United States Senate
WASHINGTON, DC 20510

June 24, 2019

Ned Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Jeffrey Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
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Dear Acting Commissioner Sharpless and Director Shuren:

We write today with serious concerns about the "progressive approval for devices" program included in the Food and Drug Administration's (FDA) Fiscal Year 2020 budget justification. The program appears to expand the FDA's "conditional approval" pathway for animal drugs to human medical products—an expansion that former FDA Commissioner Scott Gottlieb assured us would not take place. We strongly oppose the expansion of the conditional approval pathway to human drugs and devices, and we are seeking clarification on whether the FDA is pursuing this policy despite then-Commissioner Gottlieb's commitments to the contrary.

**The FDA Designed the "Conditional Approval" Pathway as a Targeted Exemption for Certain Animal Drugs**

Consumers rely on the FDA to conduct rigorous examinations of drugs and medical devices. The FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) are responsible for evaluating drugs for human use,[1] while the FDA's Center for Veterinary Medicine (CVM) regulates drugs for animal use.[2] To determine whether to approve new drugs, CDER, CBER, and CVM use multi-disciplinary review teams, including physicians, statisticians, chemists, pharmacologists, and other experts to review drug applications, which include clinical data and proposed labeling. By law, to approve a new drug for human use, the FDA must determine there is "substantial evidence" of the drug's

[1] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "Major Functions and Responsibilities," https://www.fda.gov/about-fda/center-drug-evaluation-and-research/center-drug-evaluation-and-research; U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, "CBER Vision & Mission," https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/cber-vision-mission.
[2] U.S. Food and Drug Administration, Center for Veterinary Medicine, "What CVM Regulates," https://www.fda.gov/about-fda/office-foods-and-veterinary-medicine/center-veterinary-medicine#regulates.

"effectiveness" for the conditions of use in its labeling.[3] This statutory standard applies to all drug approvals, even for those drugs granted accelerated approval.[4] The FDA's animal and human drug review processes are the global gold standard for safe and effective drug development.[5]

Following the enactment of the Minor Use and Minor Species (MUMS) Animal Health Act in 2004, the FDA established a "conditional approval" pathway to accelerate the development of animal drugs in commercially limited markets. Under the conditional approval pathway, manufacturers developing drugs for "minor species" or for "minor uses in a major species" have been able to bypass traditional FDA approval processes and market qualifying drugs without fully demonstrating their effectiveness.[6] To receive conditional approval, manufacturers must only demonstrate that a drug "ha[s] a 'reasonable expectation of effectiveness'"—a lesser standard than the "substantial evidence of effectiveness"; upon receiving conditional approval, manufacturers have been able to market their drugs for up to five one-year terms as they continue to gather the data necessary to meet the "substantial evidence" standard.[7]

For the up to five-year period until a manufacturer submits an application that meets the substantial evidence standard, conditional approval allows marketing of drugs that have not met FDA's gold standard for both safety and effectiveness. In August 2018, the Animal Drug User Fee Act (ADUFA) further expanded the conditional approval pathway by creating a 10-year pilot expansion program that allows other animal drugs to qualify, provided the drug is "intended to treat a serious or life-threatening disease or addresses an unmet animal or human health need and for which the Secretary determines that a demonstration of effectiveness would require a complex or particularly difficult study or studies."[8] We strongly objected to any expansion of the conditional approval pathways in ADUFA that would have applied to human medical products, and we remain committed to ensuring that the FDA does not extend this approval pathway to human drugs or medical devices.

**Then-Commissioner Gottlieb Opposed the Expansion of the Conditional Approval Pathway to Human Drugs or Devices**

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[3] 21 U.S.C. 355(d); 21 CFR 314.126. Biological products are approved under Section 351 of the Public Health Service Act. Under Section 351, licenses for biologics can be issued only upon a showing of "safety, purity, and potency," and "[p]otency has long been interpreted to include effectiveness." See FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998), at 4.

