IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls 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DRAFT GUIDANCE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)

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CMC

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to provide recommendations regarding the chemistry, manufacturing, and controls (CMC) information that should be provided in an investigational new drug application (IND) submitted by a sponsor-investigator[2] (hereafter referred to as sponsor) developing an individualized antisense oligonucleotide (ASO) drug product for a severely debilitating or life-threatening (SDLT) disease[3] caused by a unique genetic variant where only a small number of individuals are prospectively identified (typically one or two). These individualized ASO drug products should be from a well-characterized chemical class for which there is substantial clinical and nonclinical experience that is either publicly available or to which the sponsor has a right to reference.[4]

This guidance is limited to those individualized ASO drug products, as described above, that are unconjugated, manufactured using conventional methods, with formulations that are a simple aqueous or a lyophilized powder to be reconstituted before administration.

This guidance provides recommendations on information to be submitted in the CMC sections of an IND for an individualized ASO drug product, including the following:

[1] This guidance has been prepared by the Office of Pharmaceutical Quality and the Office of New Drugs 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).

[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).

- Nomenclature, structure, and general ASO drug substance properties
- Manufacture
- Characterization
- Control of excipients
- Control of drug substance and drug product
- Reference standards or materials
- Container closure systems
- Stability

The CMC recommendations are to support first-in-human exposure for the individualized ASO drug products covered under this guidance and do not address regulatory considerations for continued, long-term administration of an individualized ASO drug product, for use of individualized ASO drug products for diseases that are not severely debilitating or life-threatening, or for administration of ASO drug products to a population beyond the expected number of patients (typically one or two).

This guidance also does not address CMC requirements for commercial development of individualized ASO drug products.

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. GENERAL CONSIDERATIONS ON CMC INFORMATION FOR AN INITIAL IND

A. Regulatory Considerations

Under 21 CFR part 312 subpart E, FDA has determined that for drug products (e.g., individualized ASO drug products) intended to treat SDLT diseases, it is appropriate to exercise flexibility while preserving appropriate guarantees for safety and effectiveness.[5]

Generally, FDA regulations require sponsors, including sponsor-investigators, seeking to evaluate a drug or biological product in humans in a clinical investigation to submit an IND to FDA.[6] The required content and format for INDs[7] are further discussed in the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1*

[5] See 21 CFR 312.80.

[6] 21 CFR part 312.

[7] See 21 CFR 312.23.

Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products (November 1995).[8] That guidance includes clarification about the data that should be provided in the CMC section of an initial IND submission under 21 CFR 312.23(a)(7). FDA expects sponsors to submit in the CMC section of an initial IND sufficient information to ensure the proper identification, quality, purity, and strength of the investigational drug product. This information includes (1) data and information regarding drug substance; (2) data and information regarding drug product; (3) the investigational drug immediate packaging label that includes the statement "Caution: New Drug — Limited by Federal (or United States) law to investigational use";[9] and (4) a statement requesting a categorical exclusion from an environmental assessment under 21 CFR 25.30 or 25.31 or an environmental assessment under 21 CFR 25.40.[10]

This guidance provides recommendations about how to satisfy these general requirements for the CMC content of an IND for an investigational ASO drug product within the scope of this guidance and also provides specific recommendations regarding the quality (e.g., chemical structure, manufacturing process, and critical quality attributes) of an individualized ASO drug product that will be administered to an individual trial participant under the IND. To expedite the initiation of clinical investigation of an individualized ASO drug product covered under this guidance, we recommend that the sponsor first submit a pre-IND meeting request to discuss the CMC plans with FDA.

For drug products, including drug products administered under an IND, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and FDA's implementing regulations require that the methods used in or the facilities or controls used for their manufacturing, processing, packing, or holding comply with current good manufacturing practice (CGMP) (21 U.S.C. 351(a)(2)(B); 21 CFR parts 210 (general) and 211 (finished pharmaceuticals)). However, in general, the production of an investigational drug product for use in a phase 1 clinical trial is exempt under 21 CFR 210.2(c) from compliance with the regulations in part 211. As described in the preamble to the final rule amending 21 CFR 210.2(c),[11] the rationale for exempting phase 1 IND products from compliance with 21 CFR part 211 is based on many factors, including that such studies are conducted to establish the basic safety, rather than efficacy, of the drug product; are designed to determine the metabolism and pharmacologic actions of the drug product in humans; and are limited in the total number of trial participants.

In addition, the manufacturing and control conditions for the production of investigational drug products intended for use in relatively small phase 1 clinical trials are different from the

[8] 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.

[9] See 21 CFR 312.6(a).

[10] See 21 CFR 312.23(a)(7)(iv)(e) and the draft guidance for industry *Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators* (May 2015). 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.

[11] The final rule, "Current Good Manufacturing Practice and Investigational New Drugs Intended for Use in Clinical Trials," published July 15, 2008 (73 FR 40453-40462).

conditions for the production of drug products for use in larger phase 2 and phase 3 clinical trials or for commercial marketing. Therefore, many of the specific requirements in 21 CFR part 211 do not apply to the conditions under which many drug products for use in phase 1 clinical trials are produced. FDA has described applicable CGMP recommendations for phase 1 IND products in the guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008).

Individualized ASO drug products are not expected to follow the traditional investigational phases of drug development (i.e., clinical trial phases 1 through 3) as described in 21 CFR 312.21. As such, the applicability of 21 CFR part 211 for manufacturing individualized ASO drug product batches for clinical investigation under an IND (e.g., first clinical batch versus subsequent clinical batches) requires further clarification. Because the rationale used to exempt phase 1 drug products from complying with 21 CFR part 211 is generally applicable to the initiation of clinical investigation of an individualized ASO drug product, in general it would be acceptable for the first clinical drug product batch to be manufactured consistent with the CGMP recommendations in the guidance for industry *CGMP for Phase 1 Investigational Drugