U.S. GOVERNMENT ACCOUNTABILITY OFFICE

441 G St. N.W.
Washington, DC 20548

January 22, 2020

The Honorable Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

Following the December 10, 2019, hearing held by the Subcommittee on Oversight and Investigations, *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program*, we received questions for the record from Subcommittee members. This correspondence provides our responses to these questions. If you or your staff have any questions or need additional information, please contact me at 202-512-7114 or DeniganMacauleyM@gao.gov.

Sincerely yours,

Mary Denigan-Macauley
Director, Health Care

Enclosure

cc: The Honorable Greg Walden, Ranking Member, Committee on Energy and Commerce
The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations
The Honorable Brett Guthrie, Ranking Member, Subcommittee on Oversight and Investigations

Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program"

December 10, 2019

Mary Denigan-Macauley, Ph.D
Director, Health Care,
Government Accountability Office

The Honorable Brett Guthrie (R-KY)

1. **GAO has recommended that FDA take steps to improve the accuracy and completeness of information in its catalog of drug firms subject to inspection. In 2010 and 2016 reports, GAO found that FDA took steps to improve information accuracy. What steps remain for FDA to improve the accuracy and completeness of information in its catalog of drug firms subject to inspection?**

We have had concerns since our 1998 report about the information FDA maintains on drug establishments subject to inspection and have made related recommendations.

In our 2010 report we described steps FDA was taking to improve the information in its databases that identify registered foreign establishments and products imported to the United States and are used to create a catalog of establishments subject to inspection. For example, we reported that FDA began requiring registration information to be submitted electronically. We also reported that FDA contracted with external organizations to conduct site visits to verify the existence of foreign establishments registered with the agency and verify the products manufactured by those establishments. Finally, we reported that FDA initiated a project to identify and remove duplicate records from its import database.

In our 2016 report we described additional steps FDA had taken to improve the accuracy and completeness of its catalog of foreign drug establishments. First, we reported that, in accordance with the Food and Drug Administration Safety and Innovation Act, FDA began requiring establishments to provide a unique facility identifier during their annual registration process. We reported that FDA then used this number to automatically validate registration information using a Dun and Bradstreet database. We also reported that FDA added two foreign inventory coordinators to incorporate foreign registrations and annual updates into FDA's master inventory and established a data governance board to define standards, best practices, and policies for inventory data management.

Despite these efforts, we still have concerns about the accuracy and completeness of the information FDA maintains on drug establishments subject to inspection. In our 2019 testimony we reported that recent declines in the count of foreign inspections conducted by FDA were due,

in part, to data inaccuracies that affected its process for selecting establishments for inspection. Specifically, we noted that as part of its initiative to inspect approximately 1,000 foreign establishments that lacked an inspection history, FDA selected establishments for inspection but then determined that a sizeable percentage were not actually subject to inspection. FDA has noted continued challenges related to maintaining complete and accurate information on foreign drug establishments. For example, the agency reported that in fiscal year 2018 it removed approximately 50 percent of registered South Korean drug manufacturing establishments from its catalog because they did not have product in the U.S. market and did not need to be registered.

2. **My understanding is that the GAO plans to evaluate the FDA's risk-based selection model that is used to prioritize inspections. What questions does GAO have about the risk-based selection model? As part of the risk-based selection model evaluation, will GAO assess the potential benefits of using alternative methodologies or models, such as a predictive risk model?**

To prioritize establishments for surveillance inspections—that is, inspections used to ensure drugs already on the market are manufactured in compliance with FDA regulations—FDA applies a risk-based site selection model to its catalog of establishments subject to inspection. The model is used to identify those establishments (both domestic and foreign) that, based on the characteristics of the drugs being manufactured, pose the greatest potential public health risk should they experience a manufacturing defect. This model analyzes several factors—including inherent product risk, establishment type, inspection history, and time since last inspection—to develop a list of establishments that FDA considers to be a priority for inspection.

