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
Digitally signed by Kimberlee R. Trzeciak -S
Date: 2022.09.22 21:57:32 -04'00'

Kimberlee Trzeciak
Associate Commissioner for
Legislative Affairs

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

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

Patrizia Cavazzoni, M.D.,
Director, Center for Drug 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.

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

The Honorable Lisa Blunt Rochester (D-DE)

1. **The coronavirus outbreak exposed our fragile medical supply chains. Pandemic-related drug shortages challenged our country's ability to ensure that patients had reliable access to essential generic medications. What role will supply chain security play in the future of medical product approvals?**

Pandemic-related supply issues have included increased demand which led to shortages for certain medications needed for hospitalized patients, as well as shortages due to competition for limited manufacturing capacity at facilities making both vaccines and other COVID-related products on lines that also make other drugs. Another example of a recent pandemic-related shortage is the IV Contrast agent shortage caused by the shutdowns in China.

FDA is taking a number of actions to help improve the reliability of the supply chain and limit shortages. The Coronavirus Aid, Relief, and Economic Security (CARES) Act amended the Federal Food, Drug, and Cosmetic (FD&C) Act to require that manufacturers of certain prescription drugs or active pharmaceutical ingredients (API) or associated medical devices used for preparation or administration included in the drug shall develop, maintain and implement, as appropriate, a redundancy risk management plan that identifies and evaluates risks to the supply of the drug. The CARES Act also amended the FD&C Act to require FDA to prioritize and expedite, as appropriate, the review of certain applications that could help mitigate or prevent a shortage of certain critical drugs, including generic drugs. For instance, in calendar year 2021, to help increase patient access to critically needed medications in shortage or to prevent potential shortages, FDA expedited reviews for close to 100 original abbreviated new drug applications (ANDAs) and over 100 ANDA supplements. Moreover, for pandemic-related shortages, reviews of applications for additional manufacturers of these critical drugs are expedited as are reviews of applications for any changes manufacturers need to make to increase production (e.g., new facilities, manufacturing lines and suppliers).

In addition, FDA is gaining greater insight into the supply chain through implementation of the requirement added by the CARES Act that manufacturers submit annual reports to FDA regarding amounts of drug manufactured for commercial distribution. FDA has issued draft guidance and developed a portal to facilitate submission of that data. These data will be integrated with other internal data to provide insights into supply chain and risks.

FDA will continue to take all available steps working with manufacturers to minimize the risk of shortages and supply chain disruptions.

2. **As noted in your testimony, in March 2020, the U.S. Food and Drug Administration (FDA) announced the creation of the Coronavirus Treatment Acceleration Program (CTAP), an emergency review and development program for COVID-19 treatments. The Agency supported the program by reassigning staff and working continuously to review requests from companies and researchers working to develop therapies. What additional authorities, regulatory flexibilities or resources would**

enable the FDA to quickly respond to future emergency situations, while meeting key PDUFA commitments and preventing staff burn out?

FDA's existing authorities are sufficiently flexible and adequate to enable a robust response to a public health emergency while meeting key PDUFA commitments. Critical to our success during the COVID-19 pandemic was additional funding provided by Congress to secure the resources necessary for our pandemic response. For FDA to remain nimble in the face of future public health emergencies, adequate funding and resources will be critical.

3. **Alzheimer's and other dementia disproportionately affect older Black and Hispanic Americans compared to older White Americans. However, much of the Alzheimer's research to date has not included sufficient numbers of Black, Hispanic, Asian Americans/Pacific Islanders and Native Americans to be representative of the United States population. FDA has issued guidance on how to enhance the diversity of clinical trials, like ensuring clinical trial eligibility criteria are not unnecessarily restrictive and encouraging the use of adaptive clinical trial design. I've introduced a bipartisan bill with Representatives Herrera Beutler, Curtis, Smith, and Waters, the ENACT Act, to increase the participation of underrepresented populations in Alzheimer's and other dementia clinical trials, which includes these FDA recommendations. The bill would also expand education and outreach to these populations, encourage the diversity of clinical trial staff, and reduce trial participation burden, among other priorities. How important is it to ensure the population enrolled in Alzheimer's trials reflects the population most likely to need access to future treatments?**

FDA has a long-standing commitment to promoting diversity and inclusion of underrepresented populations in clinical trials. Inclusion of diverse populations likely to reflect the patient populations that will use the drug if approved can help increase our understanding of the benefit-risk profile of investigational drugs. A more diverse clinical trial population can make labeling of therapeutic products more informative for healthcare providers and patients and enhances patient safety. Enrollment of diverse populations in clinical trials may also potentially minimize the need for postmarketing studies. We note that Alzheimer's disease is most prevalent in older adult populations and that populations generally become more heterogeneous with advancing age. Therefore, enrolling diverse populations in Alzheimer's trials is important for ensuring that future treatments are safe and effective for patients affected by this disease.

