IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations

Guidance for Sponsor-Investigators

DRAFT GUIDANCE

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

January 2021
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IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 genetic disease.[3] Most often, individuals with such diseases will not have FDA-approved treatment options and their diseases will be rapidly progressing, resulting in early death and/or devastating irreversible morbidity within a short time frame. In these situations, drug development targeted at a larger number of patients with the ASO is not anticipated because of the specificity of the mechanism of action of the ASO drug product combined with the rarity of the treatment-amenable patient population.

The focus of this guidance is on administrative and procedural aspects of interacting with FDA on development programs for individualized ASO drug products, such as the approach to obtaining feedback from FDA and the expectations and process for making regulatory submissions to FDA. The guidance provides high-level recommendations about informed consent and the requirement for institutional review board (IRB) review of protocols for trials of individualized ASO drug products. 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.

[1] This guidance has been prepared by the Office of New Drug Policy 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).

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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Typically, a drug research and development program begins with identifying a moiety intended to treat a disease or condition and subsequently evaluating that drug in animal[4] and then human studies. Clinical development programs vary considerably in size and complexity, depending on disease prevalence, the heterogeneity of the condition, disease course, and many other factors. Once a drug product is approved for marketing, patients other than those who participated in clinical trials will have access to, and are expected to benefit from, treatment with that drug product for its approved use or uses.

Advances in scientific knowledge and drug development technology, however, provide an opportunity for new approaches in drug development. Contemporary approaches to genetic testing and molecular diagnosis can elucidate, in certain circumstances, the precise etiology of a specific patient's genetic disease. For a patient with an extremely rare disease-causing genetic variant, development of an individualized ASO drug product that is tailored to the patient's specific genetic variant may be possible.

III. AGENCY INTERACTIONS

A. Importance of Early FDA Interaction

Those participating in these development programs will have a severely debilitating or life-threatening genetic disease for which there is no adequate available therapy and will generally require prompt medical intervention because of rapid disease progression. Therefore, investigators will wish to initiate administration of the investigational drug product rapidly.

[4] We support the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

FDA recommends that sponsors request a pre-investigational new drug application (pre-IND) meeting with the appropriate review division as soon as a participant and at least one potential individualized ASO drug product (for which there are convincing proof-of-concept data) are identified. Early FDA interaction will help sponsors to prepare an adequate IND submission for review by the Agency and facilitate prompt administration of the investigational drug product.[5]

B. Established Communication Plan

As discussed in more detail in the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017**)**,[6] FDA recommends establishing a communication strategy with FDA.

A communication strategy can establish the preferred method (e.g., email, telephone) and frequency of communications. The strategy may also set expectations related to the timing of responses to inquiries and requests for information for both the sponsor and FDA. FDA staff will strive to respond to sponsor questions and requests promptly and comprehensively.

FDA staff will not communicate about a sponsor's development program or IND or the progress of FDA's review of the program or IND with individuals other than the sponsor (e.g., trial participant, family member, or other advocate) unless the individual has been designated by the sponsor as an authorized representative of the sponsor.

C. Confidentiality Concerns for Outside Participants

If a trial participant, family member, or other advocate attends a meeting between a sponsor and FDA to discuss the sponsor's application, whatever the sponsor or FDA shares at a meeting about the application may be considered a public disclosure of the sponsor's confidential information (confidential commercial information and/or trade secret information (21 CFR 20.61)) unless, prior to the meeting, the sponsor and the outside participant(s) have entered into a confidentiality agreement with each other. In the absence of such a confidentiality agreement, under FDA's regulations on uniform access (21 CFR 20.21), any confidential information about an application that is disclosed to an outside participant in this way generally is available to all members of the public, including under the Freedom of Information Act.

