U.S. FOOD & DRUG ADMINISTRATION

AUG 21 2019

The Honorable Elizabeth Warren
United States Senate
Washington, D.C. 20510-3508

Dear Senator Warren:

Thank you for your letter of June 24, 2019, cosigned by Senator Patty Murray, regarding the Food and Drug Administration's (FDA or the Agency) legislative proposal to create a progressive approval pathway for medical devices, which was briefly summarized in the Agency's "Overview of Legislative Proposals" in the Fiscal Year 2020 budget justification.

This pathway is intended to help enable access to medical devices which treat or diagnose life-threatening or irreversibly debilitating diseases and conditions and address unmet medical needs, particularly for children and other small and rare populations that remain perpetually underserved. Progressive approval for medical devices would provide a new lifeline between patients and promising medical devices under a controlled infrastructure with safeguards and oversight. Eligible devices that demonstrate safety and performance would receive a provisional approval for up to three years and then would be required to demonstrate a reasonable assurance of safety and effectiveness to stay on the market. The approach would allow FDA to evaluate innovative devices in a more fluid, iterative, and informative manner so that we can encourage innovation in a structured, responsible way. FDA believes this will foster development of new devices for children and other underserved populations, as well as substantially improve the quality of data available on medical devices generally. Please note that FDA does not consider a progressive approval pathway appropriate for human drugs or biological products, which have both qualitative and quantitative differences in safety and efficacy considerations affecting benefit-risk determinations.

We appreciate the opportunity to address your questions and discuss in detail how this pathway could help improve the availability of medical devices for some of the most challenging health circumstances. It is our hope that we can work with you and others in Congress on advancing this proposal so that we can address critical unmet needs in our health care system.

We have restated your questions in bold, followed by our responses.

1. **Does the FDA stand by former Commissioner Gottlieb's previous statements that the "FDA does not believe this [conditional approval] pathway would be suitable for human medical products," and that conditional approval "wouldn't make sense in other [non-animal] product areas"? If not. please explain why not.**

The July 31, 2018, letter from Commissioner Gottlieb and Center for Veterinary Medicine Director Steve Solomon to the Senate Committee on Health, Education, Labor, and Pensions presented FDA's then-current views about the proposed legislation to expand the animal drug

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conditional approval pathway, which has a statutory standard of "reasonable expectation of effectiveness." FDA continues to believe that such a pathway would be unsuitable for human drugs and biologics.

However, the Agency's views with respect to medical devices have continued to evolve – particularly as a result of ongoing discussions following the public meeting on Pediatric Medical Device Development, which occurred on August 13 and 14, 2018.[1] Discussion at that meeting underscored the fact that, despite ongoing efforts by Congress and the healthcare ecosystem—including industry, patient advocates, researchers, and others—children remain one of the most underserved populations, especially regarding access to medical devices. When FDA considered the unique challenges for medical device development, relative to drugs and biologics, and what else could be done to address the problem of continued lack of access to devices for children, it soon became clear that a progressive approval pathway could be useful and appropriate with the right statutory standard and safeguards.

It is important to understand that the development of medical devices involves a different set of challenges, as described below, than the development of drugs and biological products. Because many aspects of a device can be evaluated on the bench, we often have the ability to better understand the mechanism of action and failure modes with relatively smaller clinical trials. Accordingly, while FDA believes that progressive approval may be suitable in some circumstances for medical devices, it is not suitable for human drugs and biological products. It is also not appropriate for combination products.

Most notably, at the time of the July 2018 letter, the Humanitarian Device Exemption (HDE) provisions of the statute already included "probable benefit" as part of the approval standard for humanitarian use devices under section 520(m). The HDE pathway is an example where qualifying devices do not have to meet the reasonable assurance of effectiveness part of the premarket approval standard. The progressive approval program would mirror this and also allow qualifying devices to meet a different standard at the provisional stage. However, manufacturers would ultimately be required to demonstrate that their devices meet the reasonable assurance of safety and effectiveness standard to remain on the market.

2. Director Shuren has long advocated for the expansion of approval pathways and has himself indicated that provisional and conditional approval are one and the same. In a power point presentation detailing Center for Devices and Radiological Health's (CDRH) strategic priorities, Director Shuren referred to the "progressive/conditional approval pathway." How, if at all, is "progressive approval" different than "conditional approval"?

