FDA's 2023 Priorities and Beyond
Andi Fristedt
FDA Deputy Commissioner for Policy, Legislation, and International Affairs
Peking University, Beijing
June 14, 2023

Good morning. Thanks for having me. It's such a pleasure to meet with the students and faculty of your renowned institution. I know that the FDA has enjoyed nearly 20 years of collaborating with Peking University in helping to train the next generation of leaders in the pharmaceutical industry. Indeed, my colleague Mark Abdoo spoke here four years ago.

Today I'm going to talk about the important role of our Prescription Drug User Fee Program or PDUFA and other user fee programs, discuss the many new program enhancements for medical product development that are rolling out this year, describe a few of the significant FDA reforms enacted by Congress in late December, and look ahead to the future.

PDUFA helps the FDA fulfill its mission of protecting the public health while facilitating the timely availability of innovative FDA-regulated products, all without compromising the agency's commitment to scientific integrity, regulatory standards, patient safety, and transparency.

The program was enacted more than 30 years ago – in 1992. Before that, the FDA lacked sufficient staff to perform timely reviews, which could stretch out for more than two years.

This lack of staff meant that industry meetings with the FDA were often considered a privilege – even the required meetings. And staff didn't have time available to develop the procedures and standards they needed to ensure a consistent and predictable premarket review process. As a result, access to innovative new medicines often lagged behind in the United States compared to other countries.

In response to these obstacles, industry, with support from patient advocates, agreed to pay user fees to supplement the FDA budget in exchange for commitments to reduce review times.

In implementing this system, the FDA took steps to ensure its integrity and make sure that the program would not be perceived as a pay-to-play program, under the sway of the regulated. Thus, even though the FDA was now collecting user fees, the outcomes of its decisions – such as whether to approve a product – continue to be based on science and to be consistent with the legal and regulatory standards that govern the agency. Included in this approach was establishing a culture of transparency and a system of internal oversight, giving the staff the ability to speak their minds and challenge decisions all the way to the Commissioner, and the means for stakeholders, both industry and public interest groups to challenge the agency, including in the courts.

Since 1992, the FDA and industry have negotiated agreements on user fees every five years. As part of this process, companies within the regulated industry agree to pay fees in exchange for commitments from the FDA to meet certain performance goals, such as making decisions on drug applications within a predictable timeline --

or providing access to FDA experts via meetings, as examples. Congress then must pass legislation to reauthorize the agreements and enable the FDA to continue collecting user fees.

Other user fee programs have been adopted since then, beginning with the Medical Devices User Fee Amendments, or MDUFA in 2002 to improve the predictability and transparency of regulatory processes for medical devices, incentivize innovation and get more products to market faster. The Generic Drug User Fee Amendments or GDUFA was enacted in 2012 to help ease the backlog of marketing applications that occurred due to the growth in the number of generic drug applications and the number of foreign facilities making generic drugs. The Biosimilar User Fee Act, or BsUFA, was enacted in the same year authorizing the FDA to collect fees to expedite the review process for biosimilar biological product applications, including postmarket safety activities. The user fee model was also adopted to help fund the FDA's review of submissions for both new and generic animal drugs. Both of these user fee programs must be reauthorized this year. And by the way, user fees on domestic manufacturers and importers of certain tobacco products fund the FDA's tobacco regulatory activities to prevent people from starting to use tobacco products, encouraging tobacco users to quit and reducing the harm caused by tobacco use.

Originally, prescription drug user fees could only be used to support pre-market review of New Drug Applications, or NDAs, and Biological License Applications, or BLAs.

But there's been an evolution. Over time, other activities that relate specifically to prescription drug development, such as preclinical drug development, certain post-marketing activities, and enhancements to technology systems, have also been allowed to be funded by user fees. In addition, user fees help pay for certain FDA inspections, including those that help ensure the rights, safety, and welfare of participants in clinical trials, as well as pre-approval inspections of manufacturing establishments to assess a manufacturer's ability to design and manufacture a product in accordance with t Current Good Manufacturing Practice requirements.

Each five-year reauthorization cycle supports continuous program innovation, evaluation, and improvement. Through successive PDUFA reauthorizations, program enhancements have evolved and expanded to include extensive communication and consultation between drug sponsors and the FDA - throughout the drug development process. These interactions have given the FDA the opportunity to provide more guidance to sponsors, including setting clearer expectations of what data are necessary to properly review and evaluate a drug, getting safe and effective drugs to patients sooner, and enabling sponsors to incorporate advances in regulatory science into their development programs that in turn expedite drug development.

The ledger line is that user fees have been a win for both the FDA and for industry, addressing the reality that the agency's review work was previously under resourced. The user fee regime enabled the agency to speed up the application review process without compromising the FDA's high standards for new drug safety, efficacy, and quality – accomplished even as the FDA witnessed an unprecedented increase in submissions during the COVID-19 pandemic. These enhancements have also improved the potential for first-cycle approval, which means that safe and effective drugs can reach patients sooner.

