



March 8, 2021

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

Re: Docket No. FDA-2020-D-2199: IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations.

Dear Sir or Madam:

Thank you for the opportunity to submit comments on behalf of the National Organization for Rare Disorders, or NORD, regarding the Food and Drug Administration (FDA) Draft Guidance, *IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations*. Founded in 1983, NORD represents over 320 different rare disease patient organizations and the rare disease community at large. It is estimated that 1 in 10 Americans are afflicted with a rare disease, meaning NORD represents over 30 million Americans that are struggling with a rare disease nationally. We are committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

NORD is pleased to see the FDA publish this draft guidance that addresses the development of investigational antisense oligonucleotide (ASO) drug products for severely debilitating or life-threatening genetic diseases. Many of these diseases can affect as few as one person in the United States, and it's difficult to achieve commercial viability for products that help such small patient populations. Consequently, drug developers in this area are not typically as familiar with FDA's regulatory processes as other industry sponsors. The level of detail provided by this guidance is an excellent first step to familiarize these individuals with this process. NORD appreciates FDA recognizing that, as individualized medicine continues to advance, the need for a regulatory framework for these products will be essential to allow for patient access to these therapies.

To accomplish the goal of fostering the development of individualized therapies, FDA will need to find the balance between the development of an optimal level of evidence of safety and efficacy with efficient regulatory review for these therapies. In this guidance, FDA does focus on the need for early FDA interaction and establishing a communication plan in order to facilitate this review goal.¹ While this guidance addresses a limited set of regulatory questions, Acting Center for Drug Evaluation and Research Director, Dr. Patrizia Cavazzoni, in a statement on the

¹ FDA. IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations. Accessed 3/3/21/. <https://www.fda.gov/media/144872/download>

draft guidance, said, “FDA understands that we’ll need to work together with the developers of these drug products to bring them safely to patients, and we are willing to engage as needed to address the challenges.”² NORD appreciates the commitment to ensure that FDA will provide sponsors further information on the requirements for regulatory approval for these treatments. NORD would also encourage patient involvement in these discussions, to the extent appropriate. The types of diseases eligible for this program are life-threatening, fast developing, and their progression is often non-reversible. It is vital that the regulatory scheme allows for the approval of the administration of the therapy with enough speed and collaboration to ensure the promise of the treatment is delivered.

A key facet of the development of these “N of 1” therapies is the relationship that forms between the sponsor and the patient or their caregiver. In her statement, Dr. Cavazzoni notes that “in these situations, the individuals and their families often function more like drug development collaborators than traditional trial participants.”³ The cases reported in the media about the “N of 1” therapies similarly show the tight connection that develops throughout this process.⁴ NORD is encouraged to see this trend and is grateful for FDA considering this relationship in the development of the guidance and addressing some critical elements of the patient-centric nature of these products. For instance, as mentioned above, FDA acknowledges the collaborative role the patient or caregiver plays and lays out the process for how an “outside participant,” often the patient or caregiver, may engage in potentially confidential conversations in formal development meetings between FDA and the sponsor.⁵ FDA also encourages the sponsor to ensure that all ethical considerations are well understood and advocates for consultation with a medical ethicist when developing protocols in order to protect the patient.⁶ The guidance also includes strong language on the need for IRB approval and robust informed consent for individualized therapies.⁷

In an op-ed in the New England Journal of Medicine (NEJM), Dr. Woodcock and Dr. Marks remarked on some initial questions that they are wrestling with regarding individualized therapies, including:

[W]hat type of evidence is needed before exposing a human to a new drug? Even in rapidly progressing, fatal illnesses, precipitating severe complications or death is not acceptable, so what is the minimum assurance of safety that is needed? How persuasive should the

² FDA. FDA Takes Steps to Provide Clarity on Developing New Drug Products in the Age of Individualized Medicine. Accessed 3/2/21. https://www.fda.gov/news-events/press-announcements/fda-takes-steps-provide-clarity-developing-new-drug-products-age-individualized-medicine?utm_medium=email&utm_source=govdelivery

³ Ibid.