People have used the terms "conditional" and "progressive" interchangeably, and it is important to clarify that Dr. Shuren's use of the term "conditional" is not referring to the conditional approval that is part of FDA's animal drug program. In the referenced presentation from four years ago, "CDRH's Vision, Challenges and Needs," Dr. Shuren described the approaches being implemented by CDRH to address urgent and unmet needs, including early feasibility studies, patient preference information, benefit/risk determination frameworks, and the expedited access pathway program (now the statutorily established breakthrough devices

[1] *https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-meeting-pediatric-medical-device-development-august-13-14-2018-fda-white-oak-campus-08132018#event-materials*

program). Dr. Shuren posed the question, "Should we have a progressive/conditional approval pathway?" as part of an ongoing public dialogue that started in 2012. In the years since that presentation, and for the reasons described above, CDRH has determined that a progressive approval pathway would be an important statutory authority to have for appropriate, innovative devices and appropriate patient populations that are underserved.

Furthermore, the Federal Food, Drug, and Cosmetic Act (FD&C Act) currently includes unique innovative pathways and provisions for medical device regulation that were established by Congress to address unmet needs and balance premarket and postmarket data collection. The HDE pathway provisions in section 520(m) authorize FDA to approve eligible devices based on, among other things, a determination that "probable benefit to health outweighs the risk of injury or illness." Section 513(a)(3)(C) of the FD&C Act directs that FDA, in reviewing a premarket approval application (PMA), "shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls."

3. The description of "progressive approval for medical devices" in the FY 2020 budget proposal provides that, if a company does not make requisite demonstrations of safety and effectiveness "within a reasonable amount of time after initial approval is granted, the initial approval would automatically sunset and the device could no longer be legally marketed." How does this approach to sunsetting approval of a device comply with the requirements of procedural due process?

The progressive approval pathway is a legislative proposal to amend the FD&C Act, and the statutory provisions establishing the pathway could provide for procedural safeguards to address any due process requirements.

4. How was the decision made to include the "progressive approval for medical devices" in the budget proposal? Please provide a list of any and all outside organizations or individuals who contacted or were contacted by the FDA regarding the development of the "progressive approval for medical devices" program.

This proposal was cleared by FDA under the "A-19" legislative proposal process, which is a rigorous process involving drafting, review, comment, and revision within FDA and the Department of Health and Human Services (HHS). This process is based on Circular No. A-19 issued by the Office of Management and Budget, which can be found at this link: *https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/memoranda/2017/M-17-19-OMB.pdf.* This included clearance from former Commissioner Gottlieb, as well as FDA's medical product Centers, and formal clearance by HHS and the Administration.

5. Please provide an update on any efforts the FDA has taken to implement its "progressive approval for medical devices" program.

The progressive approval pathway is a legislative proposal that FDA would like to pursue in discussions with Congress. FDA has not taken any steps to implement this pathway because the Agency needs new statutory authority for it.

The progressive approvals pathway for medical devices proposal focuses on the need to assure safety and effectiveness while enabling access to innovative medical devices addressing unmet needs. Certain innovative medical devices can not only save lives, they can improve lives and improve outcomes, thereby providing patients with potentially more effective and safer alternatives to manage their health. Advances in medical devices oftentimes do not serve the complex needs of small populations, such as children and patients with rare diseases, because it is difficult if not impossible to conduct large enough clinical studies in these patient populations (the limited number of potential research participants and the costs of such clinical studies make device development unrealistic). These issues are further exacerbated by unique characteristics of devices and their use in medical practice, as described below.

As noted in the response to Question 1, children remain underserved in the United States when it comes to innovative medical devices. The vast majority of cutting-edge devices, those that may save lives and improve patient outcomes, are not designed, evaluated, and labeled for children. Nevertheless, doctors oftentimes use these devices on children, despite the fact that they are not approved for such use and even where there may not be evidence of safety and effectiveness for use among pediatric populations. FDA has made great efforts to address this tremendous public health need. The Agency has held public meetings[2,3] and workshops,[4] issued guidance,[5,6,7,8] and has provided millions of dollars in grants[9] through the Pediatric Device Consortia (PDC) Grants Program. Yet, our health care system still does not have a complete solution to these problems. During the past decade, for instance, only about 10 percent of class III PMA-approved devices (those that are novel and can provide great benefit) have been developed and then approved for use in children younger than 18 years of age. Only about four percent have been developed and then approved for use in newborns and toddlers, those often at highest risk of dying from critical congenital diseases.