As noted in your question, in November 2020, FDA published the final guidance Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs[2], which discusses broadening eligibility criteria and avoiding unnecessary exclusions for clinical trials, when medically appropriate and scientifically sound. This guidance is one among several guidance documents addressing diversity in clinical trials.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial

Although progress has been made to increase the enrollment of diverse populations, there is still room for improvement. One strategy that has not been scaled up in a sustainable way is engaging community clinicians and investigators in research. There is considerable evidence that clinician recommendations play an important role in helping patients consider participating in clinical investigations.[3] In addition to clinicians' recommendations playing an important role, removing barriers to participation, such as bringing trials closer to where participants live, work, worship, and typically receive their healthcare, may also help achieve more diversity in both the workforce administering the trials and the participants undergoing investigative treatment. Decentralizing clinical trials, such as by providing access to them outside of academic research settings, could be an effective mechanism to improve diverse representation by bringing trials into communities. [4]

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 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 Research (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,

[3] https://www.nejm.org/doi/full/10.1056/NEJMp2107331
[4] See, for example, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6072894/

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. **In the last quarter of 2020, FDA issued a series of four RWE draft guidances, providing recommendations on assessing electronic health records, claims data, and registries for regulatory use. The guidances reflect the Agency's incremental approach to RWE, focusing on using RWE to support new indications of previously approved drugs. Recently, CDER announced plans for additional guidances in their 2022 guidance agenda on use of RWE to support drug development and regulatory decision making. However, use of RWE to support regulatory approvals for unapproved drugs has been limited. How can the use of RWE advance to the point of supporting new regulatory approvals for unapproved drugs?**

FDA defines real-world data (RWD) as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources", and real-world evidence (RWE) as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD". Because data from routine clinical practice would not typically be available for unapproved drugs, we would not expect RWE to be available to

support new approval of investigational drugs. However, RWD is still useful for purposes such as providing insights into the natural history of a disease or informing efficient trial design. These approaches may be especially important in the rare disease area where the study populations are small and available therapies are lacking, making it difficult to conduct traditional randomized trials. In these contexts, RWD on patients with the disease can potentially be used as a control arm for a single arm trial to inform FDA's assessment of the effectiveness of the intervention. Indeed, one of our guidance documents (*Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry*[5]) is particularly relevant to that use.

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

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 often generated by other organizations who specialize in this work, do you agree that they should be included in the proposed pilot program?**

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

    The advancing RWE pilot program included in the PDUFA VII commitment letter (pending enactment of the reauthorization legislation) is designed for enhancing interaction with the Agency for specific development programs. However, organizations that may be contributing their data to the specific development program under consideration can be included in relevant meetings with FDA at the sponsor's discretion. Beyond the PDUFA program, FDA's RWE Subcommittee meets with non-sponsor organizations to provide insight into characteristics of RWD that are important in establishing data quality. Many of the related concepts are captured in our guidance on *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products.*[6] Organizations can contact the Agency with questions regarding this draft document or the Real World Evidence Program by emailing CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

The Honorable H. Morgan Griffith (R-VA)

1. **What is the process FDA uses to solicit stakeholder input prior to the rollout of REMS programs?**

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory

FDA is limited in the extent to which it can solicit stakeholder input prior to approval or implementation of a risk evaluation and mitigation strategy (REMS), because the Agency cannot publicly disclose information about applications that are under review. In some cases, FDA may receive stakeholder input when an application is brought before an Advisory Committee.

Due to the limitations on the Agency's ability to directly solicit stakeholder input, FDA strongly encourages the drug applicant(s) to seek input from stakeholders prior to submitting a REMS proposal and throughout the development and review process. The Agency urges applicants to consider how the proposed REMS will fit into the workflow of the health care providers that are impacted by the REMS and what actions can be taken to minimize burden to stakeholders.

2. **Are there statutory changes FDA needs to ensure that REMS programs do not adversely impact patient access, incur unintended risks to patients, and increase burdens on healthcare providers and systems?**

When REMS are not implemented effectively and efficiently, patient access to these products can be impacted.

