

# Congress of the United States

Washington, DC 20515

February 5, 2024

The Honorable Robert M. Califf, M.D.  
Commissioner

Patrizia Cavazzoni, M.D.  
Director, Center for Drug Evaluation and Research

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,<sup>1</sup> 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,<sup>2</sup> 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.<sup>3</sup> 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."<sup>4</sup> Like you, we are troubled that "the vast majority of rare diseases do not yet have approved treatments."<sup>5</sup> For this reason,

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<sup>1</sup> Hobbs, Ultra-Rare Disease Approvals By US FDA Could Take More 'Mechanistic,' Less 'Empirical' Approach", Pink Sheet, 01 Jul 2021

<sup>2</sup> Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field MJ, Boat TF, editors. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington (DC): National Academies Press (US); 2010. 3, Regulatory Framework for Drugs for Rare Diseases. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK56185/>

<sup>3</sup> Janiaud et al., "U.S. Food and Drug Administration Reasoning in Approval Decisions When Efficacy Evidence Is Borderline, 2013–2018", *Annals of Internal Medicine*, 2021

<sup>4</sup> U.S. Food and Drug Administration, Speech by Robert M. Califf, M.D., MACC, "Remarks by FDA Commissioner Robert M. Califf to the 2022 NORD Breakthrough Summit" (Oct. 17, 2023), <https://www.fda.gov/news-events/speeches-fda-officials/remarks-fda-commissioner-robert-m-califf-2022-nord-breakthrough-summit-10172022>

<sup>5</sup> Ibid.

members of the Rare Disease Caucus<sup>6</sup> 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: a study on the sufficiency and use of FDA mechanisms to incorporate patient/clinician perspectives in FDA processes for rare disease drug approvals; an annual report on the progress of rare disease drug applications, and the development of new approaches to improve engagement with non-FDA rare disease experts.<sup>7</sup>

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 the 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."<sup>8</sup> 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.<sup>9</sup> Certainly, we have seen examples of approvals on this basis, including: 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,"<sup>10</sup> the recent approval for fibrodysplasia ossificans progressiva based on a post hoc

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<sup>6</sup> Press release, "Klobuchar, Wicker, Bilirakis, Matsui Lead Colleagues in Urging the FDA to Improve Reliability in Reviewing Applications for Rare Disease Therapies" (May 10, 2023), <https://www.klobuchar.senate.gov/public/index.cfm/2023/5/klobuchar-wicker-bilirakis-matsui-lead-colleagues-in-urging-the-fda-to-improve-reliability-in-reviewing-applications-for-rare-disease-therapies>

<sup>7</sup> See "Implementing the HEART Act", Haystack Project: The Voices of the Rare & Ultra Rare website, <https://haystackproject.org/heart-act>. See also EveryLife Foundation for Rare Diseases, "EveryLife Foundation Applauds Bipartisan Congressional Letter Urging the FDA to Strengthen Rare Diseases Activities" (May 12, 2023), <https://everylifefoundation.org/everylife-foundation-applauds-bipartisan-congressional-letter-urging-fda-to-strengthen-rare-disease-activities/>. See also NORD Letter to Lauren K. Roth, Acting Commissioner for Policy, Food and Drug Administration, RE: Docket No. FDA-2023-D-0026- "Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making" (July 5, 2023), <https://rarediseases.org/wp-content/uploads/2023/07/NORD-Comments-on-FDA-PFDD-Guidance-Four.pdf>. See also

<https://matsui.house.gov/media/press-releases/matsui-wenstrup-wicker-klobuchar-reintroduce-benefit-act>. See also, Press Release from the office of Rep. Matsui, "Matsui, Wenstrup, Wicker, Klobuchar, Reintroduce Benefit Act" (Feb. 27, 2023), <https://rarediseases.org/wp-content/uploads/2023/05/NORD-comments-on-Considerations-for-the-Design-and-Conduct-of-Externally-Controlled-Trials-for-Drug-and-Biological-Products-Guidance-for-Industry-FINAL.pdf>

<sup>8</sup> Guidance on Rare Diseases: Natural History Studies for Drug Development Guidance for Industry, March 2019, <https://www.fda.gov/media/122425/download>; see also, Guidance on Rare Diseases: Common Issues in Drug Development, February 2019), <https://www.fda.gov/media/119757/download>

<sup>9</sup> Sponsored Insight, *STAT News*, "1 in 10 Americans have a rare disease, but few have treatments," <https://www.statnews.com/sponsor/2022/10/12/1-in-10-americans-have-a-rare-disease-but-few-have-treatments/>

