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"CHECK UP: EXAMINING FDA REGULATION OF DRUGS, BIOLOGICS, AND DEVICES"

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Introduction

Chair Guthrie, Ranking Member Eshoo, and members of the Subcommittee, thank you for the opportunity to testify before you to discuss the Food and Drug Administration's (FDA or the Agency) efforts to promote innovation and protect the public health.

FDA helps ensure that Americans can have confidence in the medical products they are using. The Agency is charged with overseeing and helping to advance innovations upon which patients, healthcare providers, and the U.S. healthcare system depend.

Staying ahead of the rapid advancements made across regulated industries is a fundamental but challenging aspect of FDA's work. Biomedical discovery, science, computing, and engineering take decades to mature as part of the development of safe and effective products. FDA is most effective when we balance innovation and our obligation to ensure that therapies are safe and effective. User fees are an integral part of these efforts and support our mission of protecting and promoting the public health, with the ultimate goal of getting treatments to the patients who need them. User fees have supported programs to strengthen input from patients and enhance product safety, resulted in reduced time to regulatory actions, supported innovative pilot programs to identify regulatory efficiencies, and allowed the Agency to recruit and retain top talent and expertise. The user fee programs helped us navigate the COVID-19 pandemic and through the latest reauthorization, will allow us to continue to support the modernization of clinical trials, leverage regulatory flexibilities to address rare diseases, and ensure medical devices are designed with adequate cybersecurity measures in place. Timely and continued reauthorization of these programs is imperative and sets up the Agency to successfully continue its important work in the face of public health emergencies, natural disasters, and times of rapid innovation.

We are at a critical point regarding innovation with gene editing for rare diseases and the application of artificial intelligence across the spectrum of products FDA regulates. The progress in these areas has been exciting, and through cooperation with researchers, Congress, and the public, we believe that FDA can stay ahead of and facilitate responsible development of these groundbreaking advances to benefit the American people.

For example, in 2023, the Center for Biologics Evaluation and Research (CBER) approved gene therapies for the treatment of rare diseases such as sickle cell disease and Duchenne muscular dystrophy. CBER also approved vaccines to prevent respiratory syncytial virus (RSV) disease (including the first maternal vaccination to protect infants from RSV disease). In 2023, the Center for Drug Evaluation and Research (CDER) approved new therapies for neurological conditions, such as ALS, Alzheimer's disease and migraines. CDER also approved drugs targeting type 2 diabetes in children, different types of anemia, and chronic weight management, among other heart, blood, kidney, and endocrine disorders. The Center for Devices and Radiological Health (CDRH) last year authorized the highest number of novel devices on record (excluding Emergency Use Authorizations (EUAs)) in CDRH's more than 40-year history.[1] This includes clearance of the first over-the-counter fentanyl test and a first-of-its kind Artificial Intelligence/Machine Learning-Based Software that identifies patients at risk for having or

[1] https://www.fda.gov/media/175479/download?attachment

developing sepsis. Since 2009, the number of innovative medical devices FDA authorized for marketing each year has increased five-fold.

Of course, we could not do this without continued support from Congress. We appreciate the efforts of the legislative branch and the members of this Subcommittee in particular, especially as it relates to the successful reauthorization of our user fee programs. Mostly recently, in December 2022, the Food and Drug Omnibus Reform Act of 2022 (FDORA) was passed into law as part of the Consolidated Appropriations Act of 2023. FDORA reauthorized key FDA programs and provided additional authorities and clarity for important efforts regarding accelerated approval, rare disease treatments, clinical trial modernization and clinical trial diversity, predetermined change control plans, animal testing alternatives, the use of platform technologies, medical device cybersecurity, and more. We are working diligently to implement this legislation and will continue to keep Congress informed of our progress.

Regulatory Pathways and New Approaches

The Agency has many extraordinary opportunities ahead, with advancements in drug target identification, medical product manufacturing, clinical trial design, and beyond. We are using the flexibilities afforded in our current regulatory framework—including those championed by Congress—to enable breakthroughs in medical science to be translated into medical products that improve health outcomes, all while ensuring that drugs and medical devices remain safe and effective.

Drugs and Biologics

Expediting the availability of drugs that treat serious diseases, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments, is one such approach. FDA has developed five distinct and successful approaches to making such drugs available as rapidly as possible:[2]

- Breakthrough Therapy Designation
- Fast Track Designation
- Priority Review
- Accelerated Approval
- Regenerative Medicine Advanced Therapy Designation[3]

Of the 55 novel drugs approved by CDER in 2023, 35 (64 percent) were approved first in the United States. Of these novel drugs, 20 (36 percent) were first-in-class. Additionally, 36 (65 percent) of the 2023 novel drug approvals were designated in one or more of the noted expedited programs. A large majority 14 (78 percent) of the 18 novel biologics approved by CBER utilized one or more of these expedited programs as well. FDA is committed to supporting these programs, while continuing to ensure that the drugs approved through these pathways are safe

[2] https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
[3] https://www.fda.gov/media/86377/download

and effective. Below, we provide more information on accelerated approval, a key approach to make drugs available as rapidly as possible.