Section 505-1 of the FD&C Act authorizes FDA to require a REMS for prescription drug products if necessary to ensure that the benefits outweigh the risks. While FDA can require manufacturers to implement certain activities under a REMS that support the safe use of the drug, such as periodic lab tests, certification of prescribers and pharmacies, or administration of the drug in a health care setting, the statute does not address specific methods for implementing or operationalizing these requirements.

Because the manufacturers are responsible for developing and implementing REMS and because the risks that are the subject of a REMS vary, standardization across different REMS has been limited and, in general, REMS are not well-integrated into existing healthcare delivery system workflows or health information technology (HIT) systems. This lack of integration and REMS data sharing across the healthcare delivery system creates burdens for providers and barriers to patient access and efficient communication about the risks of the drug and the REMS requirements. Legislative changes could help to clarify FDA's authority to require specific methods of implementation that better integrate REMS requirements into healthcare system workflows and HIT systems.

The Honorable Gus Bilirakis (R-FL)

1. **Dr. Cavazzoni, the FDA's testimony mentions the most recent GDUFA legislation required Priority Review to become available for applications for generic drugs with limited competition, as well as for generic drugs in shortage. These provisions were a direct result of legislation I co-led with Representative Schrader, the Lowering Drug Costs through Competition Act. This bill also created the Competitive Generic Therapy (CGT) program, and I was pleased to see in the fall that FDA has approved over 100 generic drug applications with CGT designation.**

This means we are starting to see more competition in the marketplace, which will help alleviate prices. Can you explain how this next GDUFA proposal will build upon the successes of these programs for generics with little to no competition in the market? Can you explain why marketing exclusivity for CGT-designation has provided additional incentives for companies to establish generics with little or no competition in the market?

Under the anticipated reauthorization of Generic Drug User Fee Agreement (GDUFA), we will continue to prioritize certain applications for generic drugs with limited competition, consistent with criteria under section 505(j)(11) of the FD&C Act (as added by the FDA Reauthorization Act of 2017), and with CDER's Manual of Policies and Procedures (MAPP) 5240.3, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, available at https://www.fda.gov/media/89061/download.

The GDUFA III commitments also include several enhancements that are aimed at increasing generic competition by reducing the number of assessment cycles for ANDAs and facilitating timely access to generic medicines. For example, the enhancements include more opportunities for applicants to engage in meetings with FDA to help facilitate their development of generic drugs and FDA's review of their ANDAs and enhancements to our regulatory science program to help support development of more complex products. The commitments also contain enhancements that would help speed the resolution of quality manufacturing issues for generic drugs, including to facilitate resolution of inspectional issues, new goals for re-inspections, and additional opportunities for meetings between FDA and applicants.

You also asked about competitive generic therapies (CGTs) and the incentive provided by the potential for CGT-exclusivity for companies to market generics with little to no competition. From what FDA has observed, generic companies are actively participating in the program and seeking CGT designations, presumably because of the potential to receive exclusivity. In addition, the structure of this exclusivity – which only blocks the approval of other applications once the product with exclusivity is marketed and which is forfeited if the applicant eligible for exclusivity does not begin marketing in a timely manner post-approval – has been very successful at encouraging applicants to make their CGTs available to consumers quickly post-approval.

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 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), Statements of Organization Practices and Procedures (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 Richard Hudson (R-NC)

1. **Given the FDA's Center for Drug Evaluation and Research (CDER) modernization efforts and the reorganization of the New Drug Regulatory Program, which includes a restructuring of the Office of New Drugs, please explain your vision for the new Division of Rare Diseases and Medical Genetics (DRDMG), particularly any new review processes CDER is considering and how CDER is working towards increased consistency in the application of current regulatory approaches to support rare disease drug development.**

Providing consistency in the application of regulatory approaches to expedite rare disease drug development was a founding principle for the new Division of Rare Diseases and Medical Genetics (DRDMG). Over the past two years, several new initiatives have been launched to further this goal:

- The rare disease consultation service was reconfigured to ensure that review staff from DRDMG with direct responsibility for rare genetic disease drug development are available to advise other review divisions as needed regarding novel trial designs for small sample sizes and best practices for considerations related to regulatory flexibility in rare disease drug development.
- The Rare Disease Drug Development Council was established. This council convenes multidisciplinary rare disease experts from across CDER, including from the Office of New Drugs (such as, DRDMG) and the Office of Translational Science, to discuss cross-cutting challenges in rare-disease drug development. The council has provided a platform for consensus building on these issues across CDER.
- DRDMG initiated the Zebragram, which is an internal newsletter that highlights practical examples from review divisions across CDER, Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) for advancing rare disease drug, device, and biological product development. The Zebragram has featured information regarding the use of novel trial designs, endpoints, and statistical approaches, and regulatory flexibility. This

type of tool helps to support rare disease product development through enhanced collaboration and communication.

