U.S. FOOD & DRUG ADMINISTRATION

September 22, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairwoman Eshoo:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the February 3, 2022 hearing before the Subcommittee on Health, House Committee on Energy and Commerce entitled "FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics." This letter is a response for the record to questions posed by the committee.

Sincerely,

Kimberlee R. Trzeciak -S
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Date: 2022.09.22 21:56:25 -04'00'

Kimberlee Trzeciak
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Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022

Peter Marks, M.D., Ph.D.,
Director, Center for Biologics Evaluation and Research,
U.S. Food and Drug Administration

The Honorable G.K. Butterfield (D-NC)

1. **Newborn screening is vital for disrupting the diagnostic odyssey for children with rare, genetic disorders by diagnosing them at birth. The Health Resources and Services Administration's ("HRSA") Advisory Committee on Heritable Diseases in Newborns and Children ("ACHDNC") is tasked with updating the Recommended Uniform Screening Panel ("RUSP") to help guide states in operating their newborn screening programs. Alarmingly, following the Pompe disease addition to the RUSP in 2013, the ACHDNC has *only* added three conditions the RUSP – mucopolysaccharidosis ("MPS") type 1, spinal muscular atrophy, and X-linked adrenoleukodystrophy. Moreover, several similarly rapidly progressing rare disorders with FDA-approved therapies, including cerebrotendinous xanthomatosis, CLN2, Fabry disease, MPS II, MPS IVA, and MPS VI, are *still* not on the RUSP. Such delays are a direct result of the ACHDNC Evidence-Based Review Group only considering disorders for addition to the RUSP if there is data from newborn screening pilot studies involving population-based screening of identifiable newborns with the proposed condition and availability of an effective treatment. It is my understanding that the pilot study requirement is particularly onerous and expensive. The bureaucracy that has slowed the RUSP clearly needs an overhaul in order to keep pace with drugs and biologicals currently in development that would be the first ever FDA-approved therapy for rapidly progressive and fatal disorders caused by an inherited or de novo genomic alteration or abnormality, such as Canavan disease, CLN1, CLN3, CLN5, CLN7, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease, metachromatic leukodystrophy, MPS IIIA, IIIB, and IIIC, Niemann-Pick type C, Sandhoff disease, and Tay-Sachs disease.**

    a. **From your perspective, how has the lack of newborn screening affected clinical trial enrollment for these investigational therapies?**

    Diagnostics that are approved, cleared, or authorized by FDA and that can safely and effectively screen newborns can help health care professionals identify and discuss potential treatment options with parents and caregivers before symptoms or effects on a baby's health may be noticeable.

Diagnostics can also help to identify potential patients to be considered for clinical trial enrollment. However, clinical trial enrollment criteria generally include a specific diagnosis and other criteria, such as signs and symptoms of disease. Given that clinical trials generally have various enrollment criteria,[1] it is challenging to directly comment on the impact of newborn screening on clinical trial enrollment.

b. What role should FDA play to ensure the tremendous work being done by its review divisions in approving therapies that are satisfying unmet need for rare pediatric diseases can benefit these children? For example, would you recommend coordination between FDA and HRSA to ensure the ACHDNC is aware of investigational breakthrough therapies that are in clinical development for non-RUSP conditions for which screening presents a high likelihood of significant public health benefit and value through the reduction of time to diagnosis?

We welcome dialogue with HRSA and appreciate the question about sharing information with HRSA's Advisory Committee. Consistent with applicable law, including federal statutes and FDA's regulations, and to protect the integrity of the review process, FDA generally cannot publicly disclose information about an unapproved application, including the existence of specific unapproved applications for investigational new drug or biologic products. There are limited exceptions to these restrictions on FDA's ability to discuss pending applications; and the availability for disclosure of information would be made in the context of a particular unapproved application, taking into account all relevant facts and applicable laws.

c. Do you think the underpinnings of the FDA's accelerated approval pathway for drug review could be applied to the RUSP process by allowing for "preliminary inclusion" on the RUSP upon the submission of an NDA or BLA for breakthrough therapy designated drugs or biologics seeking approval for a rare pediatric disease not currently on the RUSP, but for which a validated assay exists, until further evidence, including real world evidence, is generated to support full RUSP inclusion?