Accelerated approval is an important tool that allows for earlier approval of drugs that treat serious conditions, and address an unmet medical need, based on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that can be used to predict clinical benefit but is not itself a measure of clinical benefit. In some cases, a surrogate endpoint is known to predict clinical benefit and can be relied upon to support traditional approval. The use of a surrogate endpoint or intermediate clinical endpoint can considerably shorten the time prior to receiving FDA approval.

In the case of accelerated approval, there are data and other information to support the claim that the surrogate is reasonably likely to predict clinical benefit, and confirmatory studies are required that are intended to verify and describe the anticipated clinical benefit. If the confirmatory trial verifies clinical benefit, FDA considers the confirmatory trial requirement to have been met, and FDA converts the drug to traditional approval. If the confirmatory trial does not show that the drug provides clinical benefit, FDA may use regulatory procedures to withdraw approval of the drug. We aim for transparency and post information on our website about drugs granted accelerated approval that have confirmatory trials ongoing, that have completed trials that verified clinical benefit, or that have had their approval withdrawn.[4]

FDA takes seriously its responsibility to hold applicants accountable and to complete confirmatory trials that verify a drug provides clinical benefit. This is a critical element of the accelerated approval pathway—balancing the residual uncertainty associated with the use of a surrogate or intermediate endpoint with a requirement for a sponsor to complete a postmarketing confirmatory study. As part of FDORA, Congress provided FDA with additional authorities regarding accelerated approval and revised provisions in the Federal Food, Drug, and Cosmetic (FD&C) Act related to the expedited withdrawal process for a drug approved under accelerated approval that fails to confirm clinical benefit.[5]

In February 2024, FDA announced its final decision to withdraw approval of a drug that was approved under accelerated approval. The Agency determined that: (1) the confirmatory study conducted as a condition of accelerated approval did not confirm that drug's clinical benefit, and (2) the available evidence demonstrates that the drug is not shown to be safe or effective under its conditions of use. This was the first time FDA used the amended streamlined procedures for withdrawal of accelerated approval. In accordance with the new procedures, FDA provided the manufacturer with a notice of proposed withdrawal of approval, an explanation for the proposed withdrawal, and a public comment process. The manufacturer submitted a written appeal and met with the Commissioner's designee, and FDA responded with the withdrawal decision, as noted above.

[4] https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
[5] See 21 U.S.C. 356(c)

FDA has been implementing additional authorities granted under FDORA that authorize the Agency to require, when appropriate, that a postmarketing confirmatory study be underway prior to approval. This provision helps to ensure the timely completion of confirmatory studies conducted to verify and describe predicted clinical benefit. FDA recently refused to give accelerated approval to a drug, per the authorities under this section.

In an effort to ensure the consistent development and application of policies for use of accelerated approval across FDA, and as provided by FDORA, FDA established the Accelerated Approval Coordinating Council (AACC) in 2023. The Council, currently chaired by Dr. Peter Marks, Director of CBER, has met to discuss policy issues related to the new FDORA authorities to help ensure they will be used consistently across the Centers.

Medical Devices

Similarly, CDRH has created several programs and structures to advance innovation and ensure access to critical medical devices. CDRH is grateful to Congress for the authority to establish the Breakthrough Devices Program, which continues to help increase access to innovative, high-quality medical devices by expediting their development, assessment, and review, while also ensuring these devices meet FDA's statutory standards for premarket approval, 510(k) clearance, or De Novo marketing authorization. Since the launch of the Breakthrough Devices Program, the Agency has granted Breakthrough designation to 921 devices, including some originally designated under the Expedited Access Pathway program that started in 2015. In 2023 alone, CDRH granted Breakthrough designation to 167 devices and granted marketing authorization to 29 Breakthrough Devices. We also issued an updated guidance that clarifies additional considerations in designating devices, including how the Breakthrough Devices Program may be applicable to certain devices that benefit populations impacted by health or healthcare disparities. The updated guidance also clarifies that the program may be available for certain non-addictive medical products to treat pain or addiction, consistent with the SUPPORT Act.[6]

For devices that are reasonably expected to offer a significant safety improvement, but do not otherwise qualify for the Breakthrough Devices Program due to the less serious nature of the disease or condition they are intended to treat, diagnose, or prevent, the voluntary Safer Technologies Program (STeP) may be available. Similar to the Breakthrough Devices Program, STeP offers manufacturers an opportunity to interact with FDA's experts through several different program options to efficiently address topics as they arise during device development. There are currently 35 devices included in the STeP program, 15 of which were enrolled in 2023. Additionally, in 2023, two STeP Devices were authorized for marketing.[7]

CDRH's regulatory science program continues to advance upstream innovation through many efforts, including increasing the number of publicly available regulatory science tools (RSTs) for innovators. RSTs help to streamline the path to market for safe and effective technologies by allowing innovators to efficiently navigate the design and redesign loop. RSTs include methods, models, data sets, clinical outcome assessments, and more. CDRH has made more than 20 new

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program

[7] CDRH Annual Report 2023, https://www.fda.gov/media/175479/download?attachment.

tools available every year, with more than 150 RSTs now in our online catalog. RSTs have been used in over 900 premarket submissions. In one case, a single RST has been used in more than 450 premarket submissions across all eight of the Center's Offices of Health Technology (OHTs). CDRH continues to expand the number of RSTs and will continue updating the public as they become available.

In addition, in 2023, CDRH launched and then expanded the Total Product Life Cycle Advisory Program (TAP) Pilot, a key component of the latest reauthorization of the Medical Device User Fee Amendments (MDUFA). TAP is intended to foster innovation in the medical device industry by promoting early, frequent, and strategic communications between FDA and medical device sponsors, while maintaining the Agency's rigorous standards for device safety and effectiveness. The long-term vision for TAP is to help spur more rapid development and increased access to safe, effective, high-quality medical devices. A mature TAP is also intended to help ensure the sustained success of the Breakthrough Devices Program.

CDRH is enrolling devices from the OHT on cardiovascular devices and the OHT focused on neurological and physical medicine devices. As of April 30, 2024, the FDA has enrolled 45 devices in the TAP Pilot. The Center plans to continue enrolling more innovators and their devices into TAP, with the goal of enrolling up to 325 devices by 2027.

Bringing Therapies to Patients with Rare Diseases

FDA also works to facilitate, support, and accelerate the development of medical products that may benefit patients with rare diseases. CDER and CBER approved 277 orphan drugs and biologics from FY 2013 through 2023. In 2023, we continued to build on that success through programs such as CDER's Accelerating Rare disease Cures (ARC) Program and the Rare Disease Endpoint Advancement (RDEA) Pilot Program.

ARC is a CDER-wide collaborative effort that brings together expertise from many CDER Offices and Programs. The Center's Rare Diseases Team works closely with FDA's rare disease stakeholders to fulfill its user fee commitments to facilitate, support, and accelerate the development of drug and biological products, in addition to leading the development of cross-cutting rare disease guidance documents and ensuring that policies and practices are shared across the Center.

These and other efforts have contributed to CDER's approval of 28 new molecular entities (NME) for orphan-designated diseases or conditions in 2023. This represents over 50 percent of all NME approved in 2023. Those include:

- the first enzyme replacement therapy for the treatment of the non-central nervous system manifestations of alpha-mannosidosis, a rare genetic condition characterized by the lack of the alpha-mannosidase enzyme in the body;
- the first treatment for Friedreich's ataxia, a rare, inherited, degenerative disease that damages the nervous system, characterized by impaired coordination and walking; and

- an antisense oligonucleotide to treat patients with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene (SOD1-ALS). The accelerated approval was based on a reduction in plasma neurofilament light (NfL), a blood-based biomarker of axonal (nerve) injury and neurodegeneration. This was the first time this biomarker was used as a primary endpoint.

CDER's ARC has also launched the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) project. The project aims to better understand the unique challenges in bringing rare disease products to market and produce educational materials on fundamental topics. To compliment the LEADER 3D effort, CDER's Patient-Focused Drug Development staff is working with the National Organization for Rare Disorders to develop an advanced drug development education series for patients and patient groups.

Another key development for CDER is setting up the Genetic Metabolic Diseases Advisory Committee (GeMDAC), which will allow the Office of New Drug's Division of Rare Diseases and Medical Genetics to seek expert advice from a committee of clinicians, industry experts, academics, patients, caregivers and other external stakeholders when evaluating the potential benefits and risks of a new therapy for genetic metabolic diseases.

In March 2024, CDER announced the formation of the Center's Quantitative Medicine (QM) Center of Excellence (CoE). QM involves the development and application of exposure-based, biological, and quantitative modeling and simulation approaches derived from nonclinical, clinical, and real-world sources to inform drug development, regulatory decision-making, and patient care. These approaches have high potential to facilitate the development of rare disease therapies by helping to advance innovative therapeutic medical product development and informing regulatory decision-making. The CoE will spearhead QM-related policy development and best practices; facilitate systematic outreach to scientific societies, patient advocacy groups, and other key stakeholders; and coordinate CDER's efforts around QM education and training. As a result, the QM CoE is expected to help streamline and accelerate drug development and speed the delivery of safe and effective medicines to the public.

Like CDER, CBER's Rare Disease Program is dedicated to advancing the development and timely approval of safe and effective biologics to improve the lives of children and adults living with rare diseases. A critical element of CBER's Rare Disease Program is the Center's Rare Disease Coordinating Committee (RDCC), a multi-disciplinary forum with representation from each of CBER's offices that provides an opportunity for information-sharing for rare disease-related policy, activities, and events that address the program's objectives. Efforts include facilitating consideration of the patient perspective in regulatory decision making, ensuring that the Center's review offices consider flexible and feasible regulatory approaches in review, and strengthening awareness of CBER's regulatory research programs that support development of such biological products.

These coordinated efforts have become critical as the product landscape has evolved rapidly in last few years. In the past, most biological products regulated by CBER and intended or approved for use in rare diseases were derived from plasma and used to treat and manage rare blood disorders, immune deficiencies, and various toxicities. Today, new and innovative

biological products, such as cell and gene therapy products, are being evaluated for an ever-expanding array of rare disease indications. In just the past six months CBER has approved:

- the first two cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older, including the first FDA-approved treatment utilizing genome editing technology;
- a treatment for children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD);
- a treatment for ambulatory pediatric patients aged four through five years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene; and
- the first cellular therapy indicated for the treatment of adult patients with a type of skin cancer (melanoma) that is unable to be removed with surgery (unresectable) or has spread to other parts of the body (metastatic) that previously has been treated with other therapies.

Together, CBER and CDER established the Rare Disease Endpoint Advancement (RDEA) Pilot Program to support novel endpoint efficacy development for drugs that treat rare diseases. The RDEA Pilot Program is designed to:

- advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process;
- promote innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and a public-facing website; and
- develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

For fiscal years (FY) 2024 through 2027, FDA will accept up to one RDEA proposal per quarter with a maximum of three RDEA proposals per year. For each RDEA proposal that FDA admits into the pilot program, the Agency will conduct an initial meeting and, if requested, up to three follow-up meetings.

Building on lessons learned during the COVID-19 public health emergency, in 2023 CBER and CDER announced the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, where participants will be able to obtain frequent advice and regular informal communication with FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population. The program is open to sponsors of products currently in clinical trials under an active Investigational New Drug application (IND), regulated by CBER or CDER. CBER-regulated products must be a gene or cellular therapy intended to address an unmet medical need as a treatment for a rare disease or serious condition, which is likely to lead to significant disability or death within the first decade of life. CDER-regulated products must be intended to

treat rare neurodegenerative conditions, including those of rare genetic metabolic type. The Agency has selected three pilot participants for each center. The pilot launched recently, and we look forward to seeing whether this type of frequent and informal communication between sponsors and FDA staff can help to move development programs for rare diseases forward more efficiently.

CDRH has two important programs to support innovation and facilitate access to medical devices for the treatment or diagnosis of rare and life-threatening diseases. The Breakthrough Devices Program, as discussed earlier, offers manufacturers an opportunity to interact with FDA experts through several different program options to efficiently address topics as they arise during the device development phase. This interaction can help manufacturers receive feedback from FDA and identify areas of agreement in a timely way. Manufacturers can also expect prioritized review of their submission. The Breakthrough Devices Program has supported the marketing authorization of digital health technologies assisting in the management of rare conditions such as seizure disorders and obstruction to cerebrospinal fluid flow.

Another program, the Humanitarian Use Device or HUD program, was established in 1990 with enactment of the Safe Medical Devices Act and creates an alternative pathway for getting market approval for medical devices that may help people with rare diseases or conditions. A device that has received HUD designation is eligible for an Humanitarian Device Exemption (HDE) approval if, among other criteria, FDA determines that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness, while also taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Importantly, FDA approval of an HDE authorizes an applicant to market the HUD, subject to certain profit and use restrictions. HUDs cannot be sold for profit, except in certain circumstances. Most importantly, they can only be used in a facility after an IRB or appropriate local committee has approved their use in that facility, except in certain emergencies.

Through our HDE pathway, FDA has approved devices for acute kidney injury due to sepsis in children as small as 22 pounds, and a non-invasive and radiation-free therapy for osteoid osteomas, a benign but painful bone tumor that occurs predominantly in children and young adults.

Each of these efforts is part of a comprehensive effort to address challenges and advance rare disease product development. The Agency strives to take a multifaceted approach to meaningfully engage relevant stakeholders, including patients, caregivers, clinicians, and researchers, and will continue to engage with Congress. FDA knows much of the groundbreaking technology in science will benefit rare disease populations in particular, and we continue to consider creative solutions and changes to our regulatory processes that may be needed as these innovations come to the market.

Modernizing Clinical Trials

Clinical trials play a crucial role in advancing science and supporting the development of medical products to address unmet patient needs. Reliable data from well-designed trials about a medical product's safety and effectiveness are critical to FDA's decision-making about a

product's benefits and risks. Just last month, FDA announced the launch of the CDER Center for Clinical Trial Innovation (C3TI). C3TI will be a central hub within CDER to support the implementation of innovative approaches to clinical trial design and conduct. C3TI's mission is to promote existing and future clinical trial innovation through enhanced communication and collaboration. One of the goals of these efforts is to improve the efficiency of drug development, bringing safe and effective drugs to patients as quickly as possible. C3TI will help foster innovation across industry and therapeutic areas, and across new and ongoing initiatives within CDER.

C3TI will include demonstration projects with three initial project areas 1) point-of-care or pragmatic trials; 2) Bayesian statistical analyses; and 3) trials using selective safety data collection. This new initiative within CDER will enable both internal and external parties to access information on clinical trial innovation efforts more easily, identify resources that can further support the use of innovative modalities, and identify development programs where a concerted approach to the use of clinical trial innovations would be impactful. The goals of these efforts are to improve the efficiency and effectiveness of clinical trials, including increasing the participation of diverse populations in clinical trials to help fill data gaps, and, in turn, accelerate the development of safe and effective new drugs.

To help ensure the generalizability of the results of clinical research to the intended population, clinical research should be inclusive of racial and ethnic minority groups, as well as other populations that have historically been underrepresented in clinical trials. In general, clinical trials, particularly advanced stage trials, that enroll participants reflecting the diverse characteristics of patients who will use the medical product will further strengthen prescribers' and patients' confidence that the findings from clinical trials are broadly applicable and maximize the public health impact of FDA cleared or approved products. FDORA's clinical trial diversity and modernization provisions made clear that this is a shared and important area of focus, particularly for members of this Subcommittee.

In May 2023, FDA issued draft guidance providing recommendations for sponsors, investigators, and other stakeholders regarding the implementation of decentralized clinical trials (DCTs) for drugs, biological products, and devices.[8] DCTs often incorporate digital health technologies (DHTs) to capture healthcare information for the clinical trials directly from individuals. DHTs are improving, making it easier to collect, transfer, and store electronic data. DCTs and DHTs may help make clinical trials more inclusive because they can reduce barriers to participation. Of course, there can be technical hurdles as well. Aware of both the promise and challenges of DCTs and DHTs, FDA has been working on resources for sponsors, patients, healthcare providers, and the broader community. These resources include the FDA DHT for Drug Development website[9] and new opportunities for stakeholder engagement with FDA. FDA created a framework that includes workshops, demonstration projects, stakeholder engagement, a website, internal processes to evaluate DHTs, and other initiatives.[10] FDA also established an

[8] https://www.fda.gov/media/167696/download

[9] https://www.fda.gov/science-research/science-and-research-special-topics/digital-health-technologies-dhts-drug-development

[10] https://www.fda.gov/media/166396/download

internal steering committee to provide advice on the general use or feasibility and implementation of DHTs in drug and biological product development.

In addition, the Agency has numerous ongoing efforts that are designed to help ensure that participants in clinical investigations reflect the population that ultimately may use the medical product when approved. Some examples of FDA's most recent efforts include:

- Hosting the *Public Workshop to Enhance Clinical Study Diversity*[11] in collaboration with the Clinical Trials Transformation Initiative in November 2023;
- Issuing draft guidance on January 29, 2024, on the *Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products*[12,13]; and
- Issuing draft guidance on March 1, 2024, on *Key Information and Facilitating Understanding in Informed Consent* in collaboration with the HHS Office for Human Research Protections (OHRP).[14]

CDRH has made additional efforts to strengthen and streamline the clinical trial enterprise, including through significantly reducing the time to authorize well-designed clinical trials, establishing new policies for early feasibility studies, and working with partners to create clinical trial networks. CDRH has reformed its clinical trial program to make it more attractive for industry to perform studies in the United States, which can ultimately help patients have earlier access to innovative technologies that meet FDA's standards for marketing authorization. In fact, CDRH decreased the median time to clinical trial authorization by 90 percent from nearly a decade ago, and has maintained the reduced time to authorization.[15] CDRH's Early Feasibility Studies Program, in which devices are evaluated early in development, continues to be used across device areas, and has seen a doubling in growth since the program began.[16]

We understand the significance of the draft guidance on clinical trial diversity plans, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials,*[17] and FDORA's requirement to issue new draft guidance or update existing draft guidance on clinical trial diversity action plans.[18] FDA is working diligently on draft guidance related to diversity action plans. We do note that to date FDA has received approximately 250 diversity plans from sponsors subsequent to the issuance of the draft

[11] https://www.fda.gov/drugs/news-events-human-drugs/discussing-approaches-enhance-clinical-study-diversity-public-workshop-11292023#event-information.
[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials-and-clinical-studies-fda-regulated-medical.
[13] This draft guidance revises the final guidance for industry and FDA staff entitled Collection of Race and Ethnicity Data in Clinical Trials issued on October 26, 2016 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials).
[14] Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/key-information-and-facilitating-understanding-informed-consent-guidance-sponsors-investigators-and
[15] 2024 CDRH Innovation Report, https://www.fda.gov/media/177865/download
[16] https://www.fda.gov/media/176925/download
[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations
[18] See section 3602(b) of FDORA.

guidance, published in April 2022. These and other efforts reflect the Agency's longstanding commitment to promoting diversity and inclusion of underrepresented populations in clinical trials to help improve the generalizability of results.

Real World Data and Evidence

FDA also has a long history of using real-world data (RWD) and real-world evidence (RWE) to support marketing authorization of medical devices and monitor and evaluate the post-market safety of drugs and devices. CDRH, for instance, has authorized over 100 devices that leverage RWE usage in support of regulatory decision-making from the full continuum of clinical and device areas, and include Premarket Approval Applications (PMAs), 510(k)s, De Novo classification requests, Humanitarian Device Exemptions (HDEs), and PMA supplements.[19,20] The Center has worked with sponsors and other stakeholders to leverage RWE and RWD in place of conventional clinical trial data to reduce review time and answer device questions in support of regulatory decisions. CDRH has also engaged with 100 national or regional registries from 45 countries to support these efforts.[21]

In addition to the routine use of RWE to inform safety, CDER and CBER increasingly leverage RWD to inform decisions relating to effectiveness, including the expansion of the indication for a key transplant medication that relied primarily on RWE, changes in a dosing regimen for an important pediatric seizure medication, and use of registry data and confirmatory evidence in rare disease programs. The Agency continues to work with sponsors, patient advocates, and other stakeholders, such as data aggregators, to realize the full potential of RWD and RWE in clinical study design to facilitate development of novel medical products. We are committed to realizing the full potential of fit-for-purpose RWD to generate RWE that will advance the development of therapeutic products and strengthen regulatory oversight of medical products across their lifecycle.