Moreover, user fees have been a bargain. Researchers at the Department of Health and Human Services developed an analytical model of medical product development over the 2000 to 2018 period. It provided an estimate of the cost of medical product development at each stage of the process from the nonclinical stage to post-marketing. In this model, the cost of the FDA review stage was estimated using user fees paid by industry and the average time it takes for FDA to review a marketing application. The

results show that FDA user fees made up approximately 1% of the total capitalized cost of development for drugs, 2% of the total capitalized cost of development for preventive vaccines, and 0.5% of the total capitalized cost of development for complex medical devices.

In other words, user fees represented a tiny fraction of the total cost to industry of a successful medical product brought to market.

Last year saw the latest update to these user fee programs - PDUFA VII, MDUFA V, GDUFA III and BsUFA III. The U.S. Congress reauthorized all four of these programs in September for five years, from FY 2023, which began last October, to FY 2027.

Let me describe some of the important program enhancements in these programs, beginning with PDUFA VII's impact on cellular and gene therapy development.

The FDA has experienced exponential growth in cellular and gene therapy submissions over the past seven years with nearly 2,000 active development programs. To address the continued influx of submissions, our Center for Biologics Evaluation and Research, known as CBER, has committed to hire additional staff, develop multiple guidances, conduct numerous public meetings to examine new technologies and approaches, establish a patient-focused effort to better understand patient perspectives on gene therapy products, and establish the Operation Warp Speed Communications Pilot for rare diseases, which provides participating sponsors with initial FDA meetings followed by ongoing informal FDA staff interactions via email or in a live meeting, on an as needed basis.

PDUFA VII also contains enhancements to the work of our Center for Drug Evaluation and Research, known as CDER, that will enhance regulatory review and add more flexibility in the type of meetings we hold with industry. I FDA also agreed to establish some innovative new programs.

For example, the Rare Disease Endpoint Advancement Pilot program promotes innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops and public-facing website. As a result of this program, CDER and CBER staff are expected to be able to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

Another example, the Advancing Real-World Evidence Program, is designed to accomplish three things. First, identify approaches for generating real world evidence that meet regulatory requirements in support of labeling for effectiveness (e.g., new indications, populations, dosing information) or for meeting post-approval study requirements; second, to develop agency processes that promote consistent decision-making and shared learning regarding real world evidence; and third, to promote awareness of characteristics of real world evidence that can support regulatory decisions by allowing the FDA to discuss study designs considered in the Advancing Real World Evidence program in a public forum. Meetings will be conducted by both CDER and CBER as well as FDA's Oncology Center of Excellence throughout the five years of PDUFA VII.

PDUFVII also puts a focus on Digital Health Technologies, which offer a vast array of potential benefits in the development of medical products.

As the world enters the fourth industrial revolution in which rich and diverse sources of digital data are available at scale in real time with potentially unlimited storage capacity, these data are becoming

widely used as part of the clinical trial system. Digital health technologies or DHTs provide opportunities to foster more efficient conduct of clinical investigations. For instance, DHTs can facilitate the conduct of decentralized clinical trials, where data can be remotely recorded and analyzed directly from participants as part of everyday tasks wherever the participants may be such as home, school, work, or outdoors. And the use of DHTs in a clinical investigation can help improve patient access to, and participation in, clinical investigations by potentially reducing the burden of required visits to a research site.

The third reauthorization of the Generic Drug User Fee Act seeks to address the fact that only 15 percent of submissions are approved in the first cycle by including new processes and procedures designed to achieve earlier cycle approval and by enhancing the product development, pre-submission, and mid-review cycle meetings prior to submitting an Abbreviated New Drug Application to market a generic drug. In addition, the FDA is setting new goals for the completion of product specific guidances that are important for the development of complex generic drugs. Also, in GDUFA III, the FDA committed to make further enhancements to its generic drug regulatory science program. Y FDA's priority science and research initiatives involving generic drugs for FY '23 include developing methods for generics to address impurities such as nitrosamines and research on enhancing the efficiency of bioequivalence approaches for certain complex ingredients and products.

Finally, a few words about the Biosimilar User Fee Act. It was enacted in 2012 and the first biosimilar was approved by the FDA in 2015. As of January 2022, there are more than 30 FDA-approved biosimilars with dozens more in the queue. BsUFA has enabled the FDA to implement a new review model and expand staff capacity to provide increased communication with companies, facilitating biosimilar product development. With BsUFA III the FDA will introduce new supplement types and expedited review timelines to speed the review of supplements. In addition, the FDA intends to enhance communication and feedback during the product development process and during application review and also intends to introduce a new pilot program that will enhance regulatory decision making and facilitate science-based recommendations.

Congress typically uses the user fee reauthorization as a vehicle for attaching proposed reforms to the FDA regulatory framework, but last year lawmakers were unable to reach agreement on these provisions on time. And so, FDA-related provisions were included in a separate consolidated appropriations bill, signed into law on December 29, 2022. These reforms can be found in the Food and Drug Omnibus Reform Act of 2022 or FDORA and the Prepare for and Respond to Existing Viruses, Emerging New Threats, and Pandemics Act otherwise known as the PREVENT Pandemics Act in that appropriations bill.