- This spring, CDER launched the Accelerating Rare Disease Cures (ARC) Program, which will drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

As we work to promote rare disease considerations across CDER, one of the early lessons learned from these efforts is that collaboration and knowledge sharing are important as is a recognition of the unique scientific considerations within a specific disease area. For example, the kinds of strategies that work best to advance drug development for rare, rapidly progressing diseases with objective endpoints, like some cancers, blood disorders, or infections, might be different from the kinds of strategies that work best for rare, slowly progressive diseases with patient reported outcome endpoints, like many neurodegenerative or rare metabolic diseases. Our efforts support knowledge sharing and recognition of the scientific and regulatory considerations relevant to specific disease areas, which is facilitating rare disease product development.

2. **FDA issued the Framework for FDA's Real-World Evidence (RWE) Program in 2018. In the last quarter of 2020, FDA issued a series of four RWE draft guidance's, providing recommendations on assessing electronic health records, claims data, and registries for regulatory use. The guidance's reflect FDA's incremental approach to RWE, focusing on using RWE to support new indications of previously approved drugs. In CDER's Guidance Agenda for 2022, CDER announced plans for additional guidance's on the use of RWE to support drug development and regulatory decision making. This is welcome news as the current use of RWE to support regulatory approvals appears extremely limited. It is my understanding that, to date, the July 2021 approval of a new indication for Prograf is the only approval based solely on RWE. Please explain CDER's vision and plans to transition and better utilize RWE to move towards the overarching goal of supporting increased regulatory approvals.**

We are increasingly seeing sponsors submit RWD as an external control arm for a single-arm trial or to supplement their clinical trial data, and RWE has served as confirmatory evidence for applications seeking to establish substantial evidence of effectiveness through one adequate and well-controlled clinical investigation plus confirmatory evidence when appropriate. Prograf (tacrolimus) was notable in that the primary evidence for effectiveness came from RWE, but FDA's confidence was bolstered by the results of randomized controlled trials in other solid organ transplant settings and by the natural history of a transplant (e.g., 100 percent mortality) in the absence of immunosuppressive therapy, such as Prograf, and other factors. Accordingly, we see RWE as potentially providing important evidence depending on the population and disease of interest, the research question(s), and the relevance and reliability of the data sources. We also see opportunities to generate RWE through randomized clinical trials that are more integrated into clinical practice, representing a model that was leveraged during the pandemic (e.g., in the RECOVERY trial). Such a model may also have the added benefit of being more inclusive of diverse study populations.

3. **Throughout the COVID-19 pandemic, FDA has understandably been delayed in inspecting pharmaceutical manufacturing facilities for safety reasons. However, we are now more than two years into the pandemic and FDA's latest report, An Update to the Resiliency Roadmap for FDA Inspectional Oversight – November 2021, indicates only 37 foreign inspections for human drugs were completed between April and September 2021. Please provide insight as to FDA's plans to overcome the growing backlog and ensure inspections remain timely.**

As you have noted, in March 2020, at the beginning of the COVID-19 pandemic, FDA paused most foreign and domestic surveillance inspections in compliance with Federal guidelines to reduce the spread of the COVID-19 virus. Nevertheless, the Agency continued mission-critical inspectional work. In addition, FDA utilized several alternative oversight approaches to help ensure the availability of safe medicines. In July 2020, after developing a COVID-19 Advisory Rating system (COVID-19 Advisory Level), FDA resumed and prioritized certain domestic inspections across all commodities.

Since October 1, 2021, FDA has been conducting domestic inspections at pre-COVID-19 operational levels. This includes addressing surveillance inspections that were postponed during COVID-19. In February 2022, FDA resumed foreign surveillance inspections and pre-approval and pre-license inspections that were not initially identified as mission critical or otherwise prioritized during the COVID-19 pandemic.

