August 13, 2018

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-0223: Humanitarian Device Exemption (HDE) Program; Draft Guidance for Food and Drug Administration Staff

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the approximately 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA) for the opportunity to comment on the Agency's "Humanitarian Device Exemption (HDE) Program; Draft Guidance for Industry and Food and Drug Administration Staff."

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

NORD is strongly supportive of the Humanitarian Device Exemption Program and its mission of expediting the delivery of innovative devices designed to treat diseases with patient populations of less than 8,000 in the United States. Consequently, we were pleased to see the improvements made to the program included in both the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act (FDARA) of 2017.

Namely, we were supportive of the expansion of the program from devices that impact 4,000 patients to the current 8,000 patients and the requirement for FDA to issue guidance clarifying the use of the "probable benefit" standard when making HDE determinations. We believe both changes will improve the program and increase the number of medical devices developed for those with rare diseases.

We are appreciative of FDA's proposed improvements to determining probable benefit. These improvements will not only hopefully lead to more regulatory certainty for Humanitarian Use Device (HUD) developers but also, by including patient perspectives in the determination of probable benefit, should ensure innovative HUDs presented to FDA for review are truly patient-focused. That being said, we still believe there are several ways in which the draft guidance can be improved in order to truly ensure patient perspectives are considered. Patient perspectives should always be incorporated into drug and device development; however, we believe that the patient perspective becomes all the more important when FDA considers devices that are not accompanied with robust empirical effectiveness data supporting its use.

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As stated in the guidance, the statute requires that approval of an HDE application relies on FDA's ability to determine that "the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available device[s] or alternative forms of treatment."[1]

In order to make this determination, NORD believes that FDA must consider patient preference information (PPI), patient experience data (PED), and patient-reported outcomes (PROs) at every step of the process. The following comments detail our perspective on how to improve the guidance in order to ensure that the patient perspective guides each HDE decision made by FDA. We also highlight how NORD can amplify FDA efforts to include these patient-focused data in their HDE determinations through the use of our natural history data patient registry program and the over 270 patient organizations that compose our membership.

Humanitarian Use Devices (HUD) Are Unique and Must be Treated Accordingly

There are several statements posited by FDA within the draft guidance that we do not agree with. For example, on page 15 of the draft guidance, FDA states, "FDA believes that the benefit-risk framework and factors used to assess PMAs or De Novo requests…is generally appropriate for HDE applications. FDA therefore intends to consider the same factors described in FDA's benefit-risk framework for evaluating PMAs or De Novo requests when assessing probable benefits and risks for HDE applications."[2]

Unlike with PMAs or De Novo requests, HDE applications are dealing with devices designed to treat patient populations under 8,000 uses per year. Just as is the case with the rare disease community at large, patients afflicted by a disease that affects less than 8,000 individuals in the United States will almost inevitably have a different way of calculating benefits and risks than patients with common diseases. Everything from the uncertainty to the severity of the disease to the lack of existing treatments is exacerbated in such scenarios.

FDA recognizes this within the draft, stating, "given the different standards and requirements that apply to approval of an HDE application, the weighting of those factors and the nature of the evidence available regarding those factors is likely to differ in the HDE context."[3]

Furthermore, FDA recognizes that "a relatively small patient population" could be a necessary factor to consider in its deliberation, and we applaud FDA for promising commensurate flexibility within its framework.[4] However, we do not believe flexibility alone will address the problems that will inevitability arise from using an ill-fitted and misappropriated benefit-risk framework borrowed from other device classifications. Instead, given the unique way in which

[1] Pg. 14, line 485-489, sec 520(m)(2)(C) of FD&C
[2] Food and Drug Administration, Department of Health and Human Services, *Humanitarian Device Exemption (HDE) Program; Draft Guidance for Industry and Food and Drug Administration Staff.* Pg. 15
[3] Ibid, Pg. 15
[4] Ibid, Pg. 15

individuals with rare diseases approach their own benefit-risk calculations, we believe FDA should similarly approach such determinations in a unique way.

