United States Senate
WASHINGTON, DC 20510

November 4, 2019

Brett Giroir, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Jeffrey Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue
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Dear Acting Commissioner Giroir and Director Shuren:

Thank you for the Food and Drug Administration's (FDA) August 21, 2019, response to our letter sent on June 24, 2019, regarding the FDA's legislative proposal to create a "progressive approval" pathway for human medical devices.[1]

We are disappointed by FDA's clarification that the agency no longer fully stands by former-Commissioner Gottlieb's commitment made in July of 2018 that the "FDA does not believe this [conditional approval] pathway would be suitable for human medical products."[2] We strongly objected to any expansion of the conditional approval pathways in the Animal Drug User Fee Act of 2018 that would have applied to human medical products, and at the time had sought assurances from former-Commissioner Gottlieb that the agency would not pursue such an expansion. We had agreed with former-Commissioner Gottlieb's assessment that the conditional approval pathway may "address specific challenges of certain aspects of veterinary medicine that human medicine does not face."[3]

We recognize the challenges in developing medical and surgical devices for populations with unmet medical needs. However, we continue to have questions regarding the eligibility criteria the FDA envisions for this proposal; the FDA's ability to ensure the quality and completeness of post-market data collection; and the agency's ability to exercise its authority to remove medical products from the market after they have been provisionally approved. To help

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[1] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.
[2] 164 Cong. Rec. S5472-73 (daily ed. Jul. 31. 2018) (Letter from FDA Commissioner Scott Gottlieb and Center for Veterinary Medicine Director Steve Solomon to Senate HELP Committee Chairman Lamar Alexander and Ranking Member Patty Murray).
[3] *Id.*

us better understand how the FDA would address these concerns, we ask that you please provide us answers to the following questions no later than November 13, 2019:

1. The FDA envisions progressive approval as a pathway that would "expedite[] access to devices . . . intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition and address an unmet medical need."[4]

    a. For the purposes of the progressive approval pathway, how would the FDA define "unmet medical need"?

    b. In its August 21st response, the FDA repeatedly uses the example of children as an example of a population underserved by existing medical device pathways. Does the FDA envision limiting the progressive approval pathway to certain populations, such as children? If so, please provide an overview of the populations the FDA is considering.

    c. Does the FDA envision limiting the progressive approval pathway to disease populations with a certain number of patients, similar to the Humanitarian Device Exemption pathway? If so, please provide an overview of the numbers the agency is considering.

    d. What additional limits, if any, is the FDA considering on the populations and devices eligible for the progressive approval pathway?

2. In its August 21st response, the FDA pointed to the limited success of the Humanitarian Device Exemption (HDE) pathway in spurring device innovation to justify the need for a progressive approval pathway. The agency notes that the HDE pathway, as "the only existing regulatory marketing pathway intended to support medical device innovation for small populations like pediatric patients," does "not adequately meet the needs of children." It continues to state that, "despite multiple actions by Congress . . . [to] optimize the potential of the HDE program to help small patient populations . . . there has been no significant change in the number of Humanitarian Use Device (HUD) or HDE applications submitted or approved." In contrast, the agency states, "progressive approval would foster safe innovation in medical devices to meet many unmet needs."[5]

    a. What are the primary economic challenges facing device makers interested in producing devices for small, underserved populations, such as pediatric patients? For each economic challenge identified, please describe which aspects of the progressive approval pathway (as envisioned by the FDA) would mitigate the challenge and increase the number of devices available to these populations.

[4] U.S. Department of Health and Human Services, Food and Drug Administration, "Fiscal Year 2020: Justification of Estimates for Appropriations Committees," https://www.fda.gov/media/121408/download.
[5] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.

b. What specific aspects of the HDE pathway have made it unsuccessful at increasing the number of devices available to these populations? Could modifications to the HDE pathway address the problems in product development that the FDA has identified as necessitating the conditional approval pathway? If so, what are these modifications? If not, why not?

c. What additional policies, if any, should Congress consider in an effort to expand the types of devices available to these populations?

3. In its initial description of the progressive approval pathway, the FDA stated that devices approved via the pathway would "be eligible for provisional approval . . . and could remain on the market after an established time period only after a demonstration of reasonable assurance of safety and effectiveness."[6] In its August 21st response, the agency narrowed down the established time period to "up to three years."[7] How did the FDA decide upon the three-year provisional approval period?

4. According to the FDA's initial description of the progressive approval pathway, in cases where a device sponsor could *not* "demonstrate reasonable assurance of safety and effectiveness," the device's "initial approval would automatically sunset and the device could no longer be legally marketed."[8]

   a. What challenges, including those presented by patients, physicians, sponsors, investors, and other device industry stakeholders, does the agency anticipate could arise in cases where the agency seeks to remove provisionally approved devices from the market?

   b. How could uncertainty concerning the possible removal from the market of a device that has received provisional approval under the progressive approval pathway limit the pathway's ability to mitigate the economic forces inhibiting device development described in Question 2?

