



March 9, 2023

Dr. Robert Califf, Commissioner  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dr. Califf,

Haystack Project looks forward to the implementation of the rare disease provisions of the Consolidated Appropriations Act. In particular, we are keenly interested in the implementation of the HEART Act, contained in Section 3202 of the bill. The experiences of so many of the rare disease groups that participate with Haystack Project directly led to these provisions. Hence, we are very vested in sharing perspectives with you and ensuring these provisions are implemented in ways that address our members' concerns.

Haystack Project is a 501(c)(3) non-profit organization enabling rare and ultra-rare disease advocacy organizations to highlight and address systemic access barriers to the therapies they desperately need. We strive to amplify the patient and caregiver voice in disease states where unmet need is high, and treatment delays and inadequacies can be catastrophic. Our core mission is to evolve health care payment and delivery systems in ways that spur innovation and quality in care toward effective, accessible treatment options for Americans living with rare or ultrarare conditions. Haystack Project is committed to educating policymakers and other stakeholders about the unique circumstances of extremely rare conditions with respect to product development, commercialization, and fair access to care.

As you may be aware, Haystack Project crafted and championed the HEART Act to address longstanding concerns within our patient communities. We understand and appreciate that FDA has existing relationships with other rare disease advocacy groups, including NORD, that contribute to FDA's understanding of rare disease patients generally. However, it was Haystack Project's 130+ member organizations steeped in the real-world experience unique to patients and families living with an "ultra-rare" condition that resulted in the Heart Act. We can, therefore, provide the critical insights FDA will need to ensure that its HEART Act implementation addresses the concerns Haystack Project crafted the bill to resolve.

Heart Act provisions directing an FDA report, publication of final guidance, public meeting(s) on improved patient advocacy engagement, and consultation on the science of small population studies to address informational and process gaps that have a disproportionate impact on product development in ultra-rare conditions. Haystack Project and its member organizations can offer FDA important insights and pragmatic approaches that balance the needs and interests of patients, FDA, and industry stakeholders.

## **Report**

The first thing the HEART Act requires is a report summarizing FDA's activities related to designating rare disease drugs. The reason we need this information is a concern around ultra-rare disease review. The "orphan" category is fairly broad with respect to impacted population, and there may be issues in patient populations below 15-20,000 that are not present when prevalence approaches 200,000. When a review division asks questions that clearly indicate a lack of experience in ultra-rare applications, we went to see how many similar applications they had reviewed before. This data is unavailable.

This report asks what extent FDA is consulting with external experts on rare disease drugs. Our technical assistance to Capitol Hill included a strong emphasis that FDA already has the authority to meet with patient groups about broad and specific product issues. Yet, we have found that FDA limits the circumstances for and content of its meetings with patient groups.

- Our patient groups have attended repeated meetings where the majority of the time is spent listening to FDA's explanation of current law. We want to progress beyond a mere recitation of the law and have a true exchange of concerns and ideas to inform FDA's queries, processes and decisions.
- We have already heard this year that FDA would not accept some meetings requested by rare disease groups because of the concern around confidential commercial information (CCI). Our groups understand and respect FDA's limitation on sharing such information and have said as much to staff when rejected.

## **Guidance**

The second thing the HEART Act requires of FDA is publication of final guidance related to the Rare Diseases: Common Issues in Drug Development draft guidance. There are outstanding issues from the guidance that have yet to be finalized or put into practice.

- For example, the aforementioned guidance, among other FDA guidances, speaks to the importance of natural history studies. However, natural history studies are uncommon for ultra-rare disease groups. Many groups that have collected this important information have told us that FDA does not accept the data from those hard-won and often irreplicable databases.
- The guidance also speaks to the need for validated endpoints, but we hear from ultra-rare disease groups that FDA is not considering the professional standard for endpoint identification or measurement.
- The guidance includes information about the safety of potential treatments for rare diseases. As most rare diseases do not have a disease-specific treatment, much less a cure, patients are often willing to face a different risk-benefit balance than FDA typically sees. For example, the risk that patients, families and doctors tell FDA is reasonable in a rare, fatal, and/or progressive degenerative disease captures real-world experience, knowledge, hopes and fears unique to that condition. It should not be, but reportedly is, overridden by the guesses of FDA staff who may be more familiar with chronic diseases in the same body system.

## **Public Meeting**

Another provision requires FDA to convene at least one public meeting to solicit input from stakeholders regarding approaches to increase and improve engagement with rare disease patients and patient groups. Rare and ultra-rare disease patients and caregivers are often in close contact, discussing the disease, the latest science, the side effects of treatment and other life experiences. They can provide

meaningful information to FDA without sharing any CCI about the progress and design of trials – how far do patients have to travel? Is a placebo arm necessary? Is there a rescue arm? How will the FDA deal with crossover effect? How is the drug delivered? What are the right measures to monitor patient progress? What is the correct length of time to measure disease progression?

### **Consultation on the Science of Small Population Studies**

Because rare and ultra-rare disorders, by definition, have small, affected populations, traditional mechanisms related to clinical trial design and evaluation do not always provide meaningful data. The bill allows FDA to consult experts on the science of small population studies. This can help FDA better review treatments for rare and ultra-rare diseases. However, people with disease experience should be included in FDA's review. Rare and ultra-rare diseases have neither large patient populations nor large groups of experts working on the disease. Too often, those with experience are considered conflicted out of advising the FDA. Therefore, only people without familiarity with the disease can be consulted, raising serious concerns about the quality of the information they can provide the FDA. We believe that this FDA policy prevents FDA from hearing from disease-specific experts when their input is needed most, i.e., in decisions related to ultra-rare disorders.

Additionally, trial design for an ultra-rare disease may only have a handful of people in each arm, which may not provide meaningful data to those accustomed to evaluating the results of large-scale clinical trials. The addition of a rescue arm, which is ethically important, further confounds any potential measured effect of the intervention, making it even more complicated to determine the efficacy of the treatment. Expertise in designing and understanding the results of these small trials is of critical importance when evaluating the safety and efficacy of a drug or biologic.

We request a meeting to discuss the FDA's plan for implementing the HEART Act and provide further information about the genesis of the bill. We hope that this is another step to reaching a true exchange of concerns within the bounds of the law.

Sincerely,

A handwritten signature in blue ink, appearing to read "Chevese Turner".

Chevese Turner, CEO  
Haystack Project