The HDE pathway is the only existing regulatory marketing pathway intended to support medical device innovation for small populations like pediatric patients, but it does not adequately meet the needs of children. The HDE pathway is limited to certain devices designed to treat or diagnose a disease or condition affecting not more than 8,000 patients per year. For populations that involve 8,001 or more, sponsors must use the premarket approval (PMA) or de novo pathway. Despite multiple actions by Congress during the past decade[10,11,12] to address concerns and optimize the potential of the HDE program to help small patient populations by lifting certain profit constraints and increasing the population limit, only four devices with pediatric-specific labeling have come through the HDE pathway, and there has been no significant change in the number of Humanitarian Use Device (HUD) or HDE

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[2] *https://www.fda.gov/advisory-committees/committees-and-meeting-materials/pediatric-advisory-committee.*
[3] *https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-meeting-pediatric-medical-device-development-august-13-14-2018-fda-white-oak-campus-08132018.*
[4] *https://events-support.com/events/FDA_OOPD_Pediatric_Medical_Devices_Workshop.*
[5] *https://www.fda.gov/media/91889/download.*
[6] *https://www.fda.gov/media/85233/download.*
[7] *https://www.fda.gov/media/73510/download.*
[8] *https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/pediatric-expertise-advisory-panels-guidance-industry-and-fda-staff.*
[9] *https://www.fda.gov/industry/pediatric-device-consortia-grants-program/pediatric-device-consortia-grants-awarded.*
[10] *https://www.congress.gov/bill/110th-congress/house-bill/3580.*
[11] *https://www.congress.gov/bill/112th-congress/senate-bill/3187.*
[12] *https://www.congress.gov/bill/114th-congress/house-bill/34.*

applications submitted or approved. This is due primarily to a combination of established numerical cut-offs and the additional statutory requirements that must be met for patients to receive an HDE device. FDA believes progressive approval would foster safe innovation in medical devices to meet many unmet needs, including the complex needs of small populations such as pediatrics. The pathway would leverage efficient evidence-generation mechanisms to help ensure patients' timely access to life-saving medical devices, all with the requirement for sponsors to demonstrate a reasonable assurance of safety and effectiveness to remain on the market.

Progressive approval would establish a two-step approval process for certain medical devices intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition where there is an unmet need, including certain diseases/conditions impacting small patient populations. At the first stage, manufacturers would have to demonstrate safety and performance. However, unlike an HDE, devices under the first stage of progressive approval for medical devices would only be granted a "provisional" approval for up to three years, during which time the manufacturer would be required to collect additional data to demonstrate a reasonable assurance of safety and effectiveness. If this standard is not met in the prescribed time frame, the provisional approval would sunset automatically and the device could no longer be marketed. Moreover, during this provisional approval stage, the device label would have to make clear that the medical device met 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. In addition, for a device to be eligible for progressive approval, appropriate data sources, such as a registry, must be available to ensure that the necessary postmarket evidence generation would occur. If the sponsor complies with the requirement to provide data to demonstrate reasonable assurance of safety and effectiveness based on the postmarket data, the device would be approved and the label would reflect that approval. This proposal would provide accountability to ensure that devices demonstrate a reasonable assurance of safety and effectiveness to remain on the market.

In appropriate circumstances, such as pediatrics, restricting the use of devices that have received a provisional approval for patients being treated with or at health care facilities that provide additional patient oversight and engage in the required postmarket data collection could provide additional safeguards for patients. For a device to stay on the market, the sponsor 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 obtaining the initial, provisional approval, and then demonstrate a reasonable assurance of safety and effectiveness. FDA already has experience with leveraging real-world evidence (RWE) for regulatory decisions, such as label expansions for new indications for transcatheter aortic valve replacement (TAVR). The use of real-world data sources can allow the Agency to evaluate the medical device as it may be used in clinical practice, which may be particularly meaningful for unmet medical needs. FDA is in an ideal position to continue leveraging RWE, in part, due to its work to develop the National Evaluation System for health Technology (NEST).

We believe the progressive approval pathway would improve the availability of certain devices and afford patients important options that they would not have otherwise. The data collected through real-world data sources will provide more information about the use of these devices

in a real-world setting than FDA typically receives from our existing HDE or PMA with postmarket study pathways, which will result in more informative data regarding the safety and effectiveness of devices. This will inform product labeling and FDA's oversight. Most importantly, unlike a device approved under the HDE pathway, devices with provisional approval would be required to collect the additional data to demonstrate a reasonable assurance of safety and effectiveness within three years or less. This is a critical feature of the pathway and it addresses a limitation of the HDE pathway, where there currently is no statutory requirement for sponsors to ever meet the reasonable assurance of effectiveness standard. The requirement for sponsors to provide additional data to meet FDA's standard of reasonable assurance of safety and effectiveness and remain on the market is an important mandate and regulatory tool.