[4] FDA Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014), at 19.

[5] U.S. Food and Drug Administration, Janet Woodcock, M.D., "FDA Proposes Process Modernization to Support New Drug Development," June 4, 2018, https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fda-proposes-process-modernization-support-new-drug-development.

[6] 21 U.S.C. 360ccc; 21 CFR Part 516; U.S. Food and Drug Administration, "Conditional Approval Explain: A Resource for Veterinarians," https://www.fda.gov/animal-veterinary/resources-you/conditional-approval-explained-resource-veterinarians.

[7] Sponsors seeking conditional approval are still required to meet the same safety and manufacturing standards as those set through the full approval process. Drugs undergoing conditional approval must undergo an annual review by the FDA to ensure that sponsors are making progress toward meeting the effectiveness standard.

[8] P.L. 115-234

As Congress was expanding the conditional approval pathway for animal drugs under ADUFA, then-FDA Commissioner Gottlieb assured Senators that the FDA would not extend the pathway to human drugs or devices. In a July 31, 2018 letter to the Senate Committee on Health, Education, Labor, and Pensions (HELP Committee), Commissioner Gottlieb wrote that the "FDA does not believe this pathway would be suitable for human medical products." He cited the pathway's ability "to address specific challenges of certain aspects of veterinary medicine that human medicine does not face."[9] Commissioner Gottlieb reaffirmed these sentiments after his final testimony to Congress when he told MedTech Dive, "We were very clear that we thought this was a construct that made sense in the context of animal drugs. It wouldn't make sense in other product areas. We're not looking to do that, that's a concept that was narrowly tailored for the purpose of animal drug approvals."[10]

**The FDA FY2020 Budget Justification Appears to Expand the Conditional Approval Pathway to Human Medical Devices**

Despite Commissioner Gottlieb's assurances, the FDA's Fiscal Year 2020 budget justification references a FDA proposal called "progressive approval for devices." According to the budget justification, this proposal would allow certain devices to "be eligible for provisional approval based on a demonstration of safety and performance plus additional risk mitigations."[11] These approved devices "could remain on the market after an established time period only after a demonstration of reasonable assurance of safety and effectiveness."[12] As written, this "provisional approval" seems hardly distinguishable from the "conditional approval" that former-Commissioner Gottlieb had assured Congress and the public that the FDA would not pursue.

Whether "progressive," "provisional" or "conditional," the proposal is particularly alarming, given the FDA's already-lenient regulatory framework guiding medical device approval standards. While new drug sponsors must show "substantial evidence [of effectiveness]," [13] new device sponsors must only show a "reasonable assurance of…safety and effectiveness."[14] For moderate-risk device products, which are the vast majority of medical devices, the standard is even lower. The 510(k) clearance process for moderate-risk products, for example, does not require clinical trials—rather, 510(k) only requires that manufacturers show that devices are "substantially equivalent" to similar devices already on the market.[15]

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[9] 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).

[10] Med Tech Dive, "FDA Progressive Device Approval Raises Eyebrows," David Lim, April 16, 2019, https://www.medtechdive.com/news/fda-progressive-device-approval-proposal-raises-eyebrows/552778/.

[11] U.S. Department of Health and Human Services, "Fiscal Year 2020 Food and Drug Administration Justification and Estimates for Appropriations Committees," pp. 39-40, https://www.fda.gov/media/121408/download.

[12] Id.

[13] 21 USC § 355(d).

[14] 21 USC § 360c(a).

[15] U.S. Food and Drug Administration, "510(k) Clearances," September 4, 2018, https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/510k-clearances.