<sup>10</sup> Amy Dockser Marcus, "FDA Widens Path for Rare-Disease Treatments with New Approval: Reata Pharmaceuticals Used Patient Histories with Trials Data to Win Approval for New Friedreich's Ataxia Drug," *Wall Street Journal*, (March 1, 2023), [https://www.wsj.com/articles/fda-widens-path-for-rare-disease-treatments-with-new-approval-1ba99c09?st=56k69q260rfaz58&reflink=article\\_email\\_share](https://www.wsj.com/articles/fda-widens-path-for-rare-disease-treatments-with-new-approval-1ba99c09?st=56k69q260rfaz58&reflink=article_email_share)

analysis of a failed natural history control study;<sup>11</sup> and prior precedent based on the approval of a drug for Batten disease.<sup>12</sup>

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 two-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.<sup>13</sup> In that particular case, FDA refused to even file and review the NDA, and two years later, the application remains stalled despite multiple intervening interactions with the agency. Given that all Barth patients have a reduced life expectancy,<sup>14</sup> with 85% of premature deaths occurring by the age of five,<sup>15</sup> 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<sup>16</sup> has also been reported in the context of Niemann-Pick disease type C.<sup>17</sup> Other reported examples of inconsistencies in the application of regulatory flexibility include variable evidentiary standards required for utilization of the accelerated approval pathway<sup>18</sup> and variable requirements for the design and conduct of post-marketing trials.<sup>19</sup> We are extremely concerned that drug developers are increasingly less likely to consider and invest time and resources 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.<sup>20</sup> However, we know that the utilization of this information can be inconsistent. The Barth Syndrome Foundation, for example, met with the FDA four times over the past few years<sup>21</sup> to explain the severe unmet medical need affecting their small patient

<sup>11</sup> Manalac, Munger, BioSpace, 6/29/2023, <https://www.biospace.com/article/fda-warms-up-to-ipsen-s-post-hoc-analysis-for-rare-disease-drug-ahead-of-adcomm/>

<sup>12</sup> Press Release, U.S. Food and Drug Administration, "FDA Approves First Treatment for a Form of Batten Disease" (Apr. 27, 2017), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-form-batten-disease>.

<sup>13</sup> Ed Silverman, "No Magic Bullet": For Drugmakers and the FDA, Clinical Trials on Ultra-Rare Diseases Pose Thorny Challenges," *STAT NEWS*, (July 26, 2022, <https://www.statnews.com/pharmalot/2022/07/26/ultra-rare-disease-drugs-fda-clinical-trials/>); Barth Syndrome Foundation. BSF Community Petition: FDA & Stealth Biotherapeutics: Allow Individuals with Barth Syndrome Access to Elamipretide. Accessed October 31, 2022. [https://www.barthsyndrome.org/file\\_download/inline/a38907fe-95cd-421e-a06f-a147cb1f3db4](https://www.barthsyndrome.org/file_download/inline/a38907fe-95cd-421e-a06f-a147cb1f3db4).

<sup>14</sup> Finsterer, Barth Syndrome Mechanisms and Management, The Application of Clinical Genetics, 2019.

<sup>15</sup> The Voice of the Patient Report: Barth Syndrome, March 8, 2019, <https://fda.report/media/130562/EL-PFDD+Meeting+on+Barth+Syndrome+Voice+of+the+Patient+Report.pdf>

<sup>16</sup> There are also many examples of therapies approved on the basis of baseline control trial designs, including for MPS VII (<https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-rare-genetic-enzyme-disorder>) and bile acid synthesis disorders (<https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-rare-genetic-enzyme-disorder>), among others.

<sup>17</sup> <https://www.statnews.com/2022/09/07/the-fda-needs-to-be-more-flexible-in-assessing-treatments-for-rare-diseases-like-the-one-that-seemed-to-help-my-son/>.

<sup>18</sup> Saleem, "Neurology Takes a Page Out of the Oncology Playbook of FDA", ProEd Regulatory, 6/16/2023; <https://proedcomblog.com/tag/accelerated-approval/>.

<sup>19</sup> Sutter, "US FDA Has History of Pushing Sponsors On Confirmatory Trials ... Sometimes", Pink Sheet, 1/25/2023; <https://pink.pharmaintelligence.informa.com/PS147570/US-FDA-Has-History-Of-Pushing-Sponsors-On-Confirmatory-Trials--Sometimes>.

