



11/29/21

Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2020-D-2316: “Benefit-Risk Assessment for New Drug and Biological Products”**

Dear Sir or Madam:

Thank you for the opportunity to submit comments on behalf of the National Organization for Rare Disorders (NORD) regarding the Food and Drug Administration’s (FDA or Agency) Draft Guidance, *Benefit-Risk Assessment for New Drug and Biological Products*.<sup>1</sup> Founded in 1983, NORD represents 328 different rare disease patient organizations and the 25-30 million Americans living with a rare disease. We are committed to identifying, treating, and curing rare disorders through programs of education, advocacy, research, and patient services.

NORD is supportive of the draft guidance and appreciates FDA’s numerous and ongoing efforts to incorporate the patient voice into benefit-risk assessments and other parts of the regulatory review process. The draft guidance will enable stakeholders to better understand how to incorporate relevant patient experience into the benefit-risk assessment FDA utilizes when considering a product.

In the guidance, FDA reiterates that patients are experts in their own diseases and that they are the ones who ultimately accept the risks and the benefits of a treatment.<sup>2</sup> NORD recognizes the difficult task that FDA faces in terms of balancing what the Agency knows or learns about patient experiences and preferences with the Agency’s statutory mandate to make assessments about a product’s benefit-risk profile for the overall patient population. FDA cannot nor should not rely on anecdotal evidence from patient stories. NORD applauds FDA for the transparency provided in this guidance regarding how FDA approaches these difficult assessments. Transparency is critical for all stakeholders, but particularly for patient communities.

Evaluating Benefit-Risk in the Context of Unmet Need for Rare Diseases

NORD also appreciates the explicit considerations related to rare diseases in this guidance.<sup>3</sup> FDA appropriately recognizes the uncertainty and unmet need that surrounds rare diseases, as well as

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<sup>1</sup> FDA. Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry; Draft Guidance. (2021). Accessed 11/10/21. <https://www.fda.gov/media/152544/download>

<sup>2</sup> FDA. Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry; Draft Guidance. (2021). Page 11. Accessed 11/10/21. <https://www.fda.gov/media/152544/download>

<sup>3</sup> Ibid.

the increased risk tolerance for rare disease patients who have no other treatment options. Rare diseases are often not as well understood as common diseases, and the small populations make developing and evaluating a robust benefit-risk profile complicated. Additionally, over 90% of rare diseases do not have an FDA-approved treatment. Therefore, while there are often difficulties assessing the benefits and risk of a drug in rare disease patient populations, there is also significant unmet need among those patients. This complex situation warrants FDA's use of regulatory flexibility in assessing benefit-risk. NORD supports such flexibility but only to the extent that all approvals made as a result meet the appropriately high FDA standards for safety and effectiveness set forth in current law and regulations. All patients, whether they have rare or common diseases, are best served when this careful balance is met by FDA in its review of medical products.

As FDA sets forth in the guidance, consideration of unmet need in the context of rare diseases is a particularly important aspect of the benefit-risk framework. As FDA notes, when there is unmet need, it is appropriate for FDA to accept a greater level of uncertainty when it comes to approval. This is in keeping with the desires and needs of patients living with such diseases. But unmet need does not justify, for example, accepting flawed drug development programs or inadequate levels of evidence of safety or effectiveness. Upholding FDA's gold standards when it comes to drug approval is of utmost importance for patients, even in the face of unmet need.

A careful consideration of the context of unmet need is critical for other reasons as well. If there are limited or no other treatments for a given disease and FDA placed undue emphasis on that fact by approving a drug that had a questionable benefit-risk balance, that approved drug, once marketed, can become the standard of care, creating complications for future drug development efforts in that disease space, particularly around the design of future clinical trials. In rare diseases, with small disease populations, this can create further difficulties recruiting and conducting clinical trials.

### Addressing Uncertainties in Benefit-Risk for Rare Diseases

The draft guidance provides a useful description of the many uncertainties that may complicate the benefit-risk assessment.<sup>4</sup> Such uncertainties are all too familiar to stakeholders in the rare disease space. Therefore, NORD appreciates FDA identifying some of these uncertainties and agrees that incorporating the rare disease patient voice in benefit-risk can help address many aspects of benefit-risk assessments and alleviate some of these issues.<sup>5</sup> As FDA notes in the draft guidance, patient experience data can inform therapeutic context, meaningful benefits, and risk tolerance to help reduce the impact of these uncertainties.<sup>6</sup> This is particularly true when it comes to data from rare disease patients with respect to their lived experience with their diseases.

