# IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations

## Guidance for Sponsor-Investigators

***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (CDER) Eithu Lwin at 301-796-0728.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

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*10001 New Hampshire Ave., Hillandale Bldg., 4th Floor*
*Silver Spring, MD 20993-0002*
*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov*
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# IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations Guidance for Sponsor-Investigators[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

## I. INTRODUCTION

This guidance is intended for sponsor-investigators[2] (hereafter referred to as sponsors) developing individualized investigational antisense oligonucleotide (ASO) drug products for a severely debilitating or life-threatening (SDLT) genetic disease.[3] Most often, individuals with such diseases will have no alternative treatment options, and their diseases will be rapidly progressing, resulting in early death and/or devastating or irreversible morbidity within a short time frame without treatment. In these situations, drug development targeted to a larger number of patients with the same disease is not anticipated because of the specificity of the mechanism of action of the ASO combined with the rarity of the treatment-amenable patient population. The gene variant or variants that are targeted by the ASO drug product should be unique to the trial participant(s) and generally only reported in a small number of patients (typically 1 to 2) in the disease population. If more than a few patients may be candidates for targeted treatment with the ASO drug product, then the ASO is no longer considered individualized, and the sponsor should discuss a drug development plan of the investigational ASO drug product for a larger patient population with the relevant review division.

The focus of this guidance is to describe important clinical considerations for investigational new drug application (IND) submissions to support initial and continued administration, dosing, and clinical monitoring of an individual with a SDLT disease attributable to a unique genetic

[1] This guidance has been prepared by the Office of New Drugs and the Office of Translational Sciences, Office of Clinical Pharmacology, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] A *sponsor-investigator* is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual (see 21 CFR 312.3(b)).

[3] *Severely debilitating* means diseases or conditions that cause major irreversible morbidity. *Life-threatening* means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and those with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival (see 21 CFR 312.81).

variant(s) that may be amenable to an ASO drug product. The individualized ASO drug product should belong to a well-characterized chemical class[4] (i.e., a chemical class for which there is substantial nonclinical information and clinical experience that is either publicly available or to which the sponsor has right of reference).

This guidance does not address clinical and regulatory considerations for the development of an individualized ASO drug product for commercial marketing. This guidance also does not address the nonclinical data[5] or the drug product quality requirements[6] to initiate administration of an individualized ASO drug product in humans, or the administrative and procedural recommendations for an IND submission.[7]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND

Advances in technology may now allow targeting of a drug product to the molecular changes that underlie an individual's genetic disease (e.g., gene deletions, rearrangements). This field is rapidly evolving, and the clinical considerations for evaluating the safety and efficacy of these drug products may differ from the considerations for larger development programs. This guidance provides recommendations for managing the administration of the individualized ASO drug product and conducting clinical assessments of the safety and treatment response during administration of the ASO drug product. The recommendations in this guidance are informed by experience with certain classes of well-characterized ASO drug products and by the ability to anticipate and manage some of the potential adverse events based on this prior experience with

[4] Examples of well-characterized, antisense chemical classes, based on prior FDA experience, include single-stranded phosphorothioate or mixed phosphorothioate/phosphodiester, 2-methoxyethyl substituted oligonucleotides (by systemic or intrathecal route), and phosphorodiamidate morpholino oligonucleotides (by systemic route).

[5] See the draft guidance for sponsor-investigators *Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases* (April 2021). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] See the draft guidance for sponsor-investigators *IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls Recommendations* (December 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[7] See the draft guidance for sponsor-investigators *IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations* (January 2021). When final, this guidance will represent the FDA's current thinking on this topic.

the ASO drug classes. The following sections outline important clinical considerations and, when applicable, information to include in IND submissions.