If a sponsor informs FDA that an outside participant will be attending a scheduled meeting between the sponsor and FDA, the Agency will ask the sponsor 1) to certify in writing, prior to the meeting, that the sponsor understands that if an outside participant (e.g., trial participant, family member, or other advocate) attends a meeting with the Agency to discuss the sponsor's application, whatever information is discussed by the sponsor or FDA at the meeting about the

[5] Information on pre-IND meetings, including how to request such a meeting, can be found in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). 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] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

sponsor's application may be considered a public disclosure of the sponsor's confidential commercial and/or trade secret information unless, prior to the meeting, the sponsor and the outside participant(s) have entered into a confidentiality agreement with each other, and 2) if such a confidentiality agreement is in place, to certify in writing as such. If the sponsor certifies that such a confidentiality agreement is in place between it and an outside participant, FDA generally would not consider the presence of that outside participant at a scheduled meeting between the sponsor and FDA to trigger uniform access with respect to information discussed at that meeting. FDA encourages sponsors to resolve these issues promptly to avoid unnecessarily delaying the meeting.

D. Secure Email and Faxes

Outside of regulatory submissions to a sponsor's application, communication between a sponsor and FDA will often be conducted via email. Communication via unsecured email should not include confidential commercial information, trade secret information, or trial participant information (21 CFR 20.21; 21 CFR 20.63). Accordingly, FDA recommends that sponsors establish a secure email with FDA to allow for communications that may include such information. Sponsors can contact the Office of Information Management and Technology to request secure email.[7]

Faxes may be used for communication between sponsors and FDA when secure email has not been established. Before transmitting faxes, sponsors and FDA regulatory project managers should contact their counterparts to arrange for confirmation of receipt of the fax.

Communications via fax or secure email do not substitute for formal regulatory submissions, which are required, for example, for submitting original IND applications and amendments to an IND (21 CFR 312.23, 312.30, 312.31).

IV. SUBMISSION EXPECTATIONS

A. General

Complete and well-organized submissions, in a format conducive to scientific review, can help increase the efficiency of FDA's review and prevent delays in FDA responses to requests for information. All IND submissions should include overall summaries with enough detail to allow FDA staff to understand the regulatory and developmental context of the submission.

Although it is not required that research INDs[8] for developing individualized ASO drug products, and other related documents, be submitted in electronic format, FDA recommends

[7] Direct inquiries to secureemail@fda.hhs.gov.

[8] A *research IND* is an IND for which the sponsor does not intend to commercialize the product. See the information in the section on Field 6B: IND TYPE in the *Instructions for Filling Out Form FDA 1571*.

electronic submission to facilitate and expedite review of the submissions. Electronic submissions for research INDs are not required to be in electronic Common Technical Document (eCTD) format; however, they may be voluntarily submitted in that format.[9]

Under FDA's IND regulations at 21 CFR 312.23(b), a sponsor ordinarily is not required to resubmit information previously submitted to FDA but instead may incorporate the information by reference. If the information is in an existing IND application, the sponsor should identify the IND number, type of submission in which the information is located (e.g., nonclinical information amendment), the date of submission, page number(s), and, if applicable, volume number. If a sponsor seeks to reference information submitted to the Agency by a person other than the sponsor, the sponsor should include a written statement authorizing such reference that is signed by the person who submitted the information. However, in either instance, depending on when the information was submitted and its format (e.g., paper versus electronic), voluntarily resubmitting the information may facilitate and expedite FDA's review.

Formal submissions in paper or non-eCTD electronic format should be mailed to the CDER Central Document Room located at 5901-B Ammendale Road in Beltsville, Maryland. Sponsors submitting in paper format are expected to send their applications in triplicate, with one original and two copies of the submission.

B. Pre-IND Meeting Package

1. Content

The package should include information to justify the proposal to develop an individualized ASO drug product. 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. Furthermore, the package should include the nonclinical, bioinformatic (information related to the design of the oligonucleotide), and product quality data that the sponsor intends to submit with its IND.

2. Format

The content of a meeting package, including for pre-IND meetings, should be organized according to the proposed meeting agenda.[10] The package should be a sequentially paginated document with a table of contents, appropriate indices, appendices, and cross references.

The questions for discussion with FDA should be grouped by FDA review discipline and prefaced with a summary that provides context and explains the need for the question. The

[9] General information on the electronic submission of regulatory information to FDA can be found at https://www.fda.gov/drugs/forms-submission-requirements/electronic-regulatory-submission-and-review, and information on formal submissions made electronically in eCTD format can be found at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

[10] For more information, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent the FDA's current thinking on this topic.

summaries should describe the results of relevant studies. Any conclusions that result from these studies, and how they influenced the proposed treatment plan, should be stated clearly.