Generally speaking, FDA is not in a position to make recommendations regarding the Recommended Uniform Screening Panel process.

The Honorable Brett Guthrie (R-KY)

1. **One of the commitments outlined in the PDUFA agreement is to further improve how real-world data is collected and used. The data used in such studies, however, is not always generated by individual drug sponsors. Given that real-world data is**

[1] For example, requiring certain signs or symptoms upon which the investigational therapy may claim to have an effect.

often generated by other organizations who specialize in this work, do you agree that they should be included in the proposed pilot program to improve the quality and acceptability of RWE?

a. How else does FDA intend to engage with leading organizations that develop real-world data outside of the context of a specific drug development program?

The focus of the Advancing RWE Program is on identifying approaches for generating real-world evidence that can meet regulatory requirements in support of claims or to support or satisfy post-approval study requirements, which are completed by sponsors. Therefore, the Advancing RWE Program is designed for sponsors. However, FDA has several other pathways to engage with real-world data providers and has done so successfully. These pathways included direct meetings with the Center for Drug Evaluation and Research's (CDER's) RWE Subcommittee and funding of demonstration projects.

2. Knowledge management and information sharing is extremely important across FDA Centers. What types of knowledge management activities have CDER and CBER established?

Enabling comprehensive knowledge management to capture, retrieve and utilize institutional knowledge is of paramount importance to FDA. CDER and the Center for Biologics Evaluation and Review (CBER) have a number of established capabilities and in-progress initiatives supporting their knowledge management needs. CDER's informatics strategy connects a modernized workflow management capability, master data management, and a broad analytics platform to support a connected flow of information through data receipt, regulatory review, and analytics activities. CDER One, leveraged by both CDER and CBER, is a cloud-based enterprise data lake and analytical platform to provide a robust environment to underpin some of its knowledge management activities. CDER One brings data together from internal and external sources to support analytics needs across all review areas. The expanding CDER Nexus modernized workflow management capability provides a robust, process-focused workflow environment to support consistency of business processes and bringing together stronger collaborative authoring processes. As part of its ongoing modernization efforts, CDER's Office of New Drugs (OND) and CBER have established governance and processes to continually monitor and refine their strategy and program data domains and to assure integration with broader CDER and CBER knowledge management. These efforts focus on greater consistency of data capture and integration of knowledge across disciplines and the review programs through data governance, standardized and structured review templates and workflow enabled processes.

CBER and CDER are actively engaged and collaborating in FDA's implementation of an overarching Data and Technology strategy that includes new and expanding initiatives to support effective knowledge and information sharing across FDA. This work will connect with and augment program-focused capabilities. Several efforts include:

- FDA's Intelligent Data Lifecycle Ecosystem (FiDLE) – FiDLE is FDA's enterprise-wide ecosystem, designed to meet cross-center data management, advanced data science and analytics platform needs.
- Enterprise data catalog – An initiative across Centers to establish an organized inventory of data assets within FDA to help organizations and data professionals manage, collect, organize, access, and enrich their data to support discovery and governance.
- Global Substance Registration System – a database of highly curated substances within regulated products. This system currently interfaces with several FDA pre- and post-market systems to enable association of substances to products, applications, clinical trials, and adverse events for biologics, drugs and cosmetics.

3. Dr. Marks, in 2019, you and then Commissioner Gottlieb stated FDA's intent to maximize the use of expedited programs and that, for gene therapy products, accelerated approval, in particular, represents an opportunity to meet this significant unmet need.

a. Three years later, as gene therapies have advanced (despite the ongoing pandemic), how do you plan to realize these opportunities for use of accelerated approval?

FDA is committed to facilitating the development of gene therapy products to address the unmet needs of people with serious and life-threatening diseases. In 2019, FDA released guidance around expedited programs for regenerative medicine therapies for serious conditions.[2] This guidance describes the expedited programs available to sponsors of regenerative medicine therapies for serious conditions, including those products designated as Regenerative Medicine Advanced Therapies (RMATs). To that end, the guidance provides information about the provisions in the 21st Century Cures Act ("Cures") regarding the use of the accelerated approval pathway for regenerative medicine therapies that have been granted designation as an RMAT. Finally, the guidance describes considerations in the clinical development of regenerative medicine therapies and opportunities for sponsors of such products to interact with CBER review staff.

Since 2019, CBER has approved six CAR-T gene therapies for treatment of hematological malignancies, a directly administered gene therapy for spinal muscular atrophy, a fatal pediatric disease, and three tissue engineered products, one for the repair of single or multiple symptomatic full-thickness cartilage defects of the knee, one for the treatment of adults with thermal burns, and one for immune reconstitution in pediatric patients with congenital athymia. CBER is committed to using its full

[2] *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry.* 84 FR 4825 (February 19, 2019), available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions.

breadth of programs, including RMAT and accelerated approval, for eligible products. To this end, CBER has licensed three products with RMAT designation.[3]

FDA, the National Institutes of Health (NIH), 10 pharmaceutical companies and five non-profit organizations have partnered to accelerate development of gene therapies for the 30 million Americans who suffer from a rare disease. While there are approximately 7,000 rare diseases, only two gene therapy products have been approved by FDA to treat rare diseases caused by specific gene mutations. The Bespoke Gene Therapy Consortium (BGTC), part of the NIH Accelerating Medicines Partnership (AMP) program and project-managed by the Foundation for the National Institutes of Health (FNIH), aims to optimize and streamline the gene therapy development process to help fill the unmet medical needs of people with rare diseases.

b. How are you striking the right balance between pre- and post-approval data generation?

To determine the appropriate balance of pre-approval data and post-approval data for each specific drug or biologic, FDA carefully reviews the safety and efficacy results gathered during drug development. The appropriate balance may depend on those results, the specific clinical indication, and the unmet medical need. FDA utilizes our expedited programs to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of serious or life-threatening conditions. One example of FDA's use of post-approval data are accelerated approvals, which are based on a determination that the product has an "effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit."[4] Post-marketing confirmatory trials have then been required to verify and describe the predicted effect on the clinical benefit.

Additionally, when approving a drug or biologic product, FDA can impose a post-marketing requirement (PMR), which are studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use. PMRs can be required to assess a known serious risk or signals of a serious risk related to the use of the drug or biologic, or identify an unexpected serious risk when available data indicate the potential for a serious risk.[5] Also, sponsors may agree to conduct studies and clinical trials after approval as a postmarketing commitment (PMC).

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[3] *CBER Regenerative Medicine Advanced Therapy (RMAT) Approvals,* available at https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cber-regenerative-medicine-advanced-therapy-rmat-approvals.
[4] Section 506 of the FD&C Act.
[5] Section 505(o)(3)(B) of the FD&C Act; *see also Postmarketing Requirements and Commitments*, available at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments.

FDA follows the science and makes these decisions, sometimes after seeking input from an Advisory Committee, on a case-by-case basis, to ensure that we fulfill our mission to both protect patient safety and bring new, innovative therapies to market.

c. How will you ensure that any changes aimed at improving the clarity and rigor of the accelerated approval process will not upset this delicate balance and still benefit patients today?

The accelerated approval pathway has been in existence for thirty years and has worked well to ensure the safety and efficacy of products approved by FDA. Changes to this pathway that would lower the evidentiary standard would decrease protections for patient health and likely compromise public trust in therapies granted accelerated approval. However, FDA believes there are changes that could be made to the accelerated approval pathway that could help advance the timely completion of post-approval studies required for the accelerated approval of drugs and biological products and clarify the process for any subsequent withdrawal of such approval. Enhancing the timeliness and quality of confirmatory studies would help support FDA's regulatory decision-making for drugs approved through the accelerated approval pathway and minimize the time that a product is marketed based on accelerated approval before its clinical benefit can be confirmed. These types of changes would improve the clarity and rigor of the accelerated approval pathway and would not upset the balance that protects patients today.

The Honorable Michael C. Burgess, M.D. (R-TX)

1. **In its commitment letter, FDA retained language from prior letters stating that the Agency's major dispute resolution goals apply to "procedural or scientific matters." However, in 2017, FDA issued a separate guidance document on Formal Dispute Resolution that allows formal disputes only for "scientific and/or medical significance," thus excluding some procedural matters. Procedural matters are important, as you know, and ultimately, patients lose out if innovators cannot resolve issues with FDA in a timely manner.**

   a. In light of FDA's PDUFA VII language on dispute resolution, will the Agency commit to revising its 2017 guidance to align to the PDUFA VII commitments you are making now, in particular to ensure procedural matters?

   We appreciate your question about the Formal Dispute Resolution Program and agree that procedural matters are important and that innovators should have a path available to resolve procedural disputes, should they arise. CDER and CBER have current mechanisms in place to provide innovators a pathway for open and prompt discussion and resolution of procedural disputes. As outlined in the 2017 guidance document for the Formal Dispute Resolution Program, "…if a sponsor challenges specific

administrative and/or procedural decisions that arise during the course of an FDR, CDER and CBER intend to review these interim decisions as part of the review of the pending substantive scientific and/or medical dispute, and not as a separate review." Procedural matters may also be raised with the appropriate Center ombudsmen. The CDER and CBER ombudsmen informally investigate and facilitate resolution of such issues.

2. **Can we count on increased engagement from senior leaders at FDA in more routine meetings with sponsors to generate a more constructive and efficient dialogue?**

   a. **Are there plans to better facilitate engagement and communication?**

   FDA recognizes the value of direct engagement between its senior leadership and sponsors. We do assure that appropriate senior staff are present at meetings. However, given the volume of meetings (e.g., 4,558 in fiscal year 2021), there are inherent limitations regarding scheduling and availability for both sponsors and FDA senior staff. There are opportunities for senior leadership input into drug development programs and engagement with sponsors outside of meetings, such as public workshops and advisory committees.

   Sponsors will have access to additional engagement and communication with FDA's expert scientific staff via some of the proposed PDUFA VII enhancements. Examples include the new Type D meeting, INTERACT meeting, and the follow-up opportunity following sponsor meetings that confirms understanding of the communications that took place. Similar changes are also proposed with respect to biosimilar and interchangeable biological products in BsUFA III. Examples here include the new Type 2a meeting, increased flexibility in requesting Biosimilar Initial Advisory meetings, and the same post-meeting follow-up opportunity as in PDUFA.

3. **Dr. Marks, it goes without saying that CBER must be a strong, well-resourced partner to ensure safe and effective breakthrough therapies, such as cell and gene therapies, can benefit the patient. Congress established the breakthrough therapy designation in the Food and Drug Administration Safety and Innovation Act to ensure expedited review and approval of transformative therapies that are substantially improving the standard of care for a serious or life-threatening disease or condition.**

   a. **Are you aware of any instances in which the FDA did not adhere to Agency regulations and guidance governing the breakthrough therapy program or regenerative medicine advanced therapy program, especially with respect to communication, transparency, and collaboration with the sponsor? Has FDA ever applied different standards of review for these therapies than for those cell and gene therapies that have received marketing authorization?**

No, I am not aware of any instances in which FDA did not adhere to the regulations and guidance regarding breakthrough and RMAT programs. Regarding licensure, CBER has licensed three products with RMAT designation.

Because of the rapid growth in cell and gene therapy development, including the rapid growth in development programs for which we have granted breakthrough therapy designation and RMAT designation, it will be imperative that CBER be resourced appropriately. Without an investment in CBER, the benefits of these transformative products might not be realized in as timely a fashion as desired.

4. **Dr. Marks, Texas is a research leader in developing platforms for lifesaving gene therapies. Dr. Steven Gray and his team of researchers at the University of Texas ("UT") Southwestern Medical Center in Dallas have received nearly five million dollars in grants from National Institute of Neurological Disorders and Stroke ("NINDS") to develop gene therapy platforms for ultra-rare, genetic neurological disorders that are fatal in childhood, such as Rhett syndrome, giant axonal neuropathy ("GAN"), Tay Sachs disease, Sandhoff disease, Krabbe disease, and various types of Batten disease (CLN1, CLN7). According to the Massachusetts Institute of Technology, by 2030, FDA is likely to approve 30 gene therapies for rare genetic disorders, including this potentially life-saving medicine for GAN. A significant majority of these investigational gene therapies in clinical trials are for bleeding disorders, blood disorders, primary immunodeficiencies, metabolic disorders, neurodegenerative disorders, and muscle disorders for which there is significant unmet need, or the opportunity to greatly improve the current standard of care.**

    a. **What additional resources and authorities can be provided to CBER to ensure these transformative medical breakthroughs can save the lives of children with such devastating and potentially life-threatening conditions?**

A significant majority of the new resources negotiated for CBER in PDUFA VII are directed to the cell and gene therapy program. The new full-time equivalents (FTE) hired with these resources will be very important. However, we continue to see significant growth in the number of active cell and gene therapy development programs and FDA will continue to assess the resources needed to support sufficient staffing moving forward.

The Honorable Gus Bilirakis (R-FL)

1. **Dr. Marks, a Federal Register (FR) notice issued on January 3rd indicated several organizational changes across FDA and especially across CBER. While the notice provides an updated list of the organizational structures impacted — with CBER having the most changes, FDA has not disclosed details about staffing or leadership changes in the new areas. How would knowledge management and staffing or leadership changes be managed, and information be provided to sponsors for their applications including INDs?**

The Federal Register notice you refer to discusses reorganization of several FDA Centers. CBER's changes will help make the Center stronger and more effective. These include:

- streamlining and consolidating programs and operations to help support greater efficiency and better integration and alignment of work;
- minimizing organizational layers of review;
- ensuring process and policy consistency for quality assurance;
- positioning the Center to be better prepared to respond to developments and challenges in the industry they regulate and help drive innovation; and
- enhancing work life experience and professional development opportunities.

CBER information systems impacting knowledge management were updated to reflect organizational changes to ensure continuity of regulatory operations internally and with outside applicants.

As Offices adjust their structures, senior leaders are committed to ensuring that staff receive support and resources for a successful transition. The reorganization bolsters our ability to meet our mission and goals as outlined in CBER's 2021-2025 Strategic Plan.[6]

2. **Dr. Marks, the recent FR notice covering FDA reorganization also referenced the increase in applications for cell and gene therapy products and noted that the CBER reorganization will allow CBER to further advance RWE priorities for biologics. How do you specifically anticipate the reorganization – specifically the new Office of Biostatistics and Epidemiology– to further advance RWE priorities for biologics?**

Changes in CBER's Office of Biostatistics and Epidemiology (OBE), which will take on the new name Office of Biostatistics and Pharmacovigilance (OBPV) will help ensure that CBER's regulatory structures and processes are prepared to respond to innovation and development in the industry while upholding FDA's standards for safety and effectiveness for biological products. The changes will position CBER to advance real-world evidence priorities for biologics, with the newly created CBER Surveillance Program Staff which is able to drive continued innovation and successful implementation of FDA's real-world evidence framework. The new organizational structure will also better position CBER's Office of Tissues and Advanced Therapies (OTAT) to meet the increasing challenges and demands in this growing field, including continued growth in the Regenerative Medicine Advanced Therapy designation program established by the 21st Century Cures Act.

The Honorable Larry Bucshon, M.D. (R-IN)

1. **Aside from the "Four Part Harmony" approach to CMC communication and the CMC Readiness Pilot outlined in the PDUFA VII goals letter, are there other**

[6] https://www.fda.gov/media/81152/download

strategies that the CDER and CBER intend to employ to improve communication on CMC issues?

The PDUFA VII goals letter includes a robust set of activities to improve FDA and industry communication on chemistry, manufacturing and control (CMC) issues. This includes the items noted in your question, along with staff training on CMC assessment processes associated with mid-cycle and late-cycle review meetings with the goal of ensuring that mid-cycle and late-cycle meeting expectations are met, including communicating the status of the NDA and BLA CMC assessment and any identified issues that would preclude approval.

