United States Senate

WASHINGTON, DC 20510

November 10, 2020

The Honorable Stephen Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MS 20993

Dear Commissioner Hahn:

We write to request information regarding inspections of foreign drug manufacturing facilities. These inspections, previously required and conducted by the Food and Drug Administration (FDA) were suspended in March 2020 as a result of the coronavirus disease 2019 (COVID-19) pandemic and have not yet resumed, with the exception of some mission-critical inspections.[1] It is essential that FDA has the tools it needs to safeguard the quality of all pharmaceutical ingredients imported to the United States, and the health and safety of its employees once inspections resume.

FDA is responsible for maintaining the safety, effectiveness, quality, and security of drugs produced both in the United States and abroad.[2] Under its normal operating procedures, FDA performs inspections of manufacturing facilities within the United States and across the globe to ensure safety and efficacy.[3] FDA's inspectional activities include "pre-approval" inspections, routine "surveillance" inspections, and "for-cause" inspections to investigate a specific problem that has come to FDA's attention.[4] These inspections ensure manufacturers are adhering to standards that the federal government has identified as essential to protecting the health and safety of Americans.

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[1] U.S. Food and Drug Administration, Guidance for Industry, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency: Questions and Answers," August 2020, https://www.fda.gov/media/141312/download

[2] U.S. Food and Drug Administration, "FDA Fundamentals," https://www.fda.gov/about-fda/fda-basics/fda-fundamentals

[3] U.S. Food and Drug Administration, "Inspection Classification Database," September 17, 2020, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database

[4] U.S. Food and Drug Administration, "Post-Approval and Surveillance Inspection Programs for Pharmaceutical Manufacturers," 2012, https://www.fda.gov/media/88492/download

However, as a result of the COVID-19 pandemic, FDA is no longer conducting many of these inspections for foreign manufacturing facilities. On March 10, 2020, FDA announced that it would be "postponing most foreign inspections… effective immediately."[5] Currently, only "mission critical" pre-approval and for-cause inspections outside of the United States are being conducted, and only on a case-by-case basis.[6] FDA loosely defines mission critical inspections as those for products "used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute," or "have received breakthrough therapy designation or regenerative medicine advanced therapy designation," and it remains unclear what products may fall into this category.[7] Routine surveillance inspections have been postponed entirely.[8] In some cases, any inspections that are being performed are only done remotely, or by simply requesting records and other information directly from facilities and other inspected entities"[9] Even some "for-cause" inspections, have been postponed.[10] The number of foreign inspections conducted by FDA declined by over 60% in 2020.[11] To address increased risk related to this decline, FDA claims that it is increasing its use of other tools such as "physical examinations of products arriving at U.S. borders or product sampling and testing before release into commerce."[12] However, FDA's ability to keep pace with the huge number of imports arriving in the United States has long been questioned, and the effectiveness of such tools in lieu of in-person inspections is unclear.[13]

The continued postponement of inspections of foreign manufacturing facilities could pose a danger to the public health of the United States. The failure of foreign manufacturing facilities to comply with regulatory requirements has allowed low-quality and unsafe products to enter circulation in the United States, resulting in a number of large-scale drug quality issues, including the 2008 heparin contamination scandal, in which over 240 people died.[14] More

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[5] U.S. Food and Drug Administration, "Coronavirus Disease 2019 Update: Foreign Inspections," March 10, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections

[6] U.S. Food and Drug Administration, Guidance for Industry: "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency: Questions and Answers," August 2020, https://www.fda.gov/media/141312/download

[7] *Id.*

[8] U.S. Food and Drug Administration, "Coronavirus Disease 2019 Update: Foreign Inspections," March 10, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections.

[9] *Id.*

[10] U.S. Food and Drug Administration, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers," August 2020, https://www.fda.gov/media/141312/download

[11] U.S. Food and Drug Administration, "Inspections Data Dashboard," https://datadashboard.fda.gov/ora/cd/inspections.htm

[12] U.S. Food and Drug Administration, "Physical Examinations Of Products Arriving At U.S. Borders Or Product Sampling And Testing Before Release Into Commerce," August 2020, https://www.fda.gov/media/141312/download

[13] Washington Post, "FDA Inspectors Not Keeping Pace With Imports," Brad Racino, October 22, 2011, https://www.washingtonpost.com/national/health-science/fda-inspectors-not-keeping-pace-with-imports/2011/09/19/gIQAITwo7L_story.html

[14] United States-China Economic and Security Review Commission, "2019 Annual Report to Congress, Chapter 3, Section 3: Growing U.S. Reliance on China's Biotech and Pharmaceutical Products," November 2019, https://www.uscc.gov/sites/default/files/2019-11/Chapter%203%20Section%203%20-

recently, the FDA found N-Nitrosodimethylamine, a known carcinogen, in the popular blood pressure medicine valsartan.[15] The contaminant was traced back to one of the largest foreign pharmaceutical ingredient manufacturers, but only after the drug was sold to millions of people in twenty-three countries.[16] This discovery is particularly concerning, given the United States' overreliance on foreign sources of key pharmaceutical products.[17] Only 28% of facilities manufacturing active pharmaceutical ingredients (API) used in drugs and 47% of facilities manufacturing finished dosage forms (FDF) of drugs for the U.S. market are located in the United States.[18] With such a significant amount of drugs and drug ingredients arriving from abroad, it is imperative that the FDA take all steps necessary to ensure drug quality and safety.