C. Application

When the sponsor has gathered the recommended information, the sponsor should submit a research IND to FDA. To aid FDA in understanding the proposed development context and related benefit-risk considerations, the sponsor should include in the initial IND submission the justification for developing an individualized ASO drug product. 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 21 CFR 312.23 may not be relevant for this type of application.

1. Nonclinical Report Format

Because the proposed study will be first in humans, it is unlikely that human data will be available at the time of the initial IND submission. Thus, only product manufacturing and quality information, bioinformatic (information related to the design of the oligonucleotide), and nonclinical data will support the safety of initiating administration to a participant. It is critical that the nonclinical data be adequately presented and documented.

Sponsors should provide a complete report for each in vitro and in vivo study intended to characterize the pharmacological activity and the safety of the investigational drug. Each study report should include, but not be limited to, the following:

- A statement of the purpose of the study
- A detailed description of the control and test article (e.g., purity, stability), study design (e.g., control, dose levels, number of animals per sex per group), animal species or model, methodology used, and parameters assessed
- Complete data sets for all parameters evaluated (e.g., individual animal line listings and summary data tables)
- Analysis and interpretation of the results
- Conclusions

General content and format recommendations for the submission of nonclinical data and information can be found in the guidance for industry *Guideline for the Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application* (February 1987).

2. Chemistry, Manufacturing, and Controls Report Format

The guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived*

Products (November 1995) provides information on general formatting expectations, including for the chemistry, manufacturing, and control information section of the IND submission. FDA recommends that as much information as possible be provided on the drug substance and drug product, as follows:

Drug Substance

- Summary report containing a brief description of the drug substance
- Name and address of the manufacturer
- General method of preparation, including a flow diagram of the manufacture process
- Specifications
- Stability information

Drug Product

- A list of all components, and their quality, used in the manufacture of the drug product
- Quantitative composition
- Name and address of the manufacturer
- Brief, general description of manufacturing method and packaging procedures, including a flowchart
- Copy of the certificate of analysis for the clinical lot
- Specifications
- Stability information
- A copy of investigational labels and labeling per 21 CFR 312.23(a)(7)(iv)(d)
- Claim for categorical exclusion per 21 CFR 312.23(a)(7)(iv)(e)

3. Safety and Annual Reports

a. Safety reports

The sponsor of an IND must notify FDA in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days, after the sponsor determines the information qualifies for reporting (21 CFR 312.32(c)(1)).

The sponsor should submit each report in a narrative format or on Form FDA 3500A or in electronic format.[11]

b. Annual reports

The sponsor of an IND shall, within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation (21 CFR 312.33).

[11] For more information, see the draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic.

D. Ethical and Human Subject Protection Considerations

Because of the nontraditional nature of drug development in this arena, complex ethical issues may arise. As such, sponsors should consider conferring with a medical ethicist when developing their protocol.

1. IRB Review

Under FDA regulations, a protocol under which an individualized ASO drug product is administered to a human subject must be reviewed by an IRB (21 CFR Part 56), which must fully evaluate the protocol and ensure that risks to the subject are reasonable in relation to the anticipated benefits (21 CFR 56.111(a)(2)). The IRB should be provided with the results of all relevant nonclinical safety studies in animals that have been conducted. Sponsors should consider contacting their IRB as early as possible. If the ASO drug product will be administered to a child, the IRB must ensure that the protocol complies with the requirements under 21 CFR part 50, subpart D.

2. Informed Consent

Under FDA regulations, informed consent must be obtained under circumstances that provide prospective participants, or their legally authorized representatives, sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence (21 CFR 50.20). The sponsor should include a copy of the informed consent document in the original IND submission.

The informed consent document and the consent discussion should appropriately emphasize in a clear manner that the ASO drug product is experimental, the reality that the benefit is uncertain and the potential risks are unknown, and that additional costs to the participant may be associated with the administration of the drug product. When appropriate, the consent document and consent discussion should include information that the administration of the ASO drug product will be the first use in humans of the investigational drug and relevant information from nonclinical safety studies in animals that have been conducted that could potentially inform the safety of the participant.