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<sup>4</sup> FDA. Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry; Draft Guidance. (2021). Page 10. Accessed 11/10/21. <https://www.fda.gov/media/152544/download>

<sup>5</sup> FDA. Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry; Draft Guidance. (2021). Page 11. Accessed 11/10/21. <https://www.fda.gov/media/152544/download>

<sup>6</sup> Ibid.

Another key aspect of the benefit-risk assessment that has historically been challenging for rare disease drug development is the lack of understanding of the patient's disease burden. NORD has conducted a number of patient-focused activities to get patients in front of FDA to share their experience, including patient listening sessions and externally-led patient-focused drug development meetings with FDA. NORD encourages more frequent use of these activities to get more patients to share their experience with FDA. Understanding what a patient goes through, and what kind of impact a treatment that alleviates a particular symptom(s) can do for them, is essential to understanding the patient's burden.

Additionally, among the identified uncertainties is the impact of the lack of natural history of the disease and endpoint selection. NORD's participation in FDA's Rare Disease Cures Accelerator Data Analytics Platform, to characterize rare diseases, and Clinical Outcome Consortium, to create and curate a resource of information on publicly available Clinical Outcome Assessments (COAs) identified as potentially fit-for-purpose endpoint measures for rare diseases, can help to address these uncertainties.<sup>7</sup> NORD is also working with Northwestern University to develop COAs for certain conditions.<sup>8</sup> These patient-focused drug development activities aim to provide sponsors with validated, fit-for-purpose patient-centered data and tools to assist in developing treatments for rare diseases and help reduce the uncertainties of a rare disease product.

#### Additional NORD Comments

While NORD is appreciative of the considerations for benefit-risk set forth in the draft guidance, the following additional comments provide suggestions for improving it further.

NORD strongly believes that if patients are consulted and have their data used as part of an effort to develop a treatment, they should be consistently informed about the role such data played in regulatory decision-making. Patients are often willing to share their experiences, and both sponsors and FDA have expressed how important this information is to them. Therefore, NORD encourages FDA to provide robust descriptions of what data was helpful and why it was beneficial in the review process to allow external stakeholders to develop a better understanding of what kinds of data are most impactful. We believe that developing a patient's understanding of how FDA utilizes their data will lead to more effective data collection and encourage patients to be more involved in the drug development process.

NORD appreciates FDA providing information on when to collect patient experience data during drug development but believes FDA could provide more detailed information on this topic. The guidance notes that sponsors should collect patient experience information for benefit-risk early

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<sup>7</sup> FDA. Rare Disease Cures Accelerator. Accessed 11/16/21. <https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator>

<sup>8</sup> Northwestern University. Northwestern University Clinical Outcome Assessment Team (NUCOAT). Accessed 11/16/21. <https://www.scholars.northwestern.edu/en/projects/northwestern-university-clinical-outcome-assessment-team-nucoat-3>

in the drug development program.<sup>9</sup> NORD suggests FDA take this opportunity to more clearly define the window in which sponsors should collect this information to have the most impact. Doing so can provide sponsors with a clear understanding of the opportune time in order to have a substantial impact. If the timing of including patient data is one of the challenges to more robust incorporation of the patient voice, NORD suggests FDA provide more explicit guidance on when is the right time to collect data on patient experience for benefit-risk.

NORD also believes that the final guidance could be improved with the incorporation of additional examples of how FDA approaches its benefit-risk assessments. In previous guidances, FDA has included hypothetical examples or case studies to illustrate the Agency's thinking. Some examples in this guidance of the types of assessments FDA must make in the context of rare diseases based on what FDA has learned from previous applications would be extremely useful, for patients, as all stakeholders consider the regulatory review of these products. Providing examples of how FDA assessed benefit-risk in situations of unmet need or uncertainty would be helpful to understand how FDA considered those challenges.

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to the issuance of the final guidance. For questions regarding NORD or the above comments, please contact Richard White at [rwhite@rarediseases.org](mailto:rwhite@rarediseases.org).

Sincerely,

*Richard White*

Richard White  
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National Organization for Rare Disorders

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<sup>9</sup> FDA. Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry; Draft Guidance. (2021). Page 15. Accessed 11/10/21. <https://www.fda.gov/media/152544/download>