5. In its August 21st response, the FDA states that the progressive approval "proposal would provide accountability to ensure that devices demonstrate a reasonable assurance of safety and effectiveness to remain on the market."[9] The FDA also indicated that a device sponsor using the progressive approval pathway "would be required to collect additional information through a registry, electronic health records (EHRs), or another source of real-world data on more patients and for a longer duration than the time period for

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[6] U.S. Department of Health and Human Services, Food and Drug Administration, "Fiscal Year 2020: Justification of Estimates for Appropriations Committees," https://www.fda.gov/media/121408/download.
[7] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.
[8] U.S. Department of Health and Human Services, Food and Drug Administration, "Fiscal Year 2020: Justification of Estimates for Appropriations Committees," https://www.fda.gov/media/121408/download.
[9] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.

obtaining the initial, provisional approval, and then demonstrate a reasonable assurance of safety and effectiveness."[10]

a. Please provide a complete summary of the oversight that the FDA envisions conducting on progressive approval pathway participants to ensure that safety and effectiveness standards are met. What resources would be necessary to make this post-market surveillance effective?

b. Independent audits of the FDA's expedited approval pathways by the HHS Office of Inspector General and the U.S. Government Accountability Office have revealed challenges associated with implementing post-marketing requirements and indicate the need for better oversight measures.[11] How would the FDA ensure that post-market studies of provisionally approved devices are completed in a timely manner?

c. A recently published analysis of the Manufacturer and User Facility Device Experience (MAUDE) database has underscored the challenges of post-market data collection, including the underreporting of adverse events. The analysis also found a significant degree of miscategorization of deaths as reports of injury and malfunction.[12] If safety determinations will be made at least in part through post-market data collection and analysis, what will the FDA do to ensure that the information provided by sponsors is accurate—especially when there is a significant incentive for them to underreport and misclassify adverse events?

d. Is it the agency's view that real-world evidence would be sufficient to demonstrate "a reasonable assurance of safety and effectiveness"? If so, what precedent, if any, is there for relying exclusively, or almost exclusively, on real-world evidence to support the initial approval or clearance of a device?

e. The FDA notes in its response that the labeling for a provisionally approved device "would have to make clear that the medical device [meets] only the safety and performance standard, rather than the reasonable assurance of safety and effectiveness standard, to allow patients and health care professionals to make informed decisions."[13] What, if any, additional patient protections does the FDA envision being necessary for devices possessing only provisional approval?

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[10] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.

[11] U.S. Department of Health and Human Services, Office of Inspector General, "FDA is Issuing More Postmarket Requirements, but Challenges with Oversight Persist," July 20, 2016, https://oig.hhs.gov/oei/reports/oei-01-14-00390.asp; U.S. Government Accountability Office, "FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement," December 2015, https://www.gao.gov/assets/680/674183.pdf.

[12] JAMA Internal Medicine, "Miscategorization of Deaths in the US Food and Drug Administration Adverse Events Database," Lily Meier, Elizabeth Wang, Madris Tomes, et al., October 7, 2019, https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/275.

[13] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.

f. In the agency's view, are EHRs sufficiently widespread (and interoperable) that the FDA can rely on them for data collection for the purposes of the progressive approval pathway? If not, what could Congress and HHS do to increase the reliability of EHRs as a data collection tool?

g. In the agency's view, are device registries sufficiently widespread and well-developed such that the agency can rely on them for data collection for the purposes of the progressive approval pathway? If not, what could Congress and HHS do to increase the reliability of registries as a data collection tool?

6. What additional data sources are the FDA considering using to collect data for the progressive approval pathway?

7. In its August 21st response, the FDA notes that the agency "is in an ideal position to continue leveraging [real-world evidence], in part, due to its work to develop the National Evaluation System for health Technology (NEST)."[14]

   a. Does the FDA plan to require sponsors seeking progressive approval to share data with NEST? If not, why not?

   b. In the agency's view, is NEST sufficiently well-developed such that the agency could rely on it for data collection for the purposes of the progressive approval pathway? If not, what could Congress and HHS do to increase the reliability of NEST as a data collection tool?

Please contact Laura Aguilar in Senator Warren's office or Katlin McKelvie Backfield with the Senate Committee on Health, Education, Labor, and Pensions with any questions or concerns.

Sincerely,

Elizabeth Warren
United States Senator

Patty Murray
United States Senator
Ranking Member, Committee on
Health, Education, Labor, and Pensions

[14] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senators Elizabeth Warren and Patty Murray, August 21, 2019.