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ONE HUNDRED SIXTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225–2927
Minority (202) 225–3641

February 13, 2019

The Honorable Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Gottlieb:

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee continues to examine the Food and Drug Administration's (FDA) ability to ensure the safety of the nation's drug supply. We are writing to request a briefing on a series of recalls that appear to involve drugs manufactured overseas that may have been contaminated with trace amounts of known carcinogens.

Beginning in July 2018, there have been at least 15 recalls issued for a variety of angiotensin II receptor blockers (ARB),[1] which are generally used to treat high blood pressure. The roots of this ever-expanding series of recalls appear to be related to at least two foreign drug manufacturing facilities: Zhejiang Huahai Pharmaceutical in China and Hetero Labs in India.[2] Inspection reports from these two factories indicate serious problems at both factories, even before the carcinogens were detected.[3] For example, FDA inspectors found that workers at the Zhejiang Huahai Pharmaceutical plant repeatedly failed to follow up on testing anomalies in drug batches, and discovered equipment that had fraying gaskets, rusted screws, and missing pieces, as early as 2017.[4] On September 28, 2018, drugs manufactured at this plant were placed under an import alert by FDA, which is intended to stop all finished drugs and active

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[1] U.S. Food and Drug Administration, Recalls, Market Withdrawals, and Safety Alerts (www.fda.gov/Safety/Recalls/default.htm) (accessed Feb. 12, 2019).

[2] *Blood Pressure Drug Recall: FDA Investigates Foreign Plants That Made Drugs With Cancer-Causing Impurities*, USA Today (Jan. 25, 2019).

[3] *Id.*

[4] *Id.*

pharmaceutical ingredients from legally entering the United States.[5] On January 25, 2019, FDA warned of a shortage of ARBs, and "that other types of products [to treat high blood pressure] may fall into shortage soon."[6]

Also, on January 25, FDA reported that it had identified the contaminants, N-Nitrosodimethylamine and N-Nitrosodiethylamine.[7] The agency stated the contaminants may be created when "specific chemicals and reaction conditions are present . . . and may also result from the reuse of materials, such as solvents."[8] FDA said those byproducts would not have been detected in routine inspections because the process depends on scientists knowing which chemical intruders are likely to be accidentally created during the process, knowledge that they said regulators and companies lacked until recently.[9] However, a chief executive of a company that chemically validates drugs stated that drug manufacturers knew or should have known of the contamination.[10]

The Committee has long held an interest in FDA's ability to oversee the manufacturing of finished drug products (FDPs) and active pharmaceutical ingredients (APIs) intended for the U.S. drug supply. To that end, the Committee has held numerous hearings over the years to assess whether FDA has the resources and capabilities in place to accomplish adequately this critical mission. In many of those hearings, experts testified that FDA's inability to inspect foreign firms with adequate frequency placed the U.S. drug supply at risk. In response to this, the Committee acted in 2012 to give FDA the authority and flexibility to inspect foreign firms on a risk-based schedule, allowing the agency to prioritize facilities that had not been subject to a recent inspection and that posed the highest risk.

Despite this, in December 2016, the Government Accountability Office (GAO) reported that almost 1,000 foreign drug facilities, or nearly one-third of all foreign drug facilities that

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[5] U.S Food and Drug Administration, FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan (www.fda.gov/Drugs/DrugSafety/ucm613916.htm) (accessed Feb. 12, 2019); U.S Food and Drug Administration, Import Alert 66-40. (www.accessdata.fda.gov/cms_ia/importalert_189.html) (accessed Feb. 12, 2019).

[6] *FDA warns of common blood pressure medicine shortage due to recalls,* CNN (January 26, 2019).

[7] U.S. Food and Drug Administration, Statement from Commissioner Scott Gottlieb, M.D., and Director of the Center for Drug Evaluation and Research Janet Woodcock, M.D., on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues (January 25, 2019).

[8] *Id.*

[9] *FDA Identifies Contamination Source in Blood Pressure medicines used by millions,* Washington Post (January 25, 2019).

[10] *Id.*

make products sold in the United States, had not yet been inspected by FDA.[11] A more recent analysis by Kaiser Health News indicated that the agency has made progress, noting that the FDA has reduced the backlog of uninspected foreign drug facilities to roughly 400.[12]

We acknowledge FDA's efforts to clear this backlog. However, given the number of foreign drug manufacturers that produce products for the U.S. market, this will continue to be a challenge for the agency. For example, according to recent data, nearly 40 percent of all FDPs and nearly 80 percent of APIs sold in the United States in 2016 were manufactured overseas.[13] In addition, the number of foreign drug surveillance inspections declined 10 percent to 778 in fiscal year 2018 from fiscal year 2017, which had a nine percent decline from fiscal year 2016.[14] We note that while FDA drug inspections increased 18 percent in India in fiscal year 2018, FDA's inspections declined 11 percent in China.[15]

As you know, GAO has listed FDA's response to globalization as an area on its most recent High-Risk update in 2017.[16] Given our concerns in this area, we are requesting that FDA provide Committee staff with a briefing on the basis and impact of ARB recalls as well as a briefing on FDA's efforts to conduct foreign inspections and what ongoing challenges currently exist for the agency.

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[11] Government Accountability Office, *Drug Safety: FDA Has Improved Its Foreign Drug Inspection Program, But Needs to Assess the Effectiveness and Staffing of Its Foreign Office* (Dec. 2016) (GAO-17-143).

[12] *When Medicine Makes Patients Sicker,* Kaiser Health News (Jan. 4, 2019).

[13] *See* note 11.

[14] *America's Love Affair with Cheap Drugs Has a Hidden Cost,* Bloomberg (January 29, 2019).

[15] *Id.*

[16] Government Accountability Office, *High-Risk Series: Progress on Many High-Risk Areas, While Substantial Efforts Needed on Others* (Feb. 2017) (GAO-17-317).

We appreciate your attention to this matter, and if you have any questions, please contact Kevin Barstow of the Majority Committee staff at (202) 225-2927 and Alan Slobodin of the Minority Committee staff at (202) 225-3641.

Sincerely,

Frank Pallone, Jr.
Chairman

Greg Walden
Ranking Member

Anna G. Eshoo
Chairwoman
Subcommittee on Health

Michael C. Burgess, M.D.
Ranking Member
Subcommittee on Health

Diana DeGette
Chair
Subcommittee on Oversight
and Investigations

Brett Guthrie
Ranking Member
Subcommittee on Oversight
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