In our 2019 testimony we reported that a majority of foreign and domestic inspections from fiscal year 2012 through 2018 were surveillance inspections. Given FDA's history of challenges related to the management of information on drug establishments, reviewing the quality of information underlying the model used to select establishments for surveillance inspections could be important to ensure that the risks of foreign and domestic establishments are assessed in equivalent ways. We are exploring methodologies to allow us to further explore FDA's risk-based model. We would be happy to brief you on our scope, methods, and time frames, once established.

3. **Has the FDA provided any data or studies to the GAO that support conducting preannounced inspections in foreign drug inspections over unannounced or short notice inspections?**

In our 2008 report we found that, unlike domestic inspections which are almost always unannounced, FDA generally provides advanced notice of inspections to foreign establishments.

In our 2019 testimony, we reported that FDA stated that it generally preannounces its foreign inspections to avoid wasting resources and to obtain the assistance of foreign establishments when making travel arrangements. FDA did not provide us with data on the frequency with which foreign inspections are preannounced and unannounced, nor the amount of notice that is provided when inspections are preannounced. According to FDA officials, FDA does not have these data because FDA's database does not include a data field to track whether an inspection is

announced or unannounced. However, officials told us that the agency plans to include a new data field that would enable the agency to track whether an inspection is preannounced or unannounced.

Based on our interviews with investigators in FDA's dedicated foreign drug cadre and investigators based in its China and India offices, we reported in our 2019 testimony that a downside to preannounced inspections is that the advanced notice provides establishments time to fix some problems before the investigator arrives. FDA expects establishments to be in a constant state of compliance with current good manufacturing practice (CGMP) regulations, and several investigators told us that an investigator is more likely to see the true operating environment of an establishment during an unannounced inspection. Although most of the investigators we interviewed told us that unannounced inspections are preferable to preannounced inspections, some investigators said that it was still possible to identify serious deficiencies during a preannounced inspection.

4. **In 2016, GAO reported that FDA had yet to determine whether the foreign offices meaningfully contribute to drug safety, because FDA has no formal process for assessing the offices' contributions. What are the GAO's recommendations for FDA to track foreign office accomplishments to assess the extent to which those offices help ensure drug safety?**

GAO has made two recommendations directing FDA to assess whether the foreign offices are fully able to meet their mission of helping to ensure the safety of imported drugs.

- First, in a 2010 report, GAO recommended that FDA develop a set of performance goals and measures that can be used to demonstrate the foreign office contributions to the long-term outcomes related to the regulation of imported products, and that foreign office activities are coordinated with the centers and Office of Regulatory Affairs.

- Second, in a 2016 report, GAO recommended that FDA assess the effectiveness of its foreign offices' contributions by systematically tracking information to measure whether the offices' activities specifically contribute to drug safety-related outcomes, such as inspections, import alerts, and warning letters. We have designated this recommendation as a "priority recommendation," meaning that GAO believes this recommendation warrants priority attention from the heads of key department and agencies, and we will continue to monitor the agency's progress towards implementing this recommendation.

While FDA has not fully implemented these recommendations, it has taken some actions in response. Specifically, as of June 2018, FDA stated that it has developed new performance measures for the foreign offices as well as a monitoring and evaluation plan. It has also strengthened communications and collaboration between the foreign offices and other offices within FDA and conducted an assessment of the foreign offices to help set their objectives and ensure the right balance of personnel, skillsets, and resources. Despite this progress, FDA still needs to continue to develop intermediate outcomes to link with final outcomes to fully implement these recommendations. We believe it is important for FDA to track these types of outcomes, and for the agency to determine how their performance measures—whether the

existing ones or those currently being tested—can be used to demonstrate such results. Having performance measures that demonstrate results-oriented outcomes will better enable FDA to meaningfully assess the foreign offices' contributions to ensuring drug safety.

5. **In its 2010 report, the GAO recommended that FDA develop a strategic workforce plan to help recruit and retain foreign office staff. FDA released such a plan in March 2016, but there are still longstanding vacancies in the foreign offices. Your written testimony states that these vacancies raise questions about the implementation of FDA's workforce plan. What were the problems in the implementation?**

    a. **In addition to implementation issues, do you have any additional comments on FDA's workforce plan?**

    b. **What does FDA need to do to improve retention and management of inspectors, particularly in foreign offices?**

In our 2010 report, we recommended that FDA develop a strategic workforce plan for the foreign offices to help ensure that the agency is able to recruit and retain staff with the experience and skills necessary for the foreign offices and reintegrate returning staff into FDA's domestic operations. As you state, FDA finalized its plan in March 2016, which included key activities to be performed, such as establishing a succession plan for anticipated vacancies, among other things.

In addition, in our 2016 report, we recommended that FDA establish goals to achieve the appropriate staffing level for its foreign offices, which would include separating foreign office vacancies from overall vacancy rates for the Office of International Programs (now Office of Global Policy and Strategy) and setting goals by position type. In June 2018, FDA reported it had separated foreign office vacancies from the Office of International Programs-wide vacancy rate and also set staffing goals by position type, as we recommended. FDA also took other actions, including pay incentives to recruit and retain foreign office staff as well as locality pay for those deployed overseas, and it temporarily assigned staff to short-term rotations in the foreign offices.

However, as we stated in our 2019 testimony, while vacancy rates in investigators assigned to FDA's foreign offices have decreased over time, these vacancies persist. We found that, as of November 2019, FDA's China office had a 30 percent vacancy rate, while FDA's India office had a 33 percent vacancy rate. FDA officials told us that one challenge in recruiting investigators for the foreign offices is that well-qualified investigators for those positions need foreign inspection experience. Therefore, the agency recruits investigators who have experience conducting foreign inspections from the pool of domestic investigators in FDA's Office of Regulatory Affairs (ORA), including those in FDA's foreign drug cadre. However, the vacancies we identified among both the cadre and this larger group of ORA investigators can influence the number of staff available to apply for positions in the foreign offices. Further, while FDA recently filled several of the vacancies for domestic investigators, officials told us that new investigators are not typically used for foreign inspections until they have been with the agency for 2 to 3 years. Therefore, it may be many years before a recently hired investigator is eligible to

detail to a foreign office. In addition, the effort to fill vacancies is continuous, as FDA full-time foreign office staff are posted overseas for 2-year assignments, and staff can also be assigned to the foreign offices on temporary duty assignments for up to 120 days.

In addition to these challenges with hiring and filling vacancies, we also noted in our 2019 testimony that investigators face certain challenges when they conduct foreign inspections, such as long hours and a lack of flexibility with overseas travel for ORA investigators based in the United States. We plan to continue to examine these issues in our ongoing review.

The Honorable H. Morgan Griffith (R-VA)

1. **Besides banning imports to the United States, how can FDA protect the supply chain when a foreign facility refuses an FDA inspection? When an importation ban is placed on a manufacturer, what does FDA do about API it has already introduced into the United States?**

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) gave FDA new authorities to address challenges related to an increasingly global drug supply chain. Specifically, Section 707 of FDASIA allows the agency to deem adulterated any drug that is manufactured in an establishment that delays, limits, denies, or refuses to permit FDA entry or inspection. In October 2014, FDA issued final guidance on the types of conduct and circumstances that the agency considers to constitute delaying, denying, limiting, or refusing a drug inspection, which could result in a drug being deemed adulterated.[1] FDA's final guidance specifies that the delaying, denying, limiting, or refusing a request for records in advance or in lieu of an inspection may also result in a manufacturer's drugs being deemed adulterated. Drugs that have been deemed adulterated are refused entry into the United States.

We have not otherwise examined the types of actions that FDA is authorized to take against a foreign establishment if it refuses an FDA inspection, or what happens to drug products that have already been introduced into the United States when an importation ban is placed on the establishment manufacturing those products. We would be happy to discuss future work in this area with your staff.

[1]FDA guidance defining the types of actions, inaction, and circumstances that FDA considers to constitute a delay, denial, limit, or refusal to entry or inspection is publically available on FDA's website: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/circumstances-constitute-delaying-denying-limiting-or-refusing-drug-inspection