We are additionally concerned about the potential risk to FDA employees once in-person, foreign inspections resume. Many countries around the world, including the United States, are still struggling to contain the spread of COVID-19,[19] meaning that FDA employees traveling to inspect facilities abroad will be increase their risk of exposure and their health. While these inspections are crucial, FDA must also take all necessary precautions to protect the health and safety of its employees who conduct in-person inspections once they resume.

We are concerned that, absent proper oversight of our drug supply chain and the overseas facilities manufacturing products millions of Americans rely on, patients will face an increased risk of drug contamination or other problems with quality, purity, or potency. We have introduced comprehensive legislation, the *U.S. Pharmaceutical Supply Chain Defense and Enhancement Act,* which would provide the federal government with additional information regarding the nation's drug supply chain.[20] These enhanced authorities will allow the country to better protect and ensure the health and safety of imported drug products. Furthermore, we want

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%20Growing%20U.S.%20Reliance%20on%20China%E2%80%99s%20Biotech%20and%20Pharmaceutical%20Products.pdf.

[15] Bloomberg, "Pentagon Sees Security Threat in China's Drug-Supply Dominance," Anna Edney, August 5, 2019 https://www.bloomberg.com/news/articles/2019-08-05/pentagon-sees-security-threat-in-china-s-drug-supply-dominance

[16] *Id*.

[17] United States-China Economic and Security Review Commission, "2019 Annual Report to Congress, Chapter 3, Section 3: Growing U.S. Reliance on China's Biotech and Pharmaceutical Products," November 2019, https://www.uscc.gov/sites/default/files/2019-11/Chapter%203%20Section%203%20-%20Growing%20U.S.%20Reliance%20on%20China%E2%80%99s%20Biotech%20and%20Pharmaceutical%20Products.pdf

[18] Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program, December 10, 2019. Testimony of Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, https://www.fda.gov/news-events/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019 ; Active pharmaceutical ingredients are the raw chemical components of drugs that "furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease." (World Health Organization, "Definition of Active Pharmaceutical Ingredient," July 2011.)

[19] Washington Post, "Coronavirus cases hit records in Europe, surpassing U.S. numbers, Michael Birnbaum, October 15, 2020, https://www.washingtonpost.com/world/europe/covid-europe-records/2020/10/15/0126c256-0ee7-11eb-b404-8d1e675ec701_story.html

[20] Press Release, "Warren, Smith Introduce Legislation to Boost U.S. Pharmaceutical Manufacturing Capacity and End Over-Reliance on Foreign Countries for Critical Drugs," July 2, 2020, https://www.warren.senate.gov/newsroom/press-releases/warren-smith-introduce-legislation-to-boost-us-pharmaceutical-manufacturing-capacity-and-end-over-reliance-on-foreign-countries-for-critical-drugs; Congress.gov, "S.4175, U.S. Pharmaceutical Supply Chain Defense and Enhancement Act," https://www.congress.gov/bill/116th-congress/senate-bill/4175/text

to ensure that the FDA is taking all precautions to protect staff who are performing investigations abroad.

In order to better understand how Congress can support FDA's mission of protecting public health in the United States and ensuring the safety of imported drug products while also ensuring the safety of FDA employees conducting inspections during the COVID-19 pandemic, we request answers to the following questions no later than November 24, 2020.

1. How many foreign drug inspections has FDA conducted since March 10, 2020?
    a. Please provide this information by type of inspection and the date it was performed.
    b. To what extent have these inspections identified unsafe products or manufacturing practices?
2. How many scheduled foreign drug inspections have been postponed or eliminated since March 10, 2020? Please provide this information by type of inspection.
3. Please describe in detail the alternative approaches that FDA is using to ensure quality in cases where foreign drug inspections are postponed or canceled.
4. Will FDA retroactively conduct any foreign drug inspections it was forced to skip as a result of the pandemic? If so, when and how?
5. FDA has stated that it considers several factors when determining what type of inspection would be considered "mission critical."[21] Please provide a detailed explanation of each of these factors.
6. What factors will FDA consider to determine when it is safe to resume its full inspection schedule?
7. What safety measures have been implemented to protect FDA employees during inspections that are being conducted in-person?
8. What additional resources are needed by FDA to ensure that the agency is able to adequately conduct its foreign drug inspections during the pandemic?

Sincerely,

Elizabeth Warren
United States Senator

Tina Smith
United States Senator

[21] U.S. Food and Drug Administration, "Coronavirus Disease 2019 Update: Foreign Inspections," March 10, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections