IOM. When deciding whether to announce an inspection, the program division considers the type of inspection and whether the facility meets specific criteria (IOM § 5.2.1.1.1). Specifically, FDA should consider whether the facility has a history of violations related to quality system or CGMP that resulted in an OAI classification, and the facility should have a history of making identified individuals and documents reasonably available at the time of the inspection (IOM §§ 5.2.1.1.2.1 and 5.2.1.1.2.2).³⁸

For the inspections we reviewed after the programmatic changes, FDA announced inspections at several facilities with prior OAI classifications in their most recent prior inspections. Specifically, FDA announced 54 foreign for-cause drug inspections after the programmatic changes; however, 59 percent of those inspections (32 of 54) had a violative CGMP inspection history (classified as OAI) (Figure 5 on the next page).

³⁸ The quality system helps ensure overall compliance with CGMP and internal procedures and specifications. This system includes the quality control unit and all its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports). It includes all product defect evaluations and evaluation of returned and salvaged drug products.

Figure 5: Inspection Initiations



For example, on November 14, 2017, FDA notified a foreign drug facility that it planned to conduct an onsite inspection at the facility in February 2018, even though the previous inspection at the facility resulted in an OAI classification and the issuance of a warning letter.³⁹

According to FDA officials, foreign inspections may be announced. FDA cited policies in its *Guide to International Inspections and Travel* (chapter 3, subchapter 302.1) that state that announced inspections are necessary when conducting international inspections due primarily to the potential waste of resources if the establishment is not operating or not producing the product in question, political sensitivities, availability of English-speaking personnel, local holidays, and other factors.⁴⁰

If FDA announces an inspection, a facility could prepare for that inspection by correcting or concealing deficiencies or destroying records prior to the inspection. If that occurs, investigators may not identify deficiencies and recommend corrective action that would aim to achieve continued compliance with CGMP. Congress and the Government Accountability Office (GAO) have expressed similar concerns. For example, Congress has expressed concerns related to the amount of time that FDA gives foreign drug facilities prior to arriving to conduct

³⁹ The warning letter cited two violations, including: (1) failure to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance and (2) failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

⁴⁰ *Guide to International Inspections and Travel* (Nov. 2002). Available online at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/foreign-inspections>. Accessed on Dec. 9, 2021.

inspections. During a Senate hearing on June 2, 2020, Senator Grassley stated, “12-weeks, common sense tells me, is plenty of time to doctor up a facility to make sure that it passes inspection.”⁴¹ Similarly, in January 2022, GAO reported, “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. 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.”⁴²

FDA REMOVED THE REQUIREMENT TO CONSIDER FACILITIES’ INSPECTION HISTORIES FROM ITS POLICIES WHEN DETERMINING WHETHER AN INSPECTION ANNOUNCEMENT IS APPROPRIATE

FDA officials said that the requirement in the 2018 version of the IOM to consider a facility’s inspection history applied across all commodities, including drug and device inspections. After our audit period, FDA amended the IOM by removing requirements related to determining whether an announced inspection is appropriate for foreign drug inspections. Specifically, the IOM no longer requires FDA to consider facilities’ inspection histories when determining whether an announcement is appropriate.⁴³

The Food and Drug Administration Reauthorization Act of 2017 (FDARA) added a new section of the FD&C Act, 704(h), which requires that, except for for-cause inspections, all foreign and domestic inspections of medical device facilities must be announced. Implementation of FDARA provisions required FDA to review its processes and standards “applicable to inspections of domestic and foreign device establishments.” When FDA revised its processes and standards, it more broadly eliminated the requirement to consider a facility’s inspection history when determining whether to announce an inspection for all types of facilities. This revision could potentially result in fewer unannounced inspections at foreign drug facilities.

⁴¹ Senate Committee on Finance, *COVID-19 and Beyond: Oversight of the FDA’s Foreign Drug Manufacturing Inspection Process* (Jun. 2, 2020). Available online at <https://www.finance.senate.gov/hearings/covid-19-and-beyond-oversight-of-the-fdas-foreign-drug-manufacturing-inspection-process?stream=top> (00:19:44). Accessed on Feb. 22, 2022.

⁴² *FDA Should Take Additional Steps To Improve Its Foreign Inspection Program*, GAO-22-103611 (Washington, DC: Jan. 2022). Available online at <https://www.gao.gov/assets/gao-22-103611.pdf>. Accessed on Feb. 28, 2022.

⁴³ When an inspection is announced, a facility can prepare for the inspection, and the results of the inspection may not be a true representation of the actual day-to-day conditions at the facility.

APPENDIX A: SCOPE AND METHODOLOGY

SCOPE

We reviewed all 64 foreign for-cause drug inspections that FDA conducted from January 1, 2016, through March 31, 2017, and all 68 foreign for-cause drug inspections conducted by FDA between January 1, 2018, through March 31, 2019. We selected these dates based on the timing of FDA's implementation of programmatic changes in 2017. These two periods allowed us to compare timeframes throughout FDA's foreign for-cause drug inspection process for similar periods prior to and after the programmatic changes.

We performed audit work from May 2019 through February 2022.

