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**“IMPLEMENTING THE 21ST CENTURY CURES ACT:
AN UPDATE FROM FDA AND NIH”**

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Introduction

Chairman Burgess, Ranking Member Green, and Members of the Subcommittee:

Thank you for the opportunity to testify today on FDA's implementation of the 21st Century Cures Act (Cures Act). A year and a half ago, full Committee Chairman Emeritus Upton and Rep. DeGette hailed the passage of the Cures Act as a potential game-changer for patients. FDA is actively working with industry, health care providers, patients, and many others to turn that bipartisan vision into reality.

The Cures Act sought to catalyze development of new medical technologies at a unique moment in history when fundamental advances in our understanding of the genetic and protein bases of diseases and advances in medical technology have enabled us to target, arrest, and in some cases cure, these vexing conditions.

The law is helping to transform the way we support medical product development and innovation while maintaining FDA's gold standard for safety and effectiveness.

Modernizing Product Development

Revolutionary new medical opportunities require FDA to apply an innovative and nimble, regulatory approach to the products we are tasked with evaluating. I would like to highlight a few central themes of the Cures Act – and describe our approach and recent efforts.

CDER New Drug Program Modernization

FDA recently announced a new drug development modernization plan that provides the structural framework necessary to advance many goals of the Cures Act – and more closely align the scientific prospect of complex and innovative new products with methods and approaches that can best unlock these opportunities.

As part of the modernization effort, FDA's Center for Drug Evaluation and Research (CDER) plans to add review divisions and to organize the divisions more closely around disease types. The proposed changes are intended to free up resources so that our scientists and physicians have more time to focus on advancing the science and technology that can lead to future innovative therapies, particularly to address unmet medical needs. This work requires multiple collaborations with external scientists, expert physicians, patients and other stakeholders to make meaningful progress.

Over a year ago, FDA launched its Oncology Center of Excellence (OCE) to leverage the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, and devices (including diagnostics). Authorized by the Cures Act, OCE is FDA's first inter-center institute that focuses on a specific disease area rather than type of product.

OCE's interdisciplinary work is yielding significant advances. For example, last May, FDA approved, for adult and pediatric patients, the first cancer treatment based on a tumor's

biomarker rather than the tumor's site or cell type. The immunotherapy was granted accelerated approval and demonstrated efficacy in treating certain solid tumors that progressed following treatment for colorectal cancer and other cancer types. Testing was permitted using a single therapeutic approach for patients with different tumor types rather than requiring separate development programs for each disease site.

In November, using a coordinated, cross-agency approach, the Center for Devices and Radiological Health (CDRH) approved the first breakthrough-designated, next generation sequencing-based in-vitro diagnostic test to identify patients with any of five tumor types who may benefit from 15 different FDA-approved targeted cancer treatment options. OCE supported CDRH's review team in evaluating this innovative testing approach which provides patients and health care professionals with access to critical information in one test report, avoiding the need for duplicative biopsies.

We intend to apply many of the lessons we have learned in creating and operationalizing OCE to break down traditional silos in the development of treatments for other diseases and conditions. Our modernization efforts will deepen internal collaboration and enhance external scientific exchange – and we look forward to updating the Committee on important developments as we move forward.

Novel Clinical Trials

As part of FDA's broader innovation initiative, we are encouraging the use of state-of-the-art innovations such as adaptive trials, modeling, and simulations to allow an evaluation of a product's safety and effectiveness. We welcome early engagement with sponsors to discuss the use of these innovative tools to expedite product development.

Modeling and simulation, for example, play a critical role in organizing diverse data sets and exploring alternate study designs – and can provide a vital tool to help evaluate new treatments in patient population subsets, and for rare diseases where patient populations are inherently difficult to study because of their small size.

CDER and FDA's Center for Biologics Evaluation and Research (CBER) are currently deploying these tools to help predict clinical outcomes, inform trial design, support evidence of effectiveness, and evaluate potential adverse event mechanisms. The Centers are updating guidance to assist sponsors in incorporating modeling and simulation – and applying these tools, for instance, to optimize product dosing based on individual physiology and genetics. CDER is currently collaborating with scientists to develop natural history models in Parkinson's, Huntington's, Alzheimer's, and muscular dystrophy which may facilitate modeling of some aspects of product design and evaluation.

CDRH's scientists and engineers are building in silico regulatory models for product design and evaluation, including the development of a digital library of models and a family of 'virtual patients' for device testing. These tools will enhance consistency across different medical products and across the agency.

Advancing Drug Development Tools

Encouraging the identification and use of reliable Drug Development Tools (DDTs) can significantly advance development of new safe and effective drugs and biologics. The Cures Act revised and codified FDA's qualification process to expedite development of publicly available DDTs, including biomarkers and clinical outcome assessments. FDA is working to establish a regulatory process for qualifying DDTs, pursuant to this codified authority, that provides for timely and consistent review of these submissions. Once qualified, a DDT can be widely used across multiple drug and biologic development programs – facilitating efficient development of important new therapies for patients.

As a result of the Cures Act, and vital resources and commitments provided under PDUFA VI, FDA is placing a greater focus on generation of the data and evidence needed to support biomarker development. Our work is primarily focused in two distinct areas: supporting use of surrogate endpoints in individual drug and biological product development programs, including by cataloguing those previously used as well as a process to develop novel surrogate endpoints; and by facilitating a public process to support biomarker qualification as a drug development tool.

The Cures Act included important provisions for publicly sharing information about DDTs that we believe will help facilitate their development and use. In accordance with the requirements under the Cures Act, FDA will be making a publicly available a list of biomarkers that have been used to support both accelerated and traditional drug and biologics approvals, as well as surrogate endpoints the Agency believes would be acceptable to support approval. While the acceptability of these surrogate endpoints for use in a product development program will be determined on a case-by-case basis, this list is intended to serve as a reference guide to help inform discussions of potential surrogate endpoints with the relevant CBER or CDER review divisions, with the goal of facilitating product development.

We are currently working towards developing and publishing several guidances required by the Cures Act to establish the process, taxonomy, and framework for DDT qualification.

Real World Evidence

The promise of harnessing real world data to improve patient care was an important focus during this Committee's consideration of the Cures Act. We agree that data on every clinical use of a product may provide useful safety and efficacy information.

FDA is actively working to integrate real-world evidence (RWE) such as electronic health records, registries, and claims and billing data into regulatory decision making and to answer questions relevant to broader populations of patients. RWE may go beyond current post-marketing surveillance capacities, eventually becoming applicable across all phases of medical product development.

We are developing a framework to evaluate use of RWE to support approval of new indications of approved medical products, or to help satisfy post-approval study requirements for marketed

products, and are making significant progress in meeting this Cures Act requirement. We have gathered input from stakeholders including industry, academia, and patient advocacy groups. FDA has finalized guidance on the use of RWE for devices, and intends to release guidance on RWE for drugs and biologics.

Although randomized clinical trials are the gold standard for medical and scientific evidence needed to support FDA medical product approval decisions, they are often conducted in specialized and controlled research settings and can be time-consuming and costly. At the end of a development program, randomized clinical trials can still leave critical questions unanswered, particularly about the effects of a medical product after it is used by a broader population over an extended period. We are using powerful new scientific computing and data storage technologies to enhance our capabilities of gaining valuable information from RWE

Sentinel

Sentinel, FDA's national, integrated electronic system for medical product safety, allows continuous feedback on the use of medicines under real-world conditions by providing secure access to multiple data sources, with full patient privacy safeguards.

Within Sentinel, FDA has supported the development of computer programs that analyze health insurance and healthcare provider databases to search for evidence as to whether certain products are potentially associated with specific adverse events, many of which are not typically reported. For example, FDA has used Sentinel to determine whether a certain type of immune therapy is associated with heart attacks or strokes, and to better define the true rate of acute lung injury after transfusions of certain blood components.

The size of its distributed database enables identification of even small exposed populations, and rare adverse events. These investigations can be extended to include comparative studies assessing risk using appropriate adjustments for confounding factors, which is critical when using observational data. In addition, it is possible to perform descriptive analyses of off-label use, appropriate medical product use, medication errors, health outcomes after branded and generic drug use, and product uptake patterns before and after regulatory risk management actions.