As previously noted, FDA has not taken steps to implement "progressive approval" because it would require new statutory authority. It is the Agency's hope that we can work with you and other members of Congress to pass legislation creating this progressive approval pathway because we believe that it will help provide access to devices for smaller and rare disease populations and benefit patients, particularly children, who have been greatly underserved by the current pathways for marketing medical devices.

6.In the CDRH 2018-2020 Strategic Priorities report, CDRH notes its goals of the "issuance of new policies and internal procedures" in order to "complete the transition from a risk-based framework for medical device regulation to a benefit-risk framework that makes explicit the societal tradeoffs of the decisions we make and offers several regulatory options depending upon these tradeoffs." Please provide an update on the new policies and internal procedures CDRH is pursuing as part of this effort.

FDA launched the Patient Preference Initiative (PPI) as part of our medical device regulatory decision-making process in September 2013, and has since worked to include patient perspectives in our regulatory decision making where appropriate. The Agency, in fact, made Partnering with Patients[13] a strategic priority for 2016-2017, and continues shifting its approaches to transition from a system based solely on risk, to a system based on benefit-risk tradeoffs informed by patient input. FDA knows that many patients are interested in contributing their views, data, and resources to increase early access to high quality, safe and effective medical devices, reduce adverse events, and improve communication about the risks and benefits that matter most to them. The PPI is designed to identify and develop methods for assessing patient valuations of benefit and risk and outcomes that matter most to patients related to specific device types and specific diseases and conditions that can be used to inform product review decisions. These efforts help ensure a systematic and thorough approach to allow FDA to include patients' input regarding how a disease or condition impacts their daily lives and their caregivers' lives, and the types of treatment benefits and risks that matter the most to them in the regulatory decision-making process for medical devices. FDA is also looking to advance methodologies to develop patient-reported outcomes that measure outcomes important to patients as well as modify and adapt existing patient-reported outcomes for new populations and expand their uses across different disease areas.

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[13] *https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHPatientEngagement/default.htm*

FDA has reviewed well-conducted patient preference studies and has been able to leverage the information from these studies to make regulatory decisions, including expanding access to a device for end-stage renal disease. FDA cleared an expanded indication for use of the NxStage System One home hemodialysis device for patient use without a caregiver. This was based, in part, on information provided by patients through a well-conducted patient preference study. Additionally, the Agency is actively reviewing for qualification of new patient-reported outcome measures, such as the Kansas City Cardiomyopathy Questionnaire,[14] and advancing the science of patient input to better assess outcomes that are important to patients as well as the benefit-risk tradeoffs patients find acceptable and incorporate them into our decision making. Much of the work in these studies and initiatives have been done in collaboration with patient organizations such as the Michael J. Fox Foundation[15] and the National Organization for Rare Disorders (NORD).[16] FDA also established the first and only advisory committee[17] comprised solely of patients, caregivers, and representatives of patient organizations, and is working hand-in-hand with patients to incorporate their values and perspectives into all aspects of the medical device total product life cycle. FDA will not bring products to market that do not meet the required standards; at the same time, we believe that developing systematic approaches by which to include patient preference information in our medical device safety and effectiveness decisions, when appropriate, will improve the safety and well-being of patients.

We have learned from the PPI at CDRH that some patients' personal treatment goals and values make them more willing to accept certain risks related to medical devices. Our experience in the PPI is that those with a life-threatening or irreversibly debilitating disease or condition and unmet medical needs often are willing to accept greater uncertainty about effectiveness in order to have earlier access to devices that could have a meaningful impact on their health or quality of life, especially in disease areas where treatment options may be limited. And, as described in our response to Question 1 above, a number of characteristics specific to medical devices (including how they are designed and tested, the level of predictability of their mechanisms of action and modes of failure, and their limited availability for certain population groups) appear to make them potentially uniquely suited to a progressive approval pathway. This progressive approval proposal would support the efforts of CDRH's PPI because it would provide patients additional options for medical devices earlier on, and allow patients the power to make the decision whether or not to use these innovative medical devices in light of their individual circumstances, and in consultation with their healthcare professional.

Thank you, again, for your inquiry about this important proposal. We hope that you and your colleagues in Congress will work with FDA to establish this pathway so that we can foster

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[14] *https://www.fda.gov/downloads/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/UCM581761.pdf*

[15] *https://mdic.org/project/patient-centered-outcomes-research/*

[16] *http://mdic.org/wp-content/uploads/2018/05/1-Welcome-and-intro-slides.pdf*

[17] *https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PatientEngagementAdvisoryCommittee/default.htm*

development of safe, innovative devices for children and other populations who desperately need them. The same letter has been sent to your cosigner.

Sincerely,

Karas Gross
Associate Commissioner for
Legislative Affairs