



March 8, 2021

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

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

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this guidance document. ASGCT is a nonprofit professional membership organization comprised of more than 4,500 scientists, physicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies. The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

ASGCT members research a variety of molecular therapies to treat disease, including antisense oligonucleotides (ASOs). Because the Society aims to aid development of, and access to, molecular therapies for very rare diseases, ASGCT commends FDA for its attention to the issue of “n of 1” therapies, as evidenced through leadership in the Bespoke Gene Therapy Consortium organized by the Foundation for the National Institutes of Health and provision of this guidance to sponsor-investigators of early phase trials for individualized ASO drug products.¹ Since individuals who sponsor trials for very small populations are less likely to have extensive experience with regulatory processes, we appreciate the FDA’s provision of this information on the administrative and procedural aspects of interacting with FDA on development programs for these products.

The ability to develop an individualized ASO drug product that is tailored to a patient with an extremely rare disease-causing genetic variant is a promising advancement in technology. ASGCT appreciates the Agency’s recognition of the significance of the development of treatments for very rare genetic diseases which, as the guidance document notes, may be rapidly progressing, severely debilitating or life-threatening conditions. Because many very rare diseases do not currently have FDA-approved treatment options, facilitating the development of these new treatments is of utmost importance to address unmet medical need.

¹ Marks, P., Witten, C. Toward a new framework for the development of individualized therapies. *Gene Ther* (2020). <https://doi.org/10.1038/s41434-020-0143-y>

More specifically, the Society particularly appreciates the provision of detailed information on the following topics:

- The format and content of a pre-investigational new drug application (pre-IND) meeting package, including Chemistry, Manufacturing, and Controls (CMC) information on the drug substance and drug product.
- The point in development that sponsors should request a pre-IND meeting with the appropriate review division, to hopefully facilitate timely scheduling of these beneficial early communications with the Agency.

The following specific recommended changes are provided for FDA consideration:

Section/ Lines	Comment/Issue	Proposed Change
I. INTRODUCTION		
31- 36	<p>“This guidance also addresses the initial development of these individualized ASO drug products; it does not address regulatory considerations for the development of these drug products for marketing and continued, long-term treatment of patients with the disease for which the drug product is being developed. This guidance also does not address the nonclinical data, the clinical data, or the product quality requirements that must be met to initiate administration of these individualized ASO drug products in humans.”</p> <p>Comment: While the focus of this guidance is on administrative and procedural aspects and initial development of these products, reference to guidance on regulatory considerations and data and quality recommendations may be helpful to investigators who are inexperienced with FDA’s regulatory processes.</p>	<p>“This guidance also addresses the initial development of these individualized ASO drug products; it does not address regulatory considerations for the development of these drug products for marketing and continued, long-term treatment of patients with the disease for which the drug product is being developed. This guidance also does not address the nonclinical data, the clinical data, or the product quality requirements that must be met to initiate administration of these individualized ASO drug products in humans. Sponsor-investigators may find relevant regulatory, nonclinical and clinical data, and product quality recommendations in the FDA guidance for industry <i>Rare Diseases: Common Issues in Drug Development</i> (January 2019).</p>
38 – 42	<p>“Although the guidance is intended to help sponsors seeking to develop an individualized ASO drug product, the principles and practices outlined in the guidance may also be applicable to developing other types of individualized drug products (i.e., non-ASO). Sponsors who consider applying the principles outlined in this guidance for non-ASO individualized drug products should first consult with the appropriate review division.”</p>	<p>“Although the guidance is intended to help sponsors seeking to develop an individualized ASO drug product, the principles and practices outlined in the guidance may also be applicable to developing other types of individualized drug products (i.e., non-ASO). Sponsors who consider applying the principles outlined in this guidance for non-ASO individualized drug products should</p>

	<p>Comment: ASGCT appreciates that FDA suggests that these principles and practices outlined in the guidance may also be applicable to developing other types of individualized drug products, given the rapidly evolving science and pipeline of potential products.</p> <p>We would respectfully suggest that FDA provide suggestions about the situations in which the administrative and procedural aspects outlined in this guidance document would not be applicable to other therapeutic modalities, either within this guidance or separately in order to reduce burden on investigators and review divisions.</p> <p>Referencing the guidance, <i>Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators</i> (May 2015), may also be helpful.</p>	<p>first consult with the appropriate review division. The FDA guidance document, <i>Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators</i> (May 2015), may also provide beneficial guidance.</p>
IV. AGENCY INTERACTIONS		
A. General		
152 – 153	<p>“All IND submissions should include overall summaries with enough detail to allow FDA staff to understand the regulatory and developmental context of the submission.”</p> <p>Comment: Reference to the “regulatory and developmental context” of the submission may be ambiguous. We therefore suggest adding further detail to encourage articulation of sufficiently detailed content.</p>	<p>“All IND submissions should include overall summaries with enough detail to allow FDA staff to understand the regulatory strategy and clinical developmental context plan for of the submission.”</p>
B. Pre-IND Meeting Package		
1. <i>Content</i>		
182 - 184	<p>“Generally, the content of a pre-IND meeting package should also include information to support proof of concept, initial dosing in humans, and safety monitoring plans for initial human dosing, as well as the proposed clinical protocol.”</p> <p>Comment: We suggest recommending that the key toxicology findings and no-adverse-effect levels be listed as examples of information to provide in the pre-IND package to support the recommended starting dose for the first-in-human study.</p>	<p>“Generally, the content of a pre-IND meeting package should also include information to support proof of concept, initial dosing in humans (e.g., key toxicology findings and no-adverse-effect levels), and safety monitoring plans for initial human dosing, as well as the proposed clinical protocol.”</p>
C. Application		

204 – 207	<p>“During the pre-IND meeting, or at some other point before submitting the IND, the sponsor should discuss expectations for the content of the IND submission with the relevant FDA review division, since some of the content and format requirements at CFR 312.23 may not be relevant for this type of application.”</p> <p>Comment: This information may be especially helpful for sponsor-investigators. We suggest that FDA clarify whether the Sponsor needs to request a formal waiver for content that will not be provided [21 CFR 312.10]. If a waiver is necessary, additional advice on how to prepare a waiver request would be helpful.</p>	
-----------	--	--

ASGCT plans to share the useful information within this guidance document with our membership. Please let us know if you have questions on these comments by contacting Betsy Foss-Campbell, ASGCT Director of Policy and Advocacy, at bfoss@asgct.org. We appreciate your shared concern for the development of therapies for very rare diseases with great unmet need.

Sincerely,



Adora Ndu, PharmD, JD
Chairperson, ASGCT Regulatory Affairs Committee