Early last year, the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program was launched allowing public and private entities access to Sentinel. Public and private-sector entities, including regulated industry, can now conduct large scale evaluations of safety issues associated with FDA-approved medical products in a secure environment that protects patient privacy.

At the core of IMEDS' innovative approach is the fact that it embraces and enables a long-term partnership between FDA and the public and private sectors. As new tools and methods leave the development pipeline and enter production for FDA use, they also are incorporated into IMEDS. For example, FDA is working to incorporate patient-provided data as well as randomization into the Sentinel infrastructure to support clinical research in a real world setting. Such work could be accelerated through support from sponsors working through IMEDS.

Because it relies on common and transparent procedures and infrastructure that can be understood by all participants, IMEDS appropriately shifts the focus from debates over differing methods and data to the underlying clinical and public health questions of concern.

FDA is confident that IMEDS sponsors will play a key role in shaping the future of evidence generation to help answer outstanding questions about the safe and effective use of medical products in a broad range of populations.

The National Evaluation System for health Technology (NEST)

The National Evaluation System for health Technology, or NEST is a multi-stakeholder collaboration that supports the generation of more and better RWE about medical devices. NEST is designed to drive down the time and cost of bringing new devices to market, expand indications for already marketed devices, and improve surveillance of marketed devices. NEST will enable faster identification of safety issues, reducing harm to patients and enabling companies to more rapidly take any appropriate corrective actions. NEST can also be used by device manufacturers, patient groups, hospital systems, insurance providers, and others to provide data to support those groups' activities.

When fully functional, NEST will improve active surveillance by providing a tool for utilizing real world data rather than only passively relying on patients, physicians, hospitals, and manufacturers to submit information to FDA about suspected or confirmed safety issues. Moreover, the data collected by NEST may help bring safer devices to market more quickly by facilitating the use of more real-world data in approving devices, rather than the current approach of relying solely on clinical trials or bench data, which often represent how devices are used in an ideal setting and may not account for all use cases.

In 2017, CDRH documented access to more than 100 million electronic patient records, and spearheaded the work of 12 National Coordinated Registry Networks and four international Registry Consortia through grants to the Medical Device Epidemiology Network (MDEpiNet), creating infrastructure for device evaluation including minimum core data sets, harmonized definitions, basic governance, and informatics and methodological alignment.

Streamlining Medical Product Review

Since the inception of FDA's first user fee program over a quarter century ago which provided critical resources to supplement product review, FDA has dramatically reduced review time for new, safe and effective medical products. We are consistently meeting product review goals -- many in abbreviated timeframes -- utilizing one or more of FDA's expedited review pathways.

INTERACT Early Meeting Program

Recognizing that early discussions with developers can advance product development, CBER recently established a new meeting program: INitial Targeted Engagement for Regulatory Advice on CBER productTs (or INTERACT). The INTERACT meeting program was created for potential sponsors to engage with CBER staff and obtain advice on a specific topic or issue that is critical to early product development. These discussions can help answer important questions,

remove roadblocks, and ultimately help create a clearer route to getting safe and effective products to patients.

Device Program

Congress, in the Cures Act, sought to promote medical device innovation and improve patient care. Since medical device technology evolves quickly, the process for improving the performance and clinical characteristics of medical devices is highly iterative. Often, small modifications provide incremental but meaningful improvements to products. Over time, these cumulative changes make noticeable advances in the performances of different technologies. Innovators need the flexibility to efficiently make these kinds of small modifications. At the same time, FDA needs to establish modern tools and benchmarks for measuring the safety and performance of devices to make sure they are delivering the expected benefits to patients.

FDA has embraced the concept of least burdensome regulation as clarified and expanded in the Cures Act – and CDRH has made it a guiding principle for medical device regulation. In just the past few years, we have seen notable results including reduction in review times and improved quality of applications.