To that end, FDA has published a series of guidances to help advance real world evidence, most recently publishing guidance on use of non-interventional studies to contribute to a demonstration of substantial evidence of effectiveness and/or evidence of safety of a drug [22]and a guidance on use of RWE to support regulatory decision making for medical devices.

Artificial Intelligence (AI) and Machine Learning (ML)

FDA recognizes that the increased use of AI, including ML, across all our regulated industries presents new and unique opportunities and challenges. For example, FDA has seen a significant increase in the number of drug and biologic application submissions using AI/ML components over the past few years, as well as an increasing number of AI/ML-enabled devices. We have been preparing for this major technology wave and, to respond to this evolving landscape, FDA

[19] 2024 CDRH Innovation Report, https://www.fda.gov/media/177865/download
[20] Leveraging Real World Evidence in Regulatory Submissions of Medical Devices, https://www.fda.gov/news-events/fda-voices/leveraging-real-world-evidence-regulatory-submissions-medical-devices
[21] 2024 CDRH Innovation Report, https://www.fda.gov/media/177865/download
[22] https://www.fda.gov/media/177128/download

has accelerated its efforts to create an agile regulatory ecosystem that can facilitate innovation while safeguarding public health.

The Agency is also working with other parts of the Department of Health and Human Services (HHS) and the U.S. Government to further an AI healthcare-centric strategy with appropriate guardrails.[23] As part of this effort, CDER, in collaboration with the CBER and CDRH, issued a discussion paper, "Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products," in May 2023 to communicate with a range of interested parties and to explore relevant considerations for the use of AI in the development of drugs, biological products, and medical devices intended to be used with drugs.[24] FDA received over 800 distinct comments from 65 entities on the discussion paper. That feedback, in addition to CDER's experience with over 300 submissions with AI components since 2016, was used to inform the publication of another paper in March of 2024, titled "Artificial Intelligence and Medical Products: How CBER, CDER, CDRH, and OCP are Working Together,"[25] that describes how FDA's medical product Centers plan to align their efforts to advance the responsible use of AI for medical products. This entails building regulatory approaches that, to the extent feasible, can be applied across various medical products and uses within the healthcare delivery system. In addition, the feedback received on the discussion paper will be used to inform the development of an AI guidance that will be published later this year, titled *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drugs and Biological Products.*

In March 2023, CDER also released a discussion paper to solicit public and stakeholder input on AI in drug manufacturing to better identify areas of policy consideration for AI technologies. This discussion paper proposed areas of consideration based on CDER's evaluation of the existing regulatory framework: standards for developing and validating AI models, clarification on regulatory oversight for AI in pharmaceutical manufacturing, maintenance of cloud applications and continuously learning AI systems that adapt to real-time data, and data management practices commensurate with the volume of data generated.

For medical devices, digital health broadly has been a top priority for years. The Agency has been working since 2010 to help ensure developers have a clear, predictable potential path to market so patients have timely access to safe, effective, innovative devices. This includes implementing related provisions of the 21st Century Cures Act and working to provide greater regulatory clarity, particularly for smaller companies and startups, which are common in the digital health space. FDA has done so recognizing the need to strike a proper balance between promoting innovation and protecting patient safety.

FDA has approved, authorized, or cleared over 800 AI/ML devices, including:

- a cardiac ultrasound software that uses AI to guide the user;
- an AI-based device that assists clinicians in detecting lesions (such as polyps or suspected tumors) in the colon in real time during a colonoscopy;

[23] https://www.hhs.gov/sites/default/files/hhs-ai-strategy.pdf
[24] https://www.fda.gov/media/167973/download
[25] https://www.fda.gov/media/177030/download

- a diagnostic aid for autism spectrum disorder; and
- an AI-based device to detect greater than a mild level of the eye disease diabetic retinopathy in adults who have diabetes.

Overall, FDA's efforts are focused on ensuring that the United States is a global leader in AI/ML medical devices, while at the same time making sure AI is developed and deployed responsibly in healthcare. FDA believes there is no "one-size fits all" approach for AI.

FDA's Digital Health Center of Excellence (DHCoE) within CDRH leads policy and evaluation of medical devices with AI and other digital health technologies at FDA. The DHCoE is a resource for developers of cutting-edge technology, publishing an AI Action Plan, providing guidance, issuing guiding principles on good machine learning practices, and engaging on efforts towards international harmonization, among other efforts.

AI will undoubtedly play a critical role in medical product development, and FDA is making every effort to remain nimble and support innovation. As we consider and adopt a risk-based regulatory framework we will need Congress' support. We look forward to working together to promote innovation while protecting patient safety.

