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SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

December 1, 2023

The Honorable Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD, 20993

Dear Commissioner Califf,

I am reaching out to raise concerns about reports of inconsistent application of regulatory flexibility across different centers and review divisions within the Food and Drug Administration (FDA) when it comes to reviews involving rare and ultra-rare diseases.

As you may know, I am the author of the Helping Experts Accelerate Rare Treatments Act or HEART Act, legislation that was signed into law by President Biden in December of 2022. In brief, the HEART Act works to amplify the voices of patients and families living with rare diseases, as well as the voices of rare disease experts, when the FDA is evaluating treatments.

My journey on the HEART Act began more than four years ago, when I had the pleasure of meeting a constituent named Melissa, who is the Co-President of the Familial Chylomicronemia Syndrome (FCS) Foundation. Melissa's engagement with me prompted me to consider how FDA is currently engaging with patients, especially those that suffer from rare and ultra-rare diseases that do not have treatment options today. It also made me examine how FDA utilizes rare disease experts when making decisions on rare disease treatment reviews. I drafted the HEART Act to ensure that FDA is appropriately engaging with medical experts and patients during its review process. I believe that when we incorporate the voices of patients and rare disease experts in the review process, their perspectives lead to better treatment options and a better system for everyone. I look forward to the full implementation of the HEART Act and ask that you keep me fully updated on this process.

Recently, several different rare disease patient groups have raised concerns to me that the FDA review process is lacking consistency when it comes to review of treatments for rare and ultra-rare diseases. Specifically, I have heard concerns from families in my district who closely follow the FDA review process.

One of the patient groups I have heard from with concerns is the Barth Syndrome Foundation, which represents less than 150 affected patients in the United States who live with Barth Syndrome, a life-threatening genetic, multi-system disorder mostly affecting males with 85% of

premature deaths occurring by the age of five. There are several families in my district who are affected and closely following related FDA reviews.

The Barth Syndrome Foundation has shared that the developer of the first potential treatment for Barth Syndrome was transferred through four different FDA review divisions over a 2-year period prior to finally submitting its New Drug Application (NDA) on the basis of a positive Phase 3 natural history control trial. In that case, the FDA refused to file and review the NDA in 2021, and, 2 years, multiple educational efforts by BSF and leading physicians, a number of different proposed pre- and post-marketing trial designs, and more positive data later, there is still no clear regulatory path forward. I am concerned that with too much inconsistency drug developers will be less likely to invest in ultra-rare drug development because they cannot rely on FDA guidance or precedential decisions to guide their development efforts.

I also recently had the opportunity to meet with several of my constituents who have a child with Prader-Willi syndrome (PWS), a rare neurological disorder caused by a mutation on the 15th chromosome. The tragic stories they shared with me shook me to my core and I was saddened to learn that this condition lacks FDA-approved treatment options for PWS associated, life-threatening hyperphagia, an intense persistent sensation of hunger accompanied by food preoccupation, an extreme drive to seek and consume food and many of the other extremely challenging symptoms of this complex, heterogeneous disease. The PWS community has also expressed concerns to me about a lack of consistency and rare disease expertise across FDA review divisions - specifically the review of serious and life-threatening rare and ultra rare diseases for which no treatment options exist for the significant unmet needs.

Fabry disease is a rare inherited lysosomal storage disorder that affects small blood vessels, the heart, and kidneys, which can lead to renal failure, and/or cardiac disease, and early death. I've been made aware that in the case of an approved product for Fabry disease, the sponsor sought to use a baseline control study for a Phase 3 trial to treat Fabry disease. The FDA advised against using this type of control - citing it was unacceptable to meet the definition of an "adequate and well controlled" study. In light of this information, the sponsor elected to utilize a Randomized Controlled double-blinded Study in its Phase 3 trial. After the product was approved, the sponsor learned from the FDA review summary that a baseline control study was deemed suitable to meet the requirements of an adequate and well controlled study, contrary to the previous guidance that the FDA provided to a sponsor. In fact, the FDA cited that Phase 2 baseline control data was used to form the basis for approval and the Phase 3 Randomized Controlled double-blinded Study was merely used as supportive evidence.

With these concerns and examples in mind, please provide answers to each question below.

1. Can you provide an update regarding implementation of the HEART Act?
2. Can you provide a complete update on the implementation of the Interagency Council tasked with ensuring a more consistent approach within the FDA when evaluating rare disease therapies for accelerated approval across different review divisions?

3. What factors are taken into account when evaluating the rarity of a disease during the consideration of a Contract Research Organization of supplemental studies?
4. Can you provide insights into the criteria used to assign review divisions? Can you describe potential changes between different divisions when dealing with applications for rare diseases?
5. How does the FDA ensure consistency between divisions?
6. In situations involving a change in review divisions, what internal oversight mechanisms does the FDA have in place to ensure consistency of guidance to the sponsor?
7. Who does the FDA consult when determining whether a registry, open-label extension, or confirmatory trial can address outstanding concerns on the one versus several factors? Does this consultation include patients, patient groups, and treating clinicians? How is this process different for rare diseases and ultra-rare diseases?
8. How does the FDA evaluate whether the removal of one or several factors in a composite endpoint might guarantee a second trial's success or whether it is tied to the original composite endpoint? How does this evaluation differ for rare diseases and ultra-rare diseases?
9. How does the FDA decide when it will review a natural history comparison and how does it communicate this flexibility and when it is or is not appropriate to use with stakeholders?
10. How do review divisions obtain the information needed to truly understand a rare disease, how the disease is managed, and if a therapeutic “works” and is “safe” if the leading experts in that rare disease are conflicted out due to their participation in clinical trials?

Thank you for your dedication and commitment to improving the lives of patients suffering from rare and ultra-rare diseases.

Sincerely,

Paul Tonko
Member of Congress