As an example of CDRH’s least burdensome approach, the Center used streamlined authority provided in the Cures Act, to exempt more than 70 Class I device types and 1,000+ Class II device types from the requirement to submit a 510(k) following a determination that premarket review is not necessary to provide a reasonable assurance of safety and effectiveness. These medical devices may be subject to other regulatory controls, including complying with current good manufacturing practice requirements, being suitable for the intended use, being adequately packaged and properly labeled, and having current establishment registration and device listing with FDA. Eliminating the 510(k) requirement for these products saves time and resources for industry and allows FDA to focus its oversight on higher risk products while still ensuring that patients have access to safe and effective medical devices.

Digital Health

From mobile medical apps and fitness trackers to software that supports the clinical decisions doctors make every day, digital technology has been driving a revolution in health care. FDA recognizes that it can help encourage digital health innovation by making its policies and processes more efficient and modernizing its regulatory tools. The Cures Act codified into law many of the policies FDA had instituted in the years preceding the Cures Act and excluded certain digital health software functions from the statutory definition of a “device,” thereby removing them from regulatory oversight as devices. Such functions tend to be low risk but can provide great benefits by enabling patients and consumers to be more informed and engaged in their health.

In July 2017, FDA issued a Digital Health Innovation Action Plan to fully implement the provisions of the Cures Act that do provide for regulatory oversight of software, including issuing new policy on clinical and patient decision support software, establishing a dedicated Digital Health Unit in the FDA’s medical device center supported by industry user fee funding,

and implementing a new regulatory model for digital health technologies consistent with International Medical Device Regulators Forum (IMDRF) policies.

In a Digital Health Software Precertification (Pre-Cert) pilot program, FDA is also exploring a potential voluntary pathway to assess the safety and effectiveness of certain software device products by focusing on the software manufacturer/developer, rather than primarily the product. Under this potential framework, software developers could be assessed and precertified for the quality of their software design, testing, and other appropriate capabilities to qualify for a more streamlined premarket review process or in lieu of premarket review. This firm-based approach differs from the agency's traditional reliance on individual product reviews and seeks to leverage real world evidence to support evaluations of safety and effectiveness. The goal of this pilot program is to collaboratively explore this potential framework. FDA continues to assess its current statutory and regulatory authorities for this program.

New Expedited Review Programs

Congress, in the Cures Act, also authorized an expedited device review pathway, and two important, expedited review programs for drugs and biological products intended to treat serious diseases or conditions. They include the Regenerative Medicine Advanced Therapy (RMAT) designation program and the limited population pathway for antibacterial and antifungal drugs (LPAD). Each is described in greater detail below.

Breakthrough Devices Program

Through the Cures Act, Congress built on and expanded FDA's successful Expedited Access Pathway (EAP) program in the Breakthrough Devices provisions. The Breakthrough Devices Program is a voluntary program for certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. It is intended to help accelerate patient access by expediting development, assessment, and review of these devices, while preserving the statutory standards for marketing authorization, consistent with the agency's mission to protect and promote public health. For Breakthrough Devices, sponsors generally have earlier and more frequent access to FDA staff during device development and review.

Since the EAP program's inception, FDA has designated 72 devices as breakthrough and authorized the marketing of six. Among those products was a brain implant for patients with blindness caused by damage to the optic nerve. The product mimics the perception of light through a miniature video camera worn by a patient that transmits signals to an implant in their visual cortex. The Breakthrough designation facilitated early interactions between FDA and the sponsor and brought together intra-agency specialists to pose questions, solve problems, and evaluate the benefits and risks of the device for which no standard existed.

Regenerative Medicine

One of the most promising new fields of science and medicine is cell therapies used in regenerative medicine. These new technologies, most of which are in early stages of development, hold significant promise for transformative and potentially curative treatments for some of our most troubling and intractable medical maladies.

The Cures Act recognized these opportunities by building on FDA's existing expedited programs available to regenerative medicine products and by authorizing the Regenerative Medicine Advanced Therapy (RMAT) designation program. CBER moved quickly to establish the RMAT program which aims to facilitate an efficient development program, expedited review of innovative therapies, and more timely access to potentially life-saving products. Products granted RMAT designation are eligible for increased early interactions with FDA, including all the benefits available to breakthrough therapies. As of June 30, CBER has granted 24 RMAT designations since the program's inception.