FDA also ensures that it will allow for flexibility to consider "relevant factors as part of the probable benefit-risk assessment for an HDE application," and yet it does not explain how it will decide what those relevant factors are.[5] In addition, FDA states in the guidance that "[w]hen available, information characterizing patients' tolerance for risk and their perspective on probable benefit may provide useful context during [the benefit-risk] assessment."[6]

NORD strongly believes that patients should have a role in determining what the relevant factors ought to be in the HDE context. Moreover, patient input should be included at every phase of product development as patient perspectives will undoubtedly provide useful context. If not "available," then all attempts should be made to make patient perspectives available. For example, FDA could partner with NORD and its member organizations on collecting such data through natural history registries or informal listening sessions. This would allow FDA to hear from patient representatives about preferences, benefit/risk thresholds, acceptability of tradeoffs, and tolerance for uncertainty, among others.

Patients are the ones who are in desperate need of the devices and are the ones who will use the devices. Thus, patients ought to be included in the process to approve the devices.

Patient Perspective Is Paramount

It is impossible to overstate how important the patient is to this entire process. Accordingly, we thank FDA for highlighting patient perspectives. Our concern, however, to which we have already alluded, is that the guidance depicts patient perspectives as being just one aspect of a larger framework. While we appreciate that it is included in the framework, we believe that this approach is inadequate.

Within Appendices B and C, as FDA explains the various factors its reviewers will use when determining probable benefit, patient perspectives are included under the "additional relevant considerations" section of the assessment tool. We do not support this approach. Patient perspectives cannot be isolated into their own category and completely quarantined from the other considerations included within the tool. They must be considered as a facet of every other consideration listed.

As an example, while considering the severity of adverse events associated with the device, FDA should simultaneously be considering what patients with the relevant disease consider as a severe adverse event. This same approach should be applied to what constitutes a "minimal" risk, how uncertain the risks may be, what a "favorable change" may be, and any additional benefits outside of strictly clinical benefits.

Instead, the questionnaire included in Appendix B, proposed as a tool for determining whether a device could be approved for an HDE, highlights PPI in just two sub-bullets of one question. To

[5] Ibid, pg. 15
[6] Ibid, pg. 15

make the situation worse, the questionnaire merely includes the "[a]vailable patient preference information."[7] FDA must make a greater effort to pursue such data, especially considering generally only a handful of HUDs are approved each year.

Additionally, within question 1(a) of the questionnaire, FDA describes that probable benefit "may be considered in terms of how a patient feels," yet there is nothing within that particular section that calls for patient input.[8] We are perplexed by how FDA could determine how a patient feels without considering any data generated by patients.

By incorporating PPI into determinations of clinical benefit, FDA could come to find that a device previously thought lacking in clinical benefit brings significant non-clinical benefit to a patient's quality of life. We believe that would be an important distinction, and, under such a scenario, we would encourage FDA to consider approving the application.

We understand that obtaining patient input can be difficult. We also understand that obtaining data on devices intended to treat less than 8,000 individuals can be difficult. We believe, however, that the consideration and the effort must be made. This is why we are committed to assisting FDA at every opportunity possible to obtain such perspectives.

One way to obtain all of this and more is through patient registries. NORD's registry platform helps create patient-centered registries that generate a better understanding of rare diseases through the collection of the very data that are so desperately needed in HDE determinations.

NORD also has over 270 patient organizations as members and would be more than happy to connect the relevant patient communities to FDA reviewers seeking patient perspectives. We are already partnering with FDA's Patient Affairs Staff on conducting listening sessions with patients and reviewers and would be delighted to do the same with reviewers considering HDE applications.

Once again, we thank FDA for the opportunity to comment, and we look forward to working with FDA to ensure that patient perspectives are adequately included in the determination of probable benefit within the context of HDE applications. For questions regarding NORD or the above comments, please contact me at pmelmeyer@rarediseases.org or 202-545-3828.

Thank you in advance for your consideration.

Sincerely,

Paul Melmeyer
Director of Federal Policy

[7] Ibid, Pg. 48
[8] Ibid, Pg. 43