These more lenient standards have led to tangible harm. Earlier this year, the FDA restricted the sale of vaginal mesh—a medical device first approved in 2002—after more than 10,000 users complained of serious injury and nearly 80 users died.[16] The FDA also approved the contraceptive implant, Essure, in 2002. Sixteen years later, the agency restricted the sale of Essure after it had received nearly 33,000 reports of adverse events, including pain, menstrual irregularities, pregnancy loss, and death, and the product is no longer sold or distributed in the United States.[17] In 2013, over 20 years after the FDA had first approved the power morcellator, a surgical tool used to operate on the uterus, the agency was forced to issue warnings when it realized the device was inadvertently spreading cancer in some patients.[18]

Assuring patient safety and device effectiveness must be the primary goal of any approval system managed by the FDA, and the agency under Commissioner Gottlieb took some steps to improve device safety. In January 2019, for example, Commissioner Gottlieb requested public comment on a "Medical Device Safety Action Plan," a proposal to "improve [device] safety, detect safety risks earlier, and keep doctors and patients better informed" of risks.[19] Expanding a conditional approval framework to human medical devices, however, does not align with the critical goal of keeping Americans safe from harm.

**Questions**

We remain convinced that the risks of expanding conditional approval to human drugs and devices are significant. We are therefore seeking clarification on what actions the FDA intends to take with its "progressive approval for devices" proposal, and we ask that you reaffirm the commitments made by former Commissioner Gottlieb on behalf of the FDA regarding the unsuitability of conditional approval for any human medical products. To address these matters, we ask that you please provide us with answers to the following questions no later than July 8, 2019:

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"?[20] If not, please explain why not.

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[16] The New York Times, "F.D.A. Halts U.S. Sales of Pelvic Mesh, Citing Safety Concerns for Women," Sheila Kaplan and Matthew Goldstein, April 16, 2019, https://www.nytimes.com/2019/04/16/health/vaginal-pelvic-mesh-fda.html?module=inline

[17] The Washington Post, "Sale of Essure Birth Control Implant to be Halted by Bayer; U.S. Last to Sell Controversial Device," July 20, 2018, https://www.washingtonpost.com/news/to-your-health/wp/2018/07/20/sales-of-essure-birth-control-implant-halted-by-bayer-u-s-was-last-to-sell-controversial-device/?utm_term=.4e4b9374ae7c; U.S. Food and Drug Administration, "FDA Activities: Essure," May 15, 2019, https://www.fda.gov/medical-devices/essure-permanent-birth-control/fda-activities-essure.

[18] The New York Times, "Weak Reporting System Let Risky Surgical Device Stay in Use," Denise Grady, February 8, 2017, https://www.nytimes.com/2017/02/08/health/morcellator-gao-report-fda.html?module=inline.

[19] U.S. Food and Drug Administration, "Medical Device Safety Action Plan: Protection Patients, Promoting Public Health," https://www.fda.gov/about-fda/cdrh-reports/medical-device-safety-action-plan-protecting-patients-promoting-public-health.

[20] Med Tech Dive, "FDA Progressive Device Approval Raises Eyebrows," David Lim, April 16, 2019, https://www.medtechdive.com/news/fda-progressive-device-approval-proposal-raises-eyebrows/552778/.

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) 2014-15 strategic priorities, Director Shuren referred to the "progressive/conditional approval pathway."[21] How, if at all, is "progressive approval" different than "conditional approval"?

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."[22] How does this approach to sunsetting approval of a device comply with the requirements of procedural due process?

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.

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

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."[23] Please provide an update on the new policies and internal procedures CDRH is pursuing as part of this effort.

Sincerely,

Elizabeth Warren
United States Senator

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

[21] Jeff Shuren, "National Medical Device Evaluation System: CDRH's Vision, Challenges, and Needs" https://mdepinet.org/wp-content/uploads/S2_1_Shuren.pdf.
[22] U.S. Department of Health and Human Services, "Fiscal Year 2020 Food and Drug Administration Justification and Estimates for Appropriations Committees," pp. 39-40, https://www.fda.gov/media/121408/download.
[23] U.S. Food and Drug Administration, "2018-2020 Strategic Priorities: Center for Devices and Radiological Health," January 2018 , pp. 16., https://www.fda.gov/media/110478/download.