In the fall of 2017, FDA announced the agency's Comprehensive Policy Framework for Regenerative Medicine. The framework clarifies the agency's current risk-based, flexible regulatory approach and implements provisions of the Cures Act related to regenerative medicine through a series of guidance documents which, when finalized, will represent the agency's recommendations and position on these matters. The first draft guidance document addresses expedited programs for regenerative medicine therapies, including the new RMAT designation program, while the other addresses devices used in recovery, isolation, or delivery of RMAT products.

In particular, the draft guidance on expedited programs describes regenerative medicine therapies eligible for RMAT designation as including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using certain such therapies or products, as well as gene therapies that lead to a durable modification of cells or tissues (including genetically modified cells). For example, Chimeric Antigen Receptor T-cell (or CAR-T) products, have been considered by FDA to be a form of gene therapy, and RMAT designation is available to CAR-T products that meet the other criteria for designation.

CBER is also working to implement another important regenerative medicine-related provision of the Cures Act. Through a public process involving outside stakeholders, CBER is working to advance the development of standards and consensus definitions to support the development, evaluation, and review of regenerative medicine therapies and regenerative medicine advanced therapies, including the manufacturing processes and controls of such products.

In 2017, CBER approved three gene therapies, one of which was the first *in vivo* gene therapy approved, as well as two CAR-T *ex vivo* gene therapies for oncology indications. Earlier this month we unveiled six new draft guidance documents, which, when finalized, will advance the development of gene therapy products. Three draft guidance documents focus on rare diseases and two specific therapeutic areas: hemophilia and retinal disorders. These draft guidances suggest potential accelerated approval endpoints for certain gene therapy products. The other three draft guidance documents address specific manufacturing and clinical issues related to gene

therapy products. By providing clarity to developers on manufacturing parameters, safety measures, and the pathway toward clinical development, we hope to foster even greater innovation in this field.

Gene therapy was largely a theoretical promise a few decades ago. Now, there is a real possibility that these products will cure diseases. The field is moving ahead rapidly, and our FDA scientists are focused on addressing the challenges in manufacturing and clinical development that arise.

Advancing Antimicrobial Development (Limited Population Pathway for Antibacterial Drugs)

More and more bacteria are growing resistant to currently available antibacterial drugs. Members of this Committee were instrumental in providing additional tools in Cures to further tackle this serious public health threat. Several provisions of the Antibiotic Development to Advance Patient Treatment (ADAPT) Act were enacted as part of the Cures Act, including authorization of the limited population pathway for antibacterial and antifungal drugs (LPAD) to spur drug development in this area. The LPAD pathway is designed to facilitate development and approval of antibacterial and antifungal drugs intended to treat serious or life-threatening infections in a limited population of patients with unmet need. In certain circumstances, the LPAD pathway will be an important tool enabling FDA to conclude that the benefits of a drug outweigh its risks in the intended limited population.

In June, FDA published draft guidance describing the recommended criteria, processes, and other general considerations for demonstrating the safety and effectiveness of drugs approved under the LPAD pathway. We are actively reaching out to discuss the availability of this pathway within the scientific and policy community involved in antibacterial drug development, are working with drug sponsors who are interested in utilizing the LPAD pathway, and look forward to further refining the pathway in the months ahead, as the guidance is finalized.

Last December, FDA launched the susceptibility test interpretive criteria (“breakpoints”) webpages also required by the Cures Act. The Cures Act clarified FDA’s authority to remove the breakpoint information from antimicrobial drug labeling, leverage the work done by standards development organizations, and take advantage of online tools to modernize and streamline the updating of breakpoints information for these antimicrobial drugs. The breakpoints webpages are an integral part of these efforts. Laboratories and antimicrobial susceptibility testing (AST) device manufacturers need to be able to use up-to-date breakpoints for the reports provided to physicians to inform appropriate treatment choices. Up-to-date AST results also are used to determine when additional infection prevention measures need to be implemented to prevent the spread of resistance microbes.

