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United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

June 27, 2019

VIA ELECTRONIC TRANSMISSION

The Honorable Alex Azar
Secretary
Department of Health and Human Services

Dr. Norman Sharpless
Acting Commissioner
Food and Drug Administration

Dear Secretary Azar and Acting Commissioner Sharpless:

For decades, safe and affordable drugs have been for sale across our border in Canada, as well as in the United States. I've pressed FDA on importation policies and introduced legislation to help American consumers purchase those drugs. With increasing prescription drug costs, it is important that Americans have options for their much-needed medication. However, unbeknownst to many consumers, the majority of the active pharmaceutical ingredients (API) in drugs they take are produced not in Canada or the U.S., but in China and India. According to recent news reports and a GAO report highlighting safety and quality concerns at foreign drug manufacturing facilities, 80 percent of API are produced abroad, the majority in China and India; however, the FDA only inspected one in five registered human drug manufacturing facilities abroad last year.[1]

This committee has an obligation to ensure that the Food and Drug Administration (FDA) upholds its responsibility to protect the public's health by properly overseeing the nation's drug supply and ensuring that the drugs Americans use are safe and effective. I am concerned that the FDA's foreign drug inspection program in China and India is not sufficient to identify and address key risks to the health and safety of Americans who rely on these drugs.[2]

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[1] Katherine Eban, *Americans Need Generic Drugs. But Can They Trust them?*, THE NEW YORK TIMES (May 11, 2019), *available at* https://www.nytimes.com/2019/05/11/opinion/sunday/generic-drugs-safety.html. *See also,* U.S. Gov't Accountability Off., GAO-17-143, DRUG SAFETY: FDA HAS IMPROVED ITS FOREIGN DRUG INSPECTION PROGRAM, BUT NEEDS TO ASSESS THE EFFECTIVENESS AND STAFFING OF ITS FOREIGN OFFICES 1 (Dec. 2016). Didi Martinez, Brenda Breslauer & Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India,* NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at* https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.

[2] Didi Martinez, Brenda Breslauer & Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India,* NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at* https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.

For example, a recent New York Times article published in May of 2019 calls into question the quality, safety and reliability of brand and generic drugs made overseas.[3] The article chronicles a former FDA consumer safety officer's findings while inspecting foreign manufacturing plants in both China and India from 2012-2018.[4] During the course of his six years in those countries, he discovered fraud and deception in 67 of the 86 drug manufacturing plants that he inspected.[5] He routinely uncovered hidden laboratories, fake quality-control, defective sterilization machines and toxic impurities.[6] Equally alarming, the article outlines how, from 2013-2018, the FDA downgraded the regulatory sanctions against more than 100 Indian plants, changing the designation from "official action indicated" to "voluntary action indicated."[7]

An additional news article from NBC News, also published in May of 2019, highlights a different former FDA inspector who also spent time in China and India inspecting manufacturing facilities.[8] One plant in Linhai, China, had numerous issues, including anomalies in testing and "unknown impurities." The inspector recommended a warning letter to the facility which would bar it from gaining approvals to produce new drugs at the facility. The FDA reportedly overruled his recommendation.[9] After public criticism of how the FDA handled this case, the FDA said it would have been "unlikely" to catch the impurities at the source of the recall during a routine inspection and that, "our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise."[10]

A Government Accountability Office (GAO) report in December of 2016 revealed that the number of foreign drug facilities that have never been inspected by FDA inspectors was "about 1,000 of the approximately 3,000" foreign manufacturing facilities.[11] Moreover, for fiscal year 2017, the report identified 189 of the 572 facilities in India and 243 of the 535 facilities in China that "may never have been inspected."[12] Lastly, the GAO report detailed, "to address this persistent concern, the agency plans to inspect all establishments in its catalog with no prior surveillance inspection history over the next 3 years (approximately one-third each year), beginning in fiscal year 2017."[13]

Despite the serious concerns with manufacturing quality in China and India, the FDA's data suggests that it does not seem to have sufficiently enhanced scrutiny of those countries. The

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[3] Katherine Eban, *Americans Need Generic Drugs. But Can They Trust them?*, THE NEW YORK TIMES (May 11, 2019), *available at* https://www.nytimes.com/2019/05/11/opinion/sunday/generic-drugs-safety.html.
[4] *Id.*
[5] *Id.*
[6] *Id.*
[7] *Id.*
[8] Didi Martinez, Brenda Breslauer & Stephanie Gosk, *Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India*, NBC NEWS (May 10, 2019, 1:01 PM EDT), *available at* https://www.nbcnews.com/health/health-news/tainted-drugs-ex-fda-inspector-warns-dangers-u-s-meds-n1002971.
[9] *Id.*
[10] *Id.*
[11] DRUG SAFETY, *supra* note 1, at 21.
[12] *Id* at 45.
[13] *Id* at 21.