## III. CLINICAL CONSIDERATIONS

### A. Ethical and Human Subject[8] Protection Considerations

Under FDA regulations, a protocol under which an individual ASO drug product is administered to a human subject must be reviewed and approved by an institutional review board (IRB) before it is allowed to proceed (21 CFR part 56). If children[9] are to be included in the protocol, the requirements in 21 CFR part 50, subpart D (*Additional Safeguards for Children in Clinical Investigations)* also must be met. Similarly, in accordance with 21 CFR 50.20, the sponsor must obtain legally effective informed consent from the trial participant, or the participant's legally authorized representative, before administration of the investigational ASO drug product. The informed consent must include all the required basic elements under 21 CFR 50.25(a), including, but not limited to, a description of reasonably foreseeable risks or discomforts to the trial participant and any potential benefits which may reasonably be expected from the investigational ASO drug product. When appropriate, significant new findings developed during the course of the research that might have implications for the trial participant's willingness to continue in the research should be provided to the participant (and/or the participant's legally authorized representative). In addition, the sponsor should discuss with the applicable IRB how and when significant new findings will be provided to the trial participant.[10]

### B. Diagnostic and Genetic Considerations

Sponsors should consider the following recommendations for characterizing the targeted gene variant(s) and the trial participant's clinical diagnosis and include all relevant information in the IND submission:

- The trial participant's clinical and genetic diagnosis should be confirmed through relevant laboratory testing (e.g., gene sequencing, enzymatic analysis, biochemical testing, imaging evaluations, as applicable). Sponsors should appropriately validate laboratory assays for their intended use. Sponsors should provide all results in the IND submission.

- Sponsors should provide evidence that establishes the role of the gene variant(s) targeted by the ASO drug product in the pathogenesis of the trial participant's disease. If the

[8] For the purposes of this guidance, FDA uses the terms *subject* and *participant* interchangeably.

[9] 21 CFR 50.3(o) defines *children* as "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted."

[10] For additional information about FDA's recommendations on informed consent, see the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet* (July 2014). When final, this guidance will represent the FDA's current thinking on this topic.

evidence is insufficient, additional investigation(s) may be needed before initiating use of the ASO drug product.

- Sponsors should provide evidence that the identified gene variant or variants are unique to the trial participant, including (a) prevalence estimates of the targeted gene variant(s) in the disease and (b) the projected incidence of the targeted variant(s) in new cases of the disease based on molecular genetic considerations (e.g., type of mutation (missense, frameshift, other), location in the protein).

### C. Dosing Considerations

Sponsors should consider the following recommendations for dosing of investigational ASO drug products and include all relevant information in the IND submission:

- The starting dose should be based on available nonclinical data and be scientifically supported by available information from other ASO drug products in the chemical class and/or prior clinical experience. In general, the starting dose should be expected to have a pharmacologic effect, based on available nonclinical *in vitro* and/or *in vivo* data.[11]

- The sponsor should calculate the starting dose based on interspecies dose comparisons.[5]

- Given the limited nonclinical data that may be available when dosing is initiated, the sponsor should consider a dose escalation approach where dosing is initiated and escalated to higher doses based on pharmacodynamic (PD) effects and/or trial participant response to the investigational ASO drug product (tolerability or perceived benefit) and available nonclinical data. The protocol should contain a clear dosing plan and justification for selecting the starting dose, dosing interval, and plan for dose escalation or dose reduction for toxicity. If a loading dose or doses are proposed, the protocol should contain a rationale for using a loading dose(s) and maintenance dose interval(s) based on considerations such as the ASO drug product's half-life, likely distribution (e.g., target areas in the central nervous system (CNS), kidney), and anticipated toxicities with different doses.

- Sponsors should increase doses cautiously during dose escalation (e.g., by no more than a two-fold increment), allowing sufficient time to observe a response to a dose change before making further modifications. If a steep dose- or exposure-response is observed for severe toxicities in nonclinical toxicology studies or when no predictive marker of severe toxicity is available in humans, the sponsor should escalate the dose at smaller increments (e.g., fractional increments rather than dose doubling). In general, sponsors should not make concurrent changes to the dose and dosing interval without justification.

[11] For additional considerations pertaining to selection of the starting dose, see the draft guidance for sponsor-investigators *Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases*. When final, this guidance will represent the FDA's current thinking on this topic.

- The protocol should specify a plan for de-escalation/discontinuation if a dose-limiting toxicity develops, and the sponsor should inform the trial participant or the participant's legally authorized representative of the reason(s) for the dose changes.

### D. Drug Product Administration Procedures

Sponsors should consider the following recommendations for administration procedures of investigational ASO drug products:

- Sponsors should administer the starting dose and each escalation in dose in an inpatient (hospital) setting. For at least 24 hours after administration, the sponsor should monitor the participant closely for acute, serious adverse events precipitated by the administration procedure (e.g., intrathecal) or by the ASO drug product itself (e.g., hemodynamic instability, severe hypersensitivity reactions/anaphylaxis, CNS adverse effects). After the sponsor adequately characterizes the safety and tolerability at a given dose and any adverse events are identified and appropriately monitored, it generally would be acceptable to administer subsequent doses using the same dose in an outpatient (clinic) setting, if needed, with appropriate safety monitoring and interventions available for possible serious adverse events (e.g., anaphylaxis).

