United States Senate
WASHINGTON, DC 20510-0908

September 17, 2024

The Honorable Robert Califf
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf:

We write to urge the U.S. Food and Drug Administration (FDA) to promote domestic pharmaceutical supply chain resilience through the implementation of programs to manufacture drugs and Active Pharmaceutical Ingredients (APIs) using advanced manufacturing technologies (AMTs), such as continuous manufacturing processes. We commend the FDA's work to issue industry guidance for considerations specific to continuous manufacturing of APIs, but greater action is needed to promote a resilient domestic API supply chain. We are concerned that the FDA has not yet created a feasible pathway for stakeholders to invest confidently in domestic AMTs. As the FDA continues to evaluate its AMT regulations, we urge you to prioritize domestic manufacturing facilities and commit to frequent engagement with industry and patient stakeholders, ensuring a clear and efficient approval process for AMTs and their products.

For several years, the United States has grappled with a concerning uptick in shortages of key APIs and medications. Quality issues resulting from weak manufacturing standards abroad are the most common cause for shortages. Unsurprisingly, most of these quality issues occur in traditional manufacturing facilities overseas. The COVID-19 pandemic exposed the U.S.' heavy reliance on foreign entities, particularly China, for our drugs and medical supplies. The lack of domestic medical manufacturing has created dangerous vulnerabilities for American public health and national security.

AMTs, such as continuous manufacturing sites, provide a promising pathway to lower the cost of domestic drug manufacturing, and accelerate the reshoring of key API production here in the United States. Yet, the FDA has not yet invested sufficient resources toward developing clear regulatory guidelines for these innovative manufacturing tools. The FDA must quickly finalize and implement the AMT Designation Program, as directed by Congress, to provide companies regulatory clarity as they evaluate whether to invest and seek approval of AMTs for their products.

Though the FDA has identified current regulatory barriers that are preventing more companies from adopting AMTs in their manufacturing pipelines, we are concerned that the FDA has not addressed these barriers adequately. A 2021 National Academies of Science, Engineering, and Medicine report found that significant regulatory challenges to implementing advanced manufacturing for drugs include challenges within the FDA's approval process for

each step in the manufacturing process and the lack of guidance and expertise within the FDA related to advanced manufacturing technologies.[1] Industry stakeholders must be able to establish the business case for the use of an AMT, but current ambiguities in the regulatory environment exacerbate challenges for arguing the business incentives for AMTs, deterring investment in these technologies. Though the agency expressed a willingness to address the barriers the report identified, a 2023 GAO report on the status of the FDA's efforts in supporting investment in AMTs found that only a few drugs manufactured using an AMT are currently approved for marketing in the United States. Between 2015 and 2022, the FDA had only approved 16 out of the 112 applications or supplemental applications that used an AMT.[2] This low rate of approval does not inspire investor confidence and proves that the FDA has considerable work to do to improve the regulatory environment for AMTs.

As the FDA works toward finalizing its AMT Designation Program and continues to evaluate and approve AMTs for commercial use, we urge you to ensure that these efforts prioritize domestic supply chain resilience and enforce clear guidelines for manufacturers to take part in this program. As such, we request answers to the following questions:

1. What strategies has the FDA implemented to encourage greater investment by domestic drug manufacturers into AMTs, such as continuous manufacturing?
    a. How has the FDA engaged with industry to further refine its regulations and expand opportunities for approval?
2. How is the FDA ensuring that the AMT Designation program will benefit more domestic manufacturing facilities than foreign-based facilities?
3. Based on the current application pool for AMTs seeking FDA approval through currently active pathways, what is the ratio of domestic versus foreign-based facility applications that the FDA has received?
    a. What is the ratio of domestic versus foreign based facilities that have been approved?
4. Has the FDA received any new continuous manufacturing applications for generics, especially among pharmaceuticals experiencing domestic shortages?
    a. Will the FDA consider a drug or API's risk for shortage when evaluating applications for the AMT Designation program?
5. How is the FDA communicating about the AMT Designation Program to eligible entities and the public?
    a. How is the FDA ensuring the drug manufacturers of all sizes are aware of the program and understand the requirements to apply?
6. How is the FDA ensuring the timely approval of continuous manufacturing technologies?
7. Has the FDA seen continued growth in the number of approved continuous manufacturing products since 2022?
8. What is the implementation status of the AMT Designation Program?
    a. Has the FDA made progress on implementing the required program since the draft guidance period, which closed on March 13, 2024?
    b. Has the program accepted any designation requests for new technologies?

[1] https://www.gao.gov/assets/gao-23-105650.pdf#page=16
[2] https://www.gao.gov/assets/gao-23-105650.pdf#page=16

Thank you for your attention to this important matter. We look forward to your prompt response.

Sincerely,

Marco Rubio
U.S. Senator

Angus S. King, Jr.
U.S. Senator