⁴ New York Times. Scientists Designed a Drug for Just One Patient. Her Name Is Mila. Accessed 3/3/21. <https://www.nytimes.com/2019/10/09/health/mila-makovec-drug.html>

⁵ FDA. IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations. Accessed 3/3/21/. <https://www.fda.gov/media/144872/download>

⁶ Ibid.

⁷ Ibid.

mechanistic or functional data be? How should the dose and regimen be selected? How much characterization of the product should be undertaken? How should the urgency of the patient's situation or the number of people who could ultimately be treated affect the decision-making process?⁸

These are tremendously important questions that will require experience and discussion with all stakeholders to ensure that they are answered in a way that preserves both patient safety and regulatory needs. NORD hopes for robust public engagement on these issues, including further guidance or public meetings.

In the NEJM op-ed, Dr. Woodcock and Dr. Marks note that determining efficacy is also an important factor that may be much more nuanced in these diseases than in a standard clinical trial. They write, “[a]t the very least, during the time needed to discover and develop an intervention, quantifiable, objective measures of the patient's disease status should be identified and tracked, since, in an N-of-one setting, evaluation of disease trends before and after treatment will usually be the primary method of assessing effectiveness.”⁹ Understanding disease progression to determine efficacy is an area where patient groups and organizations engaged in natural history studies for similar diseases can play a role to help give clinicians a way to measure effectiveness.

Another critical question presented by Dr. Woodcock and Dr. Marks that will require additional regulatory discussion is around scaling up the therapy. They submit that “[c]onsideration also needs to be given to how to proceed if the intervention appears to be helpful and other patients with the same mutation are subsequently identified... what are the differences between treating one, ten, or thousands of patients?”¹⁰ FDA acknowledges that there is a possibility that during the course of developing a treatment for one person that more patients with the same condition could emerge, which would also necessitate treatment, likely with an individualized therapy. Dr. Cavazzoni says that FDA is “optimistic that development of these individualized drug products may spur gene sequencing that leads to the development of additional individualized drug products for the same disease (though perhaps caused by a different mutation).”¹¹ NORD agrees that these issues necessitate robust discussion and are also ones that should be encouraged. The research and technology that goes into developing an “N of 1” therapy should be studied and applied as broadly as possible. However, NORD believes that with scaling up comes the need for appropriate regulatory scrutiny and, with experience and engagement with stakeholders, FDA will be able to tackle these issues.

⁸ New England Journal of Medicine. Drug Regulation in the Era of Individualized Therapies. Accessed 3/2/21. https://www.nejm.org/doi/full/10.1056/NEJMe1911295?utm_medium=email&utm_source=govdelivery

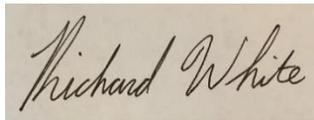
⁹ Ibid.

¹⁰ Ibid.

¹¹ FDA. FDA Takes Steps to Provide Clarity on Developing New Drug Products in the Age of Individualized Medicine. Accessed 3/2/21. https://www.fda.gov/news-events/press-announcements/fda-takes-steps-provide-clarity-developing-new-drug-products-age-individualized-medicine?utm_medium=email&utm_source=govdelivery

Finally, NORD reiterates its appreciation of FDA's consideration of these unique therapies that, by their nature, treat a very limited number of patients and are not likely to ever be commercially viable but have tremendous potential to revolutionize individualized medicine. NORD thanks the FDA for the opportunity to submit comments on this draft guidance and stands ready to be a constructive partner to the FDA in this area. For questions regarding NORD or the above comments, please contact me at rwhite@rarediseases.org or 202-588-5700.

Sincerely,

A rectangular box containing a handwritten signature in cursive script that reads "Richard White". The signature is written in dark ink on a light-colored, textured background.

Richard White
Policy Analyst, Policy and Regulatory Affairs
National Organization for Rare Disorders

