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ONE HUNDRED SEVENTEENTH 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

May 20, 2022

The Honorable Robert M. Califf, M.D., MACC
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Dear Dr. Califf,

We write to you about our concerns with the increase in clinical trials conducted in China to support Food and Drug Administration (FDA) approvals for medical products in the United States (U.S.), and how the FDA is addressing this challenge.

In 2016, 23.8 percent of trials were initiated in the U.S. and just 12.5 percent were initiated in China. In 2017, trial initiations for the U.S. remained steady at 23.7 percent while initiations in China grew to 15.5 percent. However, in 2018, the situation dramatically changed. Trial initiations in the U.S. declined to 21.6 percent while initiations in China soared to 21.6 percent. In just two years, China went from having half the initiations of the U.S. to pulling even with us.[1]

This surge of clinical trials conducted in China is starting to manifest itself in FDA submissions. For example, in oncology drug development involving checkpoint inhibitors, FDA knows of at least 25 applications planned to be submitted or already submitted, that are based either solely or predominantly on clinical data from China.[2] Many sponsors of trials performed in China began their clinical development in China after results of other checkpoint inhibitors in the disease were publicly available.[3]

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[1]Ed Miseta, Report reflects huge growth of clinical trials in China, Clinical Leader (December 14, 2021), https://www.clinicalleader.com/doc/report-reflects-huge-growth-of-clinical-trials-in-china-0001#:~:text=In%202016%2C%2023.8%25%20of%20trials,in%20China%20grew%20to%2015.5%25.

[2] FDA says it had no input as companies developed checkpoint inhibitors in China, 48 The Cancer Letter 5 (February 4, 2022).

[3] *Id.* *See also* Julia A. Beaver, M.D., and Richard Pazdur, M.D.,The Wild West of Checkpoint Inhibitor Development, New England Journal of Medicine (December 15, 2021) ("Some sponsors, however, have deployed a

The current "East to West" movement of clinical data is not mainly about innovation. Most drugs being discussed with the FDA are attempts to replicate known advances, also known as "me too" drugs, and do not fulfill an unmet medical need. These drugs are not biosimilar or generic drugs and, thus, are required to have complete clinical and non-clinical studies and manufacturing processes developed.[4] These drugs cannot rely on information generated by the already-approved checkpoint inhibitors. As such, there is a lot of redundancy and expense for questionable benefit.[5]

The first of these applications was considered by the agency's Oncologic Drugs Advisory Committee (ODAC) on February 10, 2022. The application involved a trial called ORIENT-11, which compared chemotherapy plus sintilimab, a PD-1 monoclonal antibody checkpoint inhibitor, to chemotherapy alone as initial treatment for metastatic non-small cell lung cancer. Because of the concerns over data from the Chinese clinical trial, the FDA's ODAC voted 14 to 1 in support of the agency's position that additional clinical trials demonstrating applicability to U.S. patients and U.S. medical care should be required prior to a final regulatory decision for the first such drug to be presented to the agency.[6]

Clinical data from China raises diversity issues for drugs in the U.S. market. As FDA officials Harpreet Singh and Richard Pazdur recently noted:

> Trials relying solely on enrolment from a single country might have less ethnic and racial representation relevant to the US population, notably with regards to currently underserved groups. Sponsors should prospectively address measures to ensure the representation of patients reflecting the population who will eventually use the product in the USA. Since trials coming from a single foreign country will generally have differing ethnic and racial representation in the population compared with the USA, additional data should be provided to ensure the generalizability of their results to the US population.[7]

Additionally, there are concerns about data quality. A report in the British Medical Journal in 2016 pointed to such issues in 80 percent of trials conducted in China.[8] The Chinese

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strategy of duplicating the trial of an approved checkpoint inhibitor that led to U.S. approval for the indication in question. These sponsors benefit from the knowledge of the previous trial's results, end points, statistical plan, and effect size, which reduces their risk. If these drugs were developed in the United States for an approved indication, large noninferiority trials comparing the new checkpoint inhibitor with the approved antibody would probably be required.").

[4] *Id.*
[5] *Id.*
[6] Paul Goldberg and Alice Tracey, In a 14:1 vote, ODAC nixes a PD-1 drug developed in China; data not generalizable to U.S. population, 48 The Cancer Letter 5 (February 11, 2022).
[7] Harpreet Singh and Richard Pazdur, Importing oncology trials from China: a bridge over troubled waters?, Comment, Lancet 1 (February 4, 2022).
[8] Michael Woodhead, 80% of China's clinical trial data are fraudulent, investigation finds, BMJ (October 5, 2016), https://www.bmj.com/content/355/bmj.i5396

FDA stated that data from 1308 of the 1622 applications should be withdrawn because they contained fabricated, flawed, or inadequate data from clinical trials.[9] However, this report was five years ago, and FDA officials acknowledge there have been efforts to address these issues. In general, FDA has indicated it would want to explore whether any of the sites in a particular trial were involved in these withdrawals, and what was done to rectify the specific situation.[10]

In light of these concerns, please provide the following by June 3, 2022:

1. How many biologics license applications or drug applications has FDA received that are based solely or predominantly on clinical trials from China?

2. Prior to the pandemic, how many clinical trial sites in China were inspected by the FDA between January 1, 2017 and January 1, 2020? What were the outcomes of these inspections?

3. How many clinical trial sites in China have been identified in applications to the FDA as being involved in data withdrawals? What kinds of efforts would need to be made to address data integrity issues? Did any of these sites contribute a significant number of patients in international, multi-regional clinical trials submitted to regulatory agencies, particularly FDA?

If you have any questions, please contact Alan Slobodin of the Minority Committee staff. Thank you for your attention to this request.

Sincerely,

Cathy McMorris Rodgers
Ranking Member
Committee on Energy and Commerce

Brett Guthrie
Ranking Member
Subcommittee on Health

H. Morgan Griffith
Ranking Member
Subcommittee on Oversight and Investigations

CC: The Honorable Frank Pallone, Chairman
The Honorable Anna Eshoo, Chair, Subcommittee on Health
The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations

[9] *Id.*
[10] *Supra* note 2.