Elevating Patient Voices

Consistent with the Cures Act, FDA is also actively working to elevate patient voices in developing new medical products to treat their diseases. We learn through scientific advances, but also by listening to patients. We must make the science of medical product development and review more modern and more patient-centered, so that approved products successfully address the aspects of disease that concern real-world patients and families the most.

Patient-Focused Drug Development

Through the Patient Focused Drug Development (PFDD) initiative, started as part of the commitments under the Prescription Drug User Fee Act (PDUFA) V, FDA has been addressing the need to better enable patients to provide meaningful input into drug and biologic development. To date, FDA has led more than 20 PFDD meetings to learn from patients impacted by diseases, including, autism, HIV, Parkinson's disease, and various conditions involving pain. These meetings have given the FDA's professional staff a deeper understanding of patient and caregiver experiences.

Our PFDD efforts have been important in helping to address the opioid crisis. While we work to ensure the appropriate prescribing of opioids, we remain focused on striking the right balance between decreasing exposure to opioids and ensuring that those who are suffering from chronic pain have access to treatment for their legitimate medical needs. We also continue to support the exploration of new treatments for both pain as well as addiction.

We recognize the need to engage the wider stakeholder community and provide guidance on approaches to bridge early-stage efforts, such as PFDD meetings, to more systematic, methodologically-sound approaches to collect patient input that can further inform regulatory decision-making.

In June, FDA issued the first of four methodological PFDD guidance documents required by the Cures Act. Taken together, when finalized, the guidance documents will address, in a stepwise fashion, how patient experience data and other relevant information from patients and caregivers can be collected and used for medical product development and regulatory decision-making. The first draft guidance addresses sampling methods for collecting representative information on patient experience to inform the development and evaluation of medical products throughout the medical product lifecycle. It also discusses methods to operationalize and standardize the collection, analysis and dissemination of patient experience data.

We will continue to build on these efforts. The Cures Act identified patient-focused drug development as a priority, and PDUFA VI made it a centerpiece by providing essential resources. As the nature of drug development becomes more targeted and as more of the new treatments address specific aspects of disease, our approach to development and regulation must also become more patient focused. Through the input we receive from the patient community, we can bridge this critical gap between the science and the needs of patients.

CDRH is also committed to partnering with patients. While the Cures Act did not include mandates related to patient engagement for devices, CDRH has been a leader in incorporating patient preference information (PPI) into regulatory decision-making, including by championing patient reported outcomes (PROs). We appreciate Congress' and industry's support for our patient engagement activities in the MDUFA IV reauthorization, including funding to support increasing our capacity to evaluate PPI and PROs in premarket submissions.

Other Actions Under the Cures Act

There are other activities FDA has undertaken to implement the Cures Act provisions, which will lead to greater support for medical innovation and development. These activities are spearheaded by offices other than the medical product Centers.

We are grateful that Congress recognized that the expertise of FDA's staff is essential for maintaining the high quality of our work and therefore included new human resource (HR) authorities for FDA in the Cures Act. These authorities give FDA the ability to simplify and expedite the hiring process for certain positions, and grant new pay authority so FDA can better compete with the private sector to recruit and retain outstanding, highly qualified individuals for these positions. The ability to maintain our outstanding workforce will strengthen FDA's ability to realize the Cures Act goal of accelerating the development and availability of innovative, safe, and effective medical products for patients.

FDA has implemented the Cures Act provision authorizing the establishment of a material threat medical countermeasure priority review voucher program to encourage the development of medical countermeasures. FDA recently approved the first drug with an indication for the treatment of smallpox and awarded the first Material Threat Medical Countermeasure Priority Review Voucher in conjunction with this product approval. Collaborative work continues with other agencies within HHS to address research needs in drug development involving pregnant and lactating women, to streamline regulatory requirements for research involving animals, and to harmonize human subject protection requirements.

Conclusion

These are just some of the ways the Cures Act has supported and enhanced FDA's work to further benefit patients and affirm our nation's standing as a global leader in biomedical innovation.

Thank you for the opportunity to discuss our early progress in meeting the Cure's Act requirements and goals. I look forward to continuing to work with the Committee as we build on these successes and work to achieve its underlying goals. I am happy to answer any questions.