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

Patrizia Cavazzoni, M.D.
Director Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Peter Marks, M.D.
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf, Dr. Cavazzoni, and Dr. Marks:

We write to you today about the Food and Drug Administration’s (FDA) approach towards serious, ultra-rare diseases (commonly considered to affect fewer than 1 in 50,000 people,1 or less than 7,000 people in America) and to raise concerns about FDA’s reported inconsistency in the application of regulatory flexibility across divisions. Such inconsistency jeopardizes both current and future investment into the development of therapies for serious and ultra-rare diseases, 2 and we are concerned that FDA’s regulatory inconsistency results in ultra-rare disease patients losing access to innovative treatments.

A recently published FDA-commissioned report provides compelling evidence supporting our concerns about regulatory inconsistency at FDA. The report concludes that FDA’s use of regulatory flexibility is characterized by standalone, case-by-case decisions utilizing highly variable criteria for substantial evidence.3 We are troubled with FDA’s lack of transparency, consistency, and predictability.

We recognize that FDA regulations are designed to permit agency officials to exercise scientific judgment and regulatory discretion. We also recognize and applaud the Agency’s commitment to surmounting enormous scientific challenges that come from “the nature of rare diseases itself, along with the small patient populations, [meaning] there are a limited number of people available to participate in clinical trials.”4 Like you, we are troubled that “the vast majority of

---

1 Hobbs, Ultra-Rare Disease Approvals By US FDA Could Take More ‘Mechanistic,’ Less ‘Empirical’ Approach", Pink Sheet, 01 Jul 2021
rare diseases do not yet have approved treatments.” For this reason, members of the Rare Disease Caucus recently asked that more reliability and consistency be brought to the process of reviewing rare disease therapies to address gaps in guidance and irregular decision-making with respect to ultra-rare diseases. Industry members have supported Congressional initiatives for FDA to better understand its own conduct, such as

1. a study on the sufficiency and use of FDA mechanisms to incorporate patient/clinician perspectives in FDA processes for rare disease drug approvals,
2. an annual report on the progress of rare disease drug applications, and
3. the development of new approaches to improve engagement with non-FDA rare disease/condition experts.

One example of FDA’s inconsistent use of regulatory flexibility arises from the acceptance of an externally controlled trial, or “historical control” trial, as adequate and well-controlled under 21 CFR 314.126(b)(2)(v). We believe this inconsistent use of regulatory flexibility could be improved by incorporating expert analysis into small population studies. FDA’s guidance repeatedly recognizes “historical controls as a possible control group…[for which] bias may be mitigated…where the disease course is predictable and the treatment effect dramatic…[and further that] in some cases…a baseline control study design can be used.” This guidance notes that “if the natural history of a disease is well-defined and the disease is known not to improve in the absence of an intervention or with available therapies, historical information can potentially serve as the control group.”

Notwithstanding the clear statutory and regulatory guidance we mention above, we understand that there are inconsistencies in FDA’s decisions to even review therapies for ultra-rare diseases utilizing these designs. Certainly, we have seen examples of approvals on this basis, including:

1. the recent approval of a drug for Friedreich’s ataxia based in part on a natural history control study, which has been hailed as “widening the path for rare disease treatments;”
2. a recent approval for fibrodysplasia ossificans progressiva based on a post hoc analysis of a failed natural history control study; and
3. prior precedent based on the approval of a drug for Batten disease.

Conversely, we have been made aware by the Barth Syndrome Foundation, which represents a patient population of less than 200 Americans, that the application for approval of a promising therapy for Barth syndrome has been transferred through four different FDA review divisions over a 2-year period prior to the submission of a new drug application (NDA) on the basis of a positive Phase 3 natural history control trial at the request of patient advocacy. In that particular

---

5 Ibid.
8 https://www.statnews.com/sponsor/2022/10/12/1-in-10-americans-have-a-rare-disease-but-few-have-treatments/
9 https://www.wsj.com/articles/fda-widens-path-for-rare-disease-treatments-with-new-approval-1ba909c97505d5a66599260fca5888reflink=article_email_share
case, FDA refused to even file and review the NDA, and 2 years later, the application remains stalled despite multiple intervening interactions with the agency. Given that all Barth patients have a reduced life expectancy, with 85% of premature deaths occurring by the age of five, you will appreciate our perspective that four years is far too long for a promising therapy with real world results to live in regulatory limbo.