User Fee Commitments

The efforts described above would not be possible without the support and funding provided by Congress. As you know, FDA relies on annual appropriations and user fees paid by industries that make and market FDA-regulated products, as well as user fees paid by certain other entities. User fees are critical to ensuring that FDA has the resources needed to conduct review of medical product applications and other fee-supported activities in a timely fashion without compromising the Agency's high standards. The most recent reauthorization of FDA's human drug and device user fee programs through the FDA User Fee Reauthorization Act of 2022 has allowed the Agency to build upon the programs' demonstrated success, further benefitting patients and affirming our nation's standing as a global leader in biomedical innovation. We discuss some highlights and progress below.

Prescription Drug User Fee Act (PDUFA)

In FY 2023, according to preliminary data, FDA met or exceeded nine of the 10 review performance goals. For example, 100 percent of current performance goals were achieved for Original Standard new molecular entities (NMEs) and BLAs, Original Standard non-NME, Priority NDA and BLA Efficacy Supplements, and Class 1 and Class 2 Resubmitted NDA and BLA Efficacy Supplements.

The FY 2022 cohort had a workload of 3,131 goal closing actions. FDA met or exceeded the 90 percent performance level for 12 of the 12 review performance goals for FY 2022.
For the FY 2023 cohort, FDA had completed 1,940 actions as of September 30, 2023. FDA has met or exceeded nine of the 10 review performance goals for FY 2023.

Generic Drug User Fee Amendments (GDUFA)

In FY 2023, FDA approved 782 abbreviated new drug applications (ANDAs) and tentatively approved (TAs) 172 ANDAs. As part of FDA's commitment to expanding its research collaboration and communication with industry and academia, the GDUFA-funded Center for Research on Complex Generics (CRCG) solicited detailed feedback from generic drug industry representatives and academia, helping to ensure that GDUFA Regulatory Science and Research Priority Initiatives were focused on the most pressing scientific challenges and helping generic product developers to effectively utilize GDUFA research outcomes—including technical methods, study designs, data analyses, and other scientific insights—to successfully develop complex generics that can benefit public health.

In FY 2023, FDA continued its successful implementation of the law widely known as the CREATES Act[26] by issuing Covered Product Authorizations to eligible generic product developers seeking to obtain samples of "brand" products, subject to a Risk Evaluation and Mitigation Strategy with Elements to Assure Safe Use. FDA issued 19 Covered Product Authorizations for eligible product developers seeking to develop generic products. Issuance of these Covered Product Authorizations allows generic product developers to more easily obtain the samples needed for product development and testing and, ultimately, for the submission of ANDAs.

Biosimilar User Fee Act (BsUFA)

FDA has just approved the 50th biosimilar product and released a new Biosimilar Action Plan to guide the program. In addition, FDA launched the BsUFA III regulatory research program, including a Research Roadmap that was informed by stakeholder input.[27] FDA research awards under this program, including how they map to our research priorities, are available for review.[28] The Office of Therapeutic Biologics and Biosimilars continues to grow in staff and take on increasing responsibility in the review of new biosimilars. Importantly, FDA is currently meeting or has the potential to meet all review performance goals for FY 2023.

Medical Device User Fee Amendments (MDUFA)

FDA is working to meet, and exceed where possible, goals in the MDUFA V agreement.

In FY 2023, CDRH saw the highest volume of MDUFA premarket submissions in at least a decade. However, even in the presence of this increased workload, CDRH has met or is on track to meet its FY 2023 review goals.

[26] The enactment of "CREATES" or "the CREATES Act" made available a pathway for developers of potential drug and biological products to obtain samples of brand products that they need to support their applications. This law was enacted in section 610, Actions for Delays of Generic Drugs and Biosimilar Biological Products, of Division N of Pub. L. 116-94, the Further Consolidated Appropriations Act, 2020 (21 U.S.C. 355-2), and included amendments to section 505-1 of the FD&C Act (21 U.S.C. 355-1).
[27] https://www.fda.gov/media/164751/download
[28] https://www.fda.gov/media/162361/download?attachment

FDA also met 15 of the 16 performance enhancement goals. Two additional goals due at the end of MDUFA V were met ahead of schedule.

Key accomplishments include:

- Filling 100 percent of CDRH's 141 MDUFA V hires for FY 2023. CDRH is also on track to meet the FY 2024 MDUFA V hiring goal.
- Exceeding by 20 percent the MDUFA V FY 2023 pre-submission goal of providing written feedback to an applicant within 70 calendar days or five days prior to a meeting, whichever comes sooner, 75 percent of the time.
- Expanding the submission progress tracking system in the CDRH Portal. In addition to Traditional, Special, and Abbreviated 510(k)s, now users can also track online the status of their pre-submissions.
- Updating guidance on Deficiency Letters, providing training to FDA review staff, and exceeding the FY 2023 goal for providing a "statement of basis" for deficiencies.[29]
- Transitioned the Accreditation Scheme for Conformity Assessment (ASCA) pilot to a sustainable program.

Key FDORA Provisions

There are many other important FDORA provisions that the Agency continues to address. Several have already been discussed; a few additional highlights are included here.