- For intrathecal ASO drug products, experienced medical personnel should perform the intrathecal administration and administer sedation and/or analgesics if needed for the procedure. Appropriate medical monitoring and procedural and therapeutic interventions should be available in case of complications from the procedure and/or the sedation.

### E. Safety Assessment

Sponsors should consider the following recommendations for safety assessments of investigational ASO drug products and detail all safety procedures and assessments in the IND submission:

- Sponsors should perform routine safety assessments (e.g., adverse events, vital signs, electrocardiogram, laboratory assessments) while the investigational ASO drug product is being administered and for a period after stopping administration based on the anticipated half-life of the ASO drug product. Safety monitoring should be informed by nonclinical toxicology findings, potential off-target gene knockdown effects predicted by bioinformatic tools, and previously identified safety risks associated with the use of other ASO drug products of the same chemical class. The protocol should include a detailed schedule of safety assessments.

- Sponsors should conduct the safety assessments more frequently during the initial dosing period (e.g., in the first 2 to 3 months). At a minimum, sponsors should conduct and review safety assessments before each dose, or more frequently if the interval between doses is long. Based on the initial results, the frequency of safety assessments can then be decreased. The protocol should clearly outline those assessments. Changes to the

frequency of assessments should be guided by participants' safety and tolerability of the ASO drug product and emerging data from nonclinical toxicology studies.

- Given the potential serious risk of thrombocytopenia observed with phosphorothioate or mixed-phosphorothioate backbone ASOs, if an ASO drug product of this class is administered, the sponsor should perform and review platelet count at least every 2 weeks or before each dose administration, whichever is more frequent. The sponsor should monitor closely for abnormal findings and associated adverse events (e.g., bleeding, bruising) to inform decisions about continued ASO drug product administration.

- For intrathecally administered ASO drug products, the sponsor should collect cerebrospinal fluid before each dose administration to evaluate for potential signs of inflammation and infection. The sponsor should, when feasible and appropriate, use any remaining sample(s) for pharmacokinetic (PK) assessments or relevant biochemical assessments depending on the SDLT disease.

- If the ASO drug product administration is discontinued for safety or other reasons, the sponsor should continue safety monitoring of the trial participant until resolution of the adverse event(s) and evaluate the trial participant for potential late-onset toxicities.

### F. Assessment of Clinical Response

Sponsors should consider the following recommendations for assessing participants' clinical response to investigational ASO drug products and outline in the IND submission a plan for evaluation of clinical benefit in relation to observed toxicities (as applicable):

- The assessment of whether the ASO drug product is providing clinical benefit to the participant is an important element of the overall clinical assessment throughout the administration period. To best inform decisions regarding continuation of administration, sponsors should carefully track clinical changes over time with a specific plan for adjustment of the dosing regimen to achieve a desirable clinical response. The protocol should clearly outline the specific method(s) and timing of clinical assessments.

- Sponsors can use clinical assessments to follow important disease symptoms during administration of the ASO drug product. Examples include clinical outcome assessment scales, performance-based assessments, or trial participant- or caregiver-reported changes in symptoms. Clinical assessments of response to the investigational ASO drug product will depend on the trial participant's signs and symptoms before administration of the ASO drug product and on the underlying disease, including the stage and severity of the disease at time of initiation of the investigational ASO drug product. The sponsor should administer these assessments at specified intervals determined by the disease pathophysiology as well as the PK and PD characteristics of the ASO drug product, and these assessments should be detailed in the IND submission.

- PD biomarkers (laboratory, imaging, or others) that are scientifically justified and relevant to the target disease may help to assess response to the ASO drug product. The

protocol should clearly outline those assessments, and sponsors should carefully consider potential assay/method validation issues that may affect the results and data interpretation.

- The protocol should have a prespecified plan for continually assessing the trial participants' clinical response to the investigational ASO drug product to ensure that the benefit-risk assessment remains favorable to justify continued administration. Sponsors should consider discontinuing administration if there is no or inadequate clinical response or if the observed toxicities from the product outweigh the observed clinical benefits.