Among the most notable reforms in FDORA are those having to do with the FDA's accelerated approval process for drugs and biologics. This accelerated approval pathway was established in 1992, largely in response to the HIV/AIDS epidemic, to help get products to market that treat serious or life-threatening conditions and fulfill unmet medical needs. This pathway is "accelerated" in that it allows sponsors to seek approval with data that demonstrates efficacy based on an effect on a surrogate or intermediate endpoint that is believed to predict clinical benefit for the disease or condition, rather than data demonstrating an effect on a primary clinical endpoint. For HIV/AIDS, the surrogate endpoint has been viral load. The pathway has been used primarily for drugs aimed at diseases that progress slowly and as

a result, waiting for trials that demonstrate primary clinical endpoints would mean a years-long delay before the study drug could be eligible for approval under a traditional pathway.

As a condition of receiving accelerated approval, sponsors have been required to conduct post-approval studies to confirm the clinical benefit of the drug. Once that's satisfied, the conditions of accelerated approval are removed. FDORA clarifies FDA's authority to specify the conditions for any post-approval studies. The agency has significant flexibility in setting forth such conditions, which may include, for example, enrollment targets, the study protocol and milestones – including the target date of study completion. It also gives the FDA explicit authority to require that confirmatory studies be underway prior to approval, as well as more streamlined procedures to remove drugs from the market, when necessary, that is, when the confirmatory study is not completed or fails to confirm benefit, if the data before the agency no longer shows that the product is safe and effective. We are working diligently to implement these important reforms and understand that further guidance outlining these changes to the accelerated approval pathway may be helpful.

Enhancing diversity in clinical research is also an important priority. Several FDORA provisions encourage changes that will lead to greater diversity in the populations participating in clinical studies. Sponsors are now required to submit to the FDA diversity action plans for certain late-stage trials for drugs and devices, unless otherwise waived or excepted. The FDA is tasked with updating guidance on diversity action plans for clinical studies and hosting public stakeholder workshops focused on enhancing clinical study diversity.

We were also tasked with issuing or revising guidances on the appropriate use of decentralized clinical studies in the development of drugs and devices, how digital health technologies can be best used in clinical trials, and how seamless, concurrent, and other innovative clinical trial designs can support expedited drug application development and review. Congress directed the FDA to perform that work within one year.

FDORA also addresses Bioresearch Monitoring Inspections. The new law clarifies that FDA is permitted to inspect facilities involved in the development, conduct, or analysis of clinical and non-clinical studies submitted to the FDA, as well as other persons holding study records or involved in the study process. Congress has asked the FDA to draft guidance on this additional inspection authority within 18 months.

Finally, the PREVENT Pandemics Act states that foreign drug and device manufacturing establishments are subject to registration and listing requirements even if a drug or device undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the U.S. prior to being imported or offered for import into the United States. The law requires the FDA to update its registration regulations, as appropriate, within two years to reflect this provision.

I've discussed these new reforms from the point of view of medical product development. But I want to give you some idea of the breadth of the new law. For example, in addition to many other provisions, it substantively expanded the FDA's authority to regulate cosmetics for the first time since 1938 and gave the FDA new hiring authority, to support hiring the best and the brightest into our human foods program and other critical positions across the agency. Not all of the FDA's legislative priorities were adopted in FDORA and the PREVENT Pandemics Act, and so the agency will continue to work with Congress on those priorities that weren't enacted, including the regulatory oversight of diagnostic testing, dietary supplement product listing, and the application of orphan-drug exclusivity.

We also believe there are several areas where Congress could build on our current authorities to improve our visibility into the supply chain, strengthen our ability to oversee aspects of the drug supply chain, and support continued access to critical drug products. Examples include requiring drug manufacturers to notify the FDA of an increase in demand or disruptions in the supply chain; lengthening expiration dates to mitigate critical drug shortages; requiring drug labeling to include the original manufacturer and supply chain information; and providing for enhanced reporting by drug manufacturers of suppliers and reliance on such suppliers. We are also seeking to expand our authority to prevent device shortages, removing temporal restrictions tying our authority to public health emergencies – because we know the risk of potential device shortages is not always tied to a public health emergency.

Today, I've covered a lot of detailed, complex issues. I hope this provided a solid grounding in the FDA's user fee programs for human medical products of all kinds – some of the significant new reforms to the FDA's regulatory framework found in FDORA and the Prevent Pandemics Act – and FDA's current legislative priorities.

There are two important takeaways from my remarks that I'd like to emphasize.

The first is that though the FDA collects these fees from medical product manufacturers, the outcome of our decision on approving or disapproving a product is based solely on our commitment to scientific integrity, regulatory standards, patient safety, and transparency.

The second point is that the user fee system works. It allows my agency to meet certain performance goals such as making decisions on drug applications within a predictable timeline. The system improves the potential for first-cycle approval, getting safe and effective drugs to patients sooner. As a result, the United States continues to be a global leader in drug innovation and Americans are now typically the first to benefit from new, safe, and effective medicines.

Thank you for your time today and I look forward to taking a few questions.