Section 3213 of FDORA amended the FD&C Act to authorize the Advanced Manufacturing Technologies (AMT) designation program. FDA encourages the early adoption of AMTs that have the potential to benefit patients by improving manufacturing and supply dependability and optimizing development time of drug and biological products. These technologies can be integral to ensuring quality and supporting a robust supply of drugs that are life-supporting, life-sustaining, of critical importance to providing healthcare, or in shortage. AMTs can directly improve product quality through higher capability manufacturing designs and enhanced controls (e.g., leading to fewer human errors). In December 2023, FDA issued draft guidance providing recommendations to persons and organizations interested in participating in FDA's AMT Designation Program, which is intended to facilitate the development of drugs, including biological products, manufactured using an AMT that has been designated as such under the program.[30]

Sec. 3305 provided important new authorities regarding the cybersecurity of medical devices. In March 2024, FDA issued a draft guidance to propose select updates to the FDA guidance document, *Cybersecurity in Medical Devices: Quality System Considerations and Content of*

[29] The associated goal is for FDA to provide a statement of basis for the deficiency, consistent with the updated guidance, in deficiency letters…[for] 75% of deficiencies in FY 2023…for Original PMA, Panel-Track Supplement, 510(k) and De Novo request submissions. FDA met the goal, with 78% of deficiencies including a "statement of basis" for the deficiency.

[30] https://www.fda.gov/media/174651/download

Premarket Submissions, including adding a Section VII to the Premarket Cybersecurity Guidance to address new considerations for cyber devices. The new section identifies the cybersecurity information FDA considers to generally be necessary to support obligations under section 524B of the FD&C Act. The Agency is now better positioned than ever before to ensure that the medical device industry is equipped with the tools and information it needs to prepare and address cybersecurity vulnerabilities and threats.

Sec. 3308 of FDORA established predetermined change control plans for medical devices, which provides an important improvement, allowing device developers to make certain improvements and changes to their product without having to make another submission to FDA each time. This allows for certain software updates and other changes while maintaining safety, so patients can access improved devices more quickly. The Agency published the draft guidance *Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions,*[31] which is intended to further develop a regulatory approach tailored to AI/ML-enabled devices. FDA is also working to develop a broader draft guidance on predetermined change control plans for medical devices. Further supporting these efforts, FDA released *Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles* with our partners from Health Canada and the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA), which draws upon existing guiding principles around Good Machine Learning Practices.[32] These efforts build on FDA's longstanding commitment to develop and apply innovative approaches to the regulation of medical devices, including those with software and other digital health technologies, to assure their safety and effectiveness and that timely access to such technologies is available in the United States.

Section 2503 of the "Prepare for and Respond to Existing Viruses, Emerging New Threats, and Pandemics Act" or "PREVENT Pandemics Act" requires FDA to establish a program for the designation of platform technologies to support the development and review of certain platform technologies incorporated within or utilized by multiple drug or biological products. Given that certain platforms, such as those for mRNA vaccines and CRISPR products, hold so much potential, CBER is evaluating how it can leverage data and information about platform technologies across related products during the development process. The Agency appreciated the opportunity to coordinate closely with Congress on the development of this provision and is working diligently to issue guidance on the implementation of this section.

Closing

For all the progress we have made, there are areas where we need Congress' support to ensure we can continue to effectively balance innovation, access, and safety.[33] There are existing gaps regarding the Agency's ability to effectively monitor drug and medical device supply chains, for instance. Similarly, the existing regulatory pathways do not provide adequate flexibility for

[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial
[32] https://www.fda.gov/medical-devices/software-medical-device-samd/predetermined-change-control-plans-machine-learning-enabled-medical-devices-guiding-principles
[33] FDA FY 2025 Legislative Proposals, https://www.fda.gov/media/176924/download?attachment

medical device manufacturers to adopt best practices for development, deployment, or continuous maintenance of AI/ML enabled medical devices. We look forward to working with you on this and other important challenges going forward.

For drugs, FDA is working to promote availability of generic drugs to help increase competition and to help consumers access the medications they need. Toward that end, we are seeking updates to the statutory frameworks governing drugs and biologic products, including to modernize the framework for generic drugs, which is 40 years old, to facilitate the development of complex generic drugs, including drug-device combination products. The current statutory framework does not explicitly address such products, leading to a lack of clarity that makes it more difficult for companies to develop generic versions of these products. For biological products, we are seeking amendments to eliminate the statutory distinction between biosimilars and interchangeable biosimilars, which has led to confusion and misunderstanding, including among patients and healthcare providers, about the safety and effectiveness of biosimilars and about whether interchangeable biosimilars are safer or more effective than other biosimilars. We look forward to working with you on these issues, so that we can continue to ensure that we are both encouraging innovation in drug development and accelerating public access to competitive alternatives to innovator drugs.

The user fee programs are an example of what FDA, Congress, industry, and other stakeholders can achieve when working together towards the same goal. While we have made demonstrable progress in bringing safe and effective drug and biological products and medical devices to market and thus to patients and consumers as quickly as possible, we know that more work remains to continue to enhance our review processes, invest in the hiring and retention of scientific staff, maximize new tools and regulatory science, and invest in a bioinformatics infrastructure to support the evolving needs of the programs.

Thank you for the opportunity to testify today. We will be happy to answer your questions.