In addition, CBER and CDER periodically examine communication approaches internally and formally (e.g., as part of communications assessment in previous PDUFA commitments). We update internal Manual of Policies and Procedures (MAPPs), Standard Operating Procedures and Policies (SOPPS), Q&As, and guidance on communication to reflect more efficient and effective processes and practices, share best practices and train staff on communication practices. Furthermore, information requests to applications, including those for CMC issues undergo review at various levels for content and clarity. Increases in staffing, and retention of existing staff can also facilitate communication by having trained and experienced subject matter experts to discuss technical topics.

The Honorable Earl L. "Buddy" Carter (R-GA)

1. **Dr. Marks, the biggest challenge faced by sponsors at FDA with respect to rare disease therapies are the lack of expertise on review teams with respect to the rare disease under review and the lack of knowledge and experience with rare diseases generally among different review divisions, which can lead to inconsistencies in sponsor experience and prolong the review process to the detriment of the patient. With the increase in BLAs submitted for cell and gene therapies in recent years and projected numbers for future years, from your perspective, what can be done at CBER to ensure each review division is well informed about each rare disease or condition under review, including phenotypes, rate of progression, and current standard of care? Do you believe it is feasible to conduct comprehensive training for all FDA product review staff on rare disease drug development?**

The Rare Diseases Team in CDER, Office of New Drugs (OND) coordinates with CBER, CDRH, and the Office of Orphan Product Development in the Office of the Commissioner (OOPD) to collaborate on annual staff training to share learnings and promote rare disease education regarding policy and review across the Agency. In addition, the Rare Diseases Team hosts quarterly seminars presented by internal and external experts to train and inform staff on timely and important aspects of rare disease drug development relevant to their work on rare disease applications. Trainings encompass both broad topics important across rare diseases (e.g. complex innovative design use in rare diseases) and innovative topics or policies (e.g. new scientific innovation in gene editing or new FDA guidance on the use of

real world data/evidence). Trainings include illustrative case studies, and are recorded and made available to FDA staff after the events to ensure access and availability.

OND has also established a new Rare Disease Drug Development Council comprised of leaders from across CDER's OND and from CDER's Office of Translational Sciences with expertise and experience in rare disease drug development to promote organizational cohesion across rare disease issues and drug development programs. CBER and other Centers also participate in this new council. These types of approaches will further enhance collaboration, consistency, and knowledge sharing between OND divisions and across CDER and FDA, while ensuring that each rare disease drug development program is evaluated by staff that have the disease-specific expertise needed to appropriately design and evaluate these programs.

CBER clinical review staff have diverse expertise covering a wide array of medical disciplines and most are knowledgeable about certain rare diseases within their respective disciplines. However, it is impossible for CBER clinical review staff to be knowledgeable from the outset on each of the more than 7,000 rare diseases that have been identified to date. Beside the many available cross-Agency training and information sharing opportunities about rare diseases described above, extensive online medical information resources are available to FDA review staff for obtaining the most up to date medical literature about specific rare diseases. Also, review staff have opportunities to hear first-hand from patients on their experiences in living with a specific rare disease during Patient Focused Drug Development meetings and Patient Listening Sessions, which are typically planned and held by or in collaboration with patient advocacy organizations. In addition to the programs previously noted in our response, CBER also provides monthly review management update training sessions to all staff. These trainings include refreshers on expedited review and development programs such as Fast Track, Breakthrough Therapy and Regenerative Medicine Advanced Therapy designation programs. Ensuring the appropriate application of these programs facilitates expeditious development of all eligible products including those for rare diseases. Through these various trainings and opportunities for information sharing, the effectiveness and efficiency of the review process is enhanced.

The Honorable John Joyce, M.D. (R-PA)

1. **Will the FDA and IPMG commit to seeking stakeholder input prior proposing any substantial changes to the Clozapine and iPLEDGE REMS programs going forward?**

While FDA can require manufacturers to implement elements under a risk evaluation and mitigation strategy (REMS) that are necessary for the safe use of the drug, such as periodic lab tests, certification of prescribers and pharmacies, or administration in a health care setting, the manufacturer determines the specific methods for implementing or operationalizing them. However, FDA encourages manufacturers responsible for implementing a REMS to seek stakeholder input from patient organizations and key professional organizations on the potential impact of REMS modifications to change third-

party vendors engaged by sponsors to aid in implementation of the strategies. We will continue to recommend sponsors take public input into account to achieve continuity and minimize disruption when undertaking changes that could impact REMS management.

2. **Who will be responsible for the rollout of program adjustments in the future? And how will the FDA hold them accountable?**

Manufacturers are responsible for implementing the REMS for products that are subject to REMS requirements and the rollout of any program adjustments (i.e., modifications) approved by FDA. For new products approved with a REMS, the REMS must be operational for the drug to be introduced into interstate commerce.

Based on recent experience with the unsatisfactory implementation of modifications to the Clozapine and iPLEDGE REMS, we have asked other manufacturers that are currently proposing REMS modifications that involve changes in third-party vendors engaged by manufacturers to aid in implementation and management of the strategy, to perform a Failure Mode and Effect Analysis (FMEA) before implementation. The FMEA would identify potential failures and a proposed contingency plan to address such circumstances. Our primary objectives are to support a smooth transition and to prevent interruptions in treatment for patients.

The Agency believes it is important to hold manufacturers accountable for the efficient and smooth implementation of a REMS and any subsequent modifications.

3. **Will there be test runs for future program changes before rolling them out to the general public for physicians, pharmacists, and patients?**

FDA does and will continue to recommend that, prior to informing the public of a new or modified REMS program, manufacturers seek stakeholder input and test any platforms that will be used.

4. **Will stakeholders (professional organizations representing physicians and pharmacists) be provided a direct point of contact to work with and respond to questions and concerns in a timely manner?**

Stakeholders with questions may contact the applicable product center (CBER, CDER, etc.) for that particular REMS.

Although FDA does not administer the product-specific REMS programs, FDA's Division of Drug Information (DDI) is a resource that is available for stakeholders and professional organizations if they have questions, concerns, or want to report an issue about a particular REMS program. This resource was a particularly helpful mechanism for FDA to hear about stakeholder concerns related to the implementation of modifications to third-party vendors in the Clozapine and iPLEDGE REMS.

5. How can we ensure physicians, pharmacists and patients across the country have full proper access to the Clozapine and the iPLEDGE program?

FDA strives to ensure stakeholders have access to all REMS programs without undue burden, including the Clozapine and iPLEDGE REMS. The goal is to maintain patient access while still preserving safe use of a drug.

Due to implementation issues, stakeholder access was impacted by the modifications to the iPLEDGE and Clozapine REMS. The modifications to these programs were necessary due to a change in the REMS vendor for both programs. The Clozapine REMS modification required stakeholders to recertify, and the iPLEDGE REMS required previous certified and enrolled stakeholders to update their log-in accounts. For both programs there were significant challenges with implementing these modifications. As the implementation of the changes to these REMS have begun to stabilize, stakeholders have been more successful in accessing the REMS programs, but the issues have not been entirely eliminated.

6. How can we ensure that the FDA and REMS do not reinstitute provisions of the REMS that risk interrupted treatment and result in harm to patients?

Since December 2021, FDA has been temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine.[7] The Agency is analyzing metrics about the implementation of the Clozapine REMS and considering whether implementation issues affecting patient access to the medication have been addressed. Despite allowing additional time for stakeholders to enroll and certify, we have heard that some stakeholders will not certify in the REMS until it is absolutely necessary (e.g., once the enforcement discretion ends). Our highest priorities are continuity of care, patient access, and patient safety.

7. How can we ensure that the FDA does not reinstitute provisions of the REMS such as retroactive reporting of data that are not clinically useful?

The Clozapine REMS requires enrollment of all patients into a patient registry. The data collected through the registry, including repeated absolute neutrophil count (ANC), time to onset of neutropenia (if applicable), patient demographics, and patient health outcomes, can be used to evaluate the impact and frequency of the ANC monitoring. This information can be used to determine if changes are needed for labeling or the REMS to improve safety or reduce burden. While we believe this information will be very helpful, FDA does not intend to require retroactive reporting of ANC values and other information in the patient registry that was not collected during the period of enforcement discretion.

[7] *FDA is temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine*, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-temporarily-exercising-enforcement-discretion-respect-certain-clozapine-rems-program.