FDA/CDER Office of Pharmaceutical Quality report from May 2019 suggests that the percentage of inspections in those two countries (22 percent) is on par with the number of facilities in those countries (23 percent)—not an outcome that would suggest increased scrutiny given the reported problems.[14]

The news articles and GAO report are troubling. In order to better understand the scope and nature these issues, please provide written responses to the following questions no later than July 17, 2019:

1. How many manufacturing plants in China and India currently manufacture drugs or APIs intended for the U.S. market?

    a. For each facility, if the facility produces final dosage form drugs, please provide a list of drugs and the corresponding NDAs and ANDAs.
    b. For each facility, if the facility produces API, please provide the name of the API as well as the associated NDAs and ANDAs for the finished dosage form using that API.

2. Please provide a list of all registered manufacturing facilities, either for API or final dosage form drugs, located outside of the United States. In addition, for all drug manufacturing facilities currently registered with the FDA in the United States, China, and India, please provide the following information for all inspections from 2010 to the present:

    a. Facility identifier;
    b. Whether the facility is an API or final dosage form facility;
    c. The API or final dosage form that is manufactured;
    d. Country where the facility is located;
    e. The date of each inspection;
    f. Inspection type;
    g. Whether the inspection was unannounced;
    h. Whether the inspection was conducted by an in-country inspector or an inspector who travelled from the United States or another country;
    i. The initial recommendation of the inspector;[15]
    j. The final FDA recommendation;[16] and a
    k. Description of the resolution to FDA's concerns.

[14] U.S. FOOD & DRUG ADMIN., REPORT ON THE STATE OF PHARMACEUTICAL QUALITY 4, 6 (2019), *available at* https://www.fda.gov/media/125001/download.
[15] This request would include official action indicated, voluntary action indicated, and no action indicated results.
[16] *Id*.

3. If a foreign pharmaceutical manufacturing plant used subcontractors or imports API or dosage from other plants, does the FDA inspect these subcontractors or other plants before the primary plant is approved to export to the United States? If not, why not?

4. What criteria does the FDA use to determine which facilities to inspect for an initial inspection? In addition, does a change in ownership trigger a subsequent inspection? Do the criteria differ for API and finished dosage form facilities? Please explain.

5. After the FDA identifies problems at a facility, what steps does the FDA take to ensure that problems are corrected? For example, does the FDA conduct follow-up inspections to ensure that corrective action has been taken? If so, how often are follow-up inspections made to ensure compliance with FDA safety standards? Please provide all records relating to follow-up inspections at manufacturing facilities in China and India from 2010 to the present to the extent they are not covered by Question 2.

6. Does the inspection process in China and India differ from U.S.-based inspections? If so, how and why? In addition, does the approach differ for API and finished dosage form facilities?

7. Please explain the FDA's review process and grading criteria in changing a foreign manufacturing plant designation from "official action indicated" to "voluntary action indicated." In addition, since 2010 to the present, please provide all instances of "official action indicated" being downgraded to "voluntary action indicated" and the rationale for those changes.

8. With regards to the 1,000 foreign manufacturing facilities that the GAO found had not been inspected as of December 2016, how many have been inspected since then? Please provide all records relating to the inspection findings for each facility to the extent they are not covered by Question 2. In addition, has the FDA changed any of its policies to increase the inspection rate at foreign facilities to ensure compliance with safety protocols? If so, please explain. If not, why not?

9. How many FDA personnel and investigative personnel have been stationed in China and India from 2010 to the present? How does it compare to FDA's planned staffing levels?

10. What is the average cost for a foreign inspection for fiscal years 2010-2019?

I anticipate that your written reply and most responsive documents will be unclassified. Please send all unclassified material directly to the Committee. In keeping with the requirements of Executive Order 13526, if any of the responsive documents do contain classified information, please segregate all unclassified material within the classified documents, provide all unclassified information directly to the Committee, and provide a classified addendum to the Office of Senate Security. Although the Committee complies with all laws and regulations governing the handling of classified information, it is not bound, absent its prior agreement, by any handling restrictions.

Thank you in advance for your prompt attention to these matters. Should you have any questions, please contact Joshua Flynn-Brown of my Committee staff at (202) 224-4515.

Sincerely,

Charles E. Grassley
Chairman
Committee on Finance