<sup>20</sup> Cavazzoni, Stein, Dunn, *JAMA Internal Medicine*, 7/13/2021, doi:10.1001/jamainternmed.2021.4607.

<sup>21</sup> Barth Syndrome Foundation. BSF Regulatory Pathway Workshop with FDA. Published September 22, 2022. Accessed October 31, 2022. <https://www.barthsyndrome.org/advocacy/advocacy-updates.html/article/2022/09/22/bsf-regulatory-pathway-workshop-with->

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.<sup>22</sup>

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 the following information be provided no later than February 26, 2024:

1. All documents and communications that instruct FDA reviewers on how to consult regulatory guidance when determining the possible application of regulatory flexibility that concern therapies for ultra-rare and serious diseases, including how such reviewers are to consult regulatory precedent.
2. A description of how the current internal system tracks regulatory such flexibility petitions described in Question #1.
3. For years spanning 2015-2023, a list of all orphan drug approvals that 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), and a notation sufficient to indicate how many of those cases were drugs ultimately pulled from the market.
4. For the years spanning 2015-2023, a list of all refusals to file (RTFs) that the FDA has issued for orphan drug therapies on the basis that the filing did not include sufficient evidence of effectiveness to formally review the filing. Please provide a list of:
  - a. 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. NDAs that were ultimately accepted for review, with a notation to indicate:
    - i. Which NDAs were ultimately approved,
    - ii. Which NDAs were for ultra-rare diseases (diseases affecting fewer than 7,000 Americans)?<sup>23</sup>
    - iii. Which NDAs used "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?<sup>24</sup>
5. For the years spanning 2015-2023, with respect to approvals for rare diseases under the Accelerated Approval pathway, please provide a list of cases for which "patient experience data," as defined under

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<sup>22</sup> Emily Milligan and Katherine R. McCurdy, "Aduhelm Backlash Threaten to Reverse Progress in FDA's Reviews of Rare and Ultra-Rare Disease Drugs," *STAT News* (Sept. 14, 2021), <https://www.statnews.com/2021/09/14/aduhelm-backlash-may-imperil-fda-reviews-ultra-rare-disease-drugs/>.

<sup>23</sup> Id footnote 1.

<sup>24</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 3001, 130 Stat. 1033, 1083-1085 (2016).

the 21st Century Cures Act (including patient tolerance for risk of uncertainty of benefit), a consideration in the approval decision?<sup>25</sup> For such list, please indicate:

- a. Which approvals were based on a statistically significant finding on a surrogate endpoint, which was the pre-specified primary endpoint for the pivotal study on which approval was based.
- b. Which approvals are based on a significant finding on an exploratory or secondary surrogate endpoint, where the primary endpoint was not met (and which of these were for ultra-rare diseases).
- c. Which cases had a significant correlation demonstrated between the surrogate endpoint and clinical benefit in the study population (and which of these cases involved ultra-rare diseases).
- d. Which cases had the post-marketing trial protocol approved by the FDA prior to Accelerated Approval, including which cases had the post-marketing trial fully enrolled prior to Accelerated Approval, and which cases had the post-marketing trial required to be placebo controlled.

Thank you for your attention to this matter.

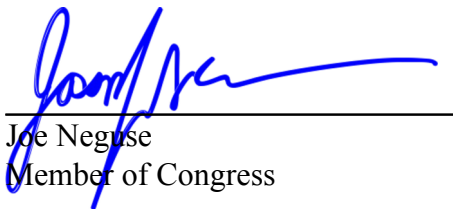
Sincerely,



Gus M. Bilirakis  
Member of Congress



Terri A. Sewell  
Member of Congress



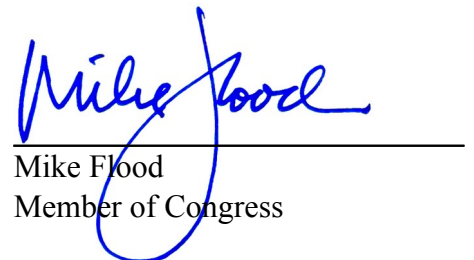
Joe Neguse  
Member of Congress



Michael Guest  
Member of Congress




Earl L. "Buddy" Carter  
Member of Congress




Mike Flood  
Member of Congress

<sup>25</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 3001, 130 Stat. 1033, 1083-1085 (2016).



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Jake Auchincloss  
Member of Congress



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C. A. Dutch Ruppertsberger  
Member of Congress