FDA is committed to continue its return to a consistent state of operations as expeditiously as possible. As always, FDA will first focus on the most critical public health work and prioritize other responsibilities, including product-specific pre-approval and pre-license inspections, based on risk. FDA is developing and implementing strategies to address the postponed surveillance inspections. These strategies include reprioritizing drug inspections based on our review of records and information that firms provided under section 704(a)(4) of the FD&C Act, and refining the way the risk-based Site Selection Model is applied to prioritize sites for surveillance inspection. In addition, to maximize the use of our inspectional resources, FDA has begun to add surveillance inspection coverage to pre-approval, pre-license, and post-approval inspections, where appropriate. The Agency seeks to optimize the use of its existing inspectional authorities and use other oversight tools to maximize the public health impact of its resources.

In the same report, FDA cites the use of "new oversight approaches" and "expanded use of a variety of surveillance tools" as reasons that FDA was able to exceed its Base-Case Scenario projections for domestic surveillance oversight activities for FY 2021. Please provide specific insight and details as to how FDA is currently utilizing these and additional alternative tools to ensure patient access to medicines is not further delayed.

The Agency expanded its use of Remote Regulatory Assessments (RRAs), which include voluntary remote interactive evaluations (such as remote livestreaming video of operations, teleconferences and screen sharing) and requests to review records and other information

under statutory authority. In addition, FDA has relied upon reviewing trusted foreign regulator inspection records under existing Mutual Recognition Agreements (MRAs).

These alternative tools have enabled the Agency to better meet its oversight responsibilities when traveling and in-person contact were restricted. Throughout the pandemic, FDA has used these tools, domestically and abroad, to help the Agency conduct oversight, mitigate risk, and meet critical public health needs.

Specifically, RRAs have helped FDA to verify that firms have taken promised corrective actions in response to findings from previous inspections and in gaining compliance insight when it was not practicable to inspect. RRAs have provided information about deficient practices, which led FDA to take regulatory actions and conduct inspections, and have informed future inspection planning. RRAs have also been used to help support, and reduce delays of, approval or authorization of marketing submissions for FDA-regulated products during the COVID-19 pandemic. Since the start of the pandemic, FDA has initiated over 1,000 RRAs to assess establishments engaged in manufacturing operations for human drugs. These assessments have enabled FDA to assess compliance with Current Good Manufacturing Practice (CGMP), and supported assessments and approval decisions for drug applications.

While these activities are not inspections under Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act, they can be used in combination with other oversight approaches to provide FDA investigators and supporting subject matter experts with a means to assess compliance with CGMP regulations, and the degree of process and product control at a site where product related operations are taking place or have taken place.

FDA will continue to use these alternative tools in appropriate circumstances beyond the pandemic to help ensure patient access to medicines and ensure the safety and integrity of the supply chain.

According to same report, there was also an increase in the number of drug applications that were delayed solely because of an overdue inspection – specifically, the number increased from 48 to 52 between May and September 2021. Please explain how FDA is prioritizing the resumption of foreign inspections and the growing backlog of affected applications, including any specific criterion applied. In addition, please provide FDA's expected timeline to fully resume foreign inspections.

Since October 1, 2021, FDA has been performing domestic inspections as per normal operations and in February 2022 resumed foreign surveillance inspections and pre-approval and pre-license inspections that were not initially identified as mission critical or otherwise prioritized during the COVID-19 pandemic. The specific criteria applied for determining the prioritization of inspections are outlined in Table 6 of the May 2021 Resiliency Roadmap for FDA Inspectional Oversight. This document states that mission critical inspections are to be performed first, which includes application approval inspections for high priority products, followed by for-cause application approval inspections (non-mission critical) and compounding inspections, and then routine surveillance and post approval inspections. As

FDA works through the inventory of postponed surveillance inspections, the Agency is prioritizing higher-risk establishments. For example, a sterile manufacturing site that has not been previously inspected and is making therapeutic index drugs would likely be deemed a higher risk than a site that had a well-known inspectional and compliance history that is making solid oral dosage form drugs. This means that postponed inspections will be prioritized based on risk and conducted on a schedule that allows FDA to strategically focus on products that present the greatest risk to public health.

FDA continues to make progress to facilitate and conduct inspections delayed or postponed due to the COVID-19 pandemic and strategies have been established to ensure that postponed facility inspections are risk assessed for prioritization.

The Agency continues to proceed with previously planned foreign surveillance inspections that have received country clearance and are within the CDC's Level 1 or Level 2 COVID-19 travel recommendation and has resumed surveillance inspections and pre-approval inspections that were not initially identified as mission critical.

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

1. **Dr. Cavazzoni, 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. It is well-established that rare disease therapy sponsor experience is inconsistent across review divisions at CDER. From your perspective, what can be done at CDER 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 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.

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 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.