METHODOLOGY

To accomplish the audit objective, we:

- reviewed Federal laws and regulations, FDA's internal written policies and procedures, and industry guidance published by FDA regarding inspections of drug facilities and investigator qualifications;
- interviewed FDA personnel responsible for overseeing foreign for-cause drug inspections;
- validated data provided by FDA by:
 - interviewing FDA personnel responsible for maintaining the electronic data,
 - tracing electronic data to source documents, including EIRs and information from the inspection reporting and tracking system,
 - reconciling the number of inspections provided to published reports and other publicly available information, and
 - performing other procedures such as verifying that the data conformed to our request and that the data did not contain duplicates;
- calculated timeframes for various steps in the inspection and followup process—specifically, we:
 - determined whether an inspection was announced or unannounced and calculated how far in advance FDA announced the inspection to the firm (if applicable),
 - calculated how long it took investigators to complete the onsite inspection from the inspection start to end date,
 - calculated the final classification timeframe based on the final classification date and the inspection end date,

- determined how long it took FDA to issue a warning letter or import alert or to hold a regulatory meeting with a facility after the inspection end date, and
- calculated how long it took FDA to conduct a followup inspection at a facility when the sampled inspection resulted in a final classification of OAI and was not subject to an import alert from the date that FDA took action related to the sampled inspection;
- compared the calculated timeframes for the period before the programmatic changes to the calculated timeframes in the period after the programmatic change to determine whether any improvements had been made;
- reviewed inspection announcements, data, reports, and evidence of further actions taken to verify that inspections conformed to FDA's policies and procedures;
- interviewed FDA personnel responsible for conducting, overseeing, and managing drug investigator training and documentation;
- identified the lead investigator assigned to each foreign for-cause drug inspection to determine which investigator training records to review;
- reviewed records provided by FDA to determine if lead investigators had obtained the necessary trainings and certifications prior to leading a drug facility inspection;
- determined whether a lead investigator, who did not have evidence of certification or who was not certified, had a certified investigator with them during inspections; and
- discussed the results of our review with FDA officials.

We conducted this performance audit 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.

APPENDIX B: FDA COMMENTS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

DATE: April 13, 2022
TO: Christi A. Grimm, Inspector General
FROM: Director, Public Health Strategy and Analysis
SUBJECT: FDA's General Comments to OIG's Draft Report, "The Food and Drug Administration's Foreign For-Cause Drug Inspection Program Can Be Improved to Protect the Nation's Drug Supply" (A-01-19-01500)

Enclosed are the Food and Drug Administration's general comments to the Office of Inspector General's Draft Report, "The Food and Drug Administration's Foreign For-Cause Drug Inspection Program Can Be Improved to Protect the Nation's Drug Supply" (A-01-19-01500).

We appreciate the opportunity to review and comment on this draft report prior to publication.

Digitally signed by
Lisa B. Rovin -S
Date: 2022.04.13
13:10:14 -0400'
Lisa Rovin, J.D.
Director, Public Health Strategy and Analysis

Attachment

FDA's General Comments to the Office of Inspector General's Draft Report, "The Food and Drug Administration's Foreign For-Cause Drug Inspection Program Can Be Improved to Protect the Nation's Drug Supply" (A-01-19-01500)

The Food and Drug Administration (FDA) appreciates the opportunity to review and comment on this draft report.

Recommendation 1

FDA should identify and implement additional ways to improve the timeliness of its foreign for-cause inspection process.

FDA Response

FDA concurs with OIG's recommendation. FDA has identified areas where the timeliness of the overall foreign for-cause inspection process can be improved and are working to make progress in these areas. Furthermore, pending approval by Congress, FDA has committed to goals regarding timing of certain foreign for-cause inspections under reauthorization of the Generic Drug User Fee Act (GDUFA). Please see section VII - Facilities of the proposed GDUFA III commitment letter, which can be found at (<https://www.fda.gov/media/153631/download>).

Recommendation 2

FDA should consider streamlining the process for writing and reviewing EIRs to minimize potential delays due to unexpected events.

FDA Response

FDA concurs with this recommendation and is currently addressing ways to streamline and reduce the time spent writing and reviewing the establishment inspection reports (EIR). The expected increase in overall efficiencies should help minimize the impact of unexpected events on completing the EIR writing and reviewing process.

Recommendation 3

FDA should conduct an analysis of the workloads of individuals responsible for determining final classification, issuing warning letters, holding regulatory meetings, and address any potential issues identified by this analysis.

FDA Response

FDA concurs with OIG's recommendation. FDA is currently conducting a work-load analysis in accordance with the recommendation.

Recommendation 4

FDA should implement policies and procedures to ensure that lead investigators assigned to inspections have completed the Level 1 Investigator Certification Process.

FDA Response

FDA concurs with this recommendation and has implemented additional procedures for documenting training. For the longer term, FDA will soon begin implementing a new system to better document and track the qualification and Level 1 certification status of investigators. The investigator qualification procedures will ensure and document that investigators assigned to lead inspections have completed the Level 1 Investigator Certification Process along with other required training courses.

Recommendation 5

FDA should ensure that supervisors review investigators' qualifications and document that they meet applicable training requirements when the investigator training records do not exist.

FDA Response

FDA concurs with OIG's recommendation and will follow procedures for supervisors to verify ORA investigators' qualifications and that training requirements have been met if an investigator's training records are not available.

Recommendation 6

FDA should review the training records of the lead investigators that were outside the scope of the audit to verify that the documentation supports either that the investigators completed the required training courses, Level 1 Performance Audit, and Level 1 Investigator Certification, or that the investigators are recommended "experienced investigators" by supervisors and have completed training courses equivalent to the current required training courses.

FDA Response

FDA concurs with this recommendation but would note that FDA's goal is to adhere to our formal training processes to ensure Level 1 Investigator Certification. Supervisor verification would be reserved for exceptional circumstances, for example where an investigator's training pre-dated the current training scheme. FDA is conducting a review of past training records to verify that all required training has been completed and documented. If there are any instances of missing documentation, these will be addressed.