FDA’s unwillingness to consider natural history and within-patient comparisons has also been reported in the context of Niemann-Pick disease type C. Other reported examples of inconsistencies in the application of regulatory flexibility include variable evidentiary standards required for utilization of the accelerated approval pathway and variable requirements for the design and conduct of post-marketing trials. We are extremely concerned that drug developers are increasingly less likely to invest in ultra-rare drug development because they cannot rely on FDA guidance or precedent to guide their development efforts.

Senior FDA officials recently cited patient preference information regarding risk of uncertainty of clinical benefit in exchange for earlier access to a potentially effective drug. However, we have heard that the utilization of this information can be inconsistent. The Barth Syndrome Foundation met with the FDA four times over the past few years, including last summer, to explain the severe unmet medical need affecting their small patient population, the unique challenges of developing therapies for such an ultra-rare disease, and the patient community’s overwhelming willingness to tolerate the risk of uncertainty of benefit.

We welcome the opportunity to work with you to bring more consistency and specialized small population expertise to your review of therapies for ultra-rare and serious diseases. To that end, we request individual responses to each of the following questions no later than October 2023:

1. In order for us to better understand FDA’s application of regulatory flexibility, please describe:
   a. The process by which FDA reviewers consult regulatory guidance;
   b. The process by which FDA reviewers consult regulatory precedent.

In the event FDA is not currently tracking the processes described above, please indicate whether the tracking of such processes would be useful.

---

21 https://www.statnews.com/2021/09/14/aduhelm-backlash-may-imperil-fda-reviews-ultra-rare-disease-drugs/
2. For years 2015-2023, how many orphan drug approvals involved the use of data generated outside of randomized placebo-controlled clinical trials (for example, baseline control, single arm, or natural history control clinical trials)? In how many of those cases were drugs ultimately pulled from the market?

3. For the years 2015-2023, how many refusals to file (RTFs) has FDA issued for orphan drug therapies on the basis that the filing did not include sufficient evidence of effectiveness to formally review the filing?

   a. Please provide a breakdown of the number of any RTFs issued on the above-described basis for NDAs submitted under rare pediatric designation, orphan drug designation, fast-track designation and breakthrough designation, including an indication of how many of these were seeking approval through FDA’s Accelerated Approval pathway.

   b. How many of these NDAs were ultimately accepted for review and how many were ultimately approved?

   c. How many of these NDAs were for ultra-rare diseases (diseases affecting fewer than 7,000 Americans)?

   d. In how many of these NDAs was “patient experience data” (as defined under the 21st Century Cures Act), including patient tolerance of risk of uncertainty of benefit, a consideration in the decision of whether to review the NDA?

   e. In how many of these NDAs were external experts familiar with the care and treatment of the disease consulted by the Agency? What extent did their consultation play in the Agency’s decision-making regarding the applications?

4. For the years 2015-2023, with respect to approvals for rare diseases under the Accelerated Approval pathway:

   a. In how many cases was “patient experience data,” as defined under the 21st Century Cures Act (including patient tolerance for risk of uncertainty of benefit) a consideration in the approval decision?

   b. In how many of these NDAs were external experts familiar with the care and treatment of the disease consulted by the FDA?

   c. In how many cases were approvals based on a statistically significant finding on a surrogate endpoint, which was the prespecified primary endpoint for the pivotal study on which approval was based?

   d. In how many cases was the approval based on a significant finding on an exploratory or secondary surrogate endpoint, where the primary endpoint was not met? How many of these were for ultra-rare diseases?

   e. In how many cases was there a significant correlation demonstrated between the surrogate endpoint and clinical benefit in the study population? How many of these cases involved ultra-rare diseases?

---

22 Id footnote 1
f. In how many cases was the post-marketing trial protocol approved by the Agency prior to Accelerated Approval? In how many cases was the post-marketing trial fully enrolled prior to Accelerated Approval? In how many cases was the post-marketing trial required to be placebo controlled?

5. The Consolidated Appropriations Act, 2023 (P.L. 117-328) authorized FDA to implement an Interagency Council to ensure a more consistent approach by FDA across review divisions in considering rare disease therapies for accelerated approvals. Please provide an update on the implementation of the Interagency Council.

6. Americans living with ultra-rare diseases are some of the most vulnerable and underserved patients in the country. You have made remarks about the FDA’s work to “embrace greater regulatory flexibility to help meet unmet medical needs” in the rare disease space and have outlined a number of regulatory flexibilities available to the FDA, including “accepting clinical trials that have lower sample sizes.” Please provide an account of the steps FDA is taking to apply regulatory flexibility in the setting of serious, ultra-rare diseases.

Thank you for your attention to this matter. Responses to the above questions should be directed to Jacob_Chebowski@braun.senate.gov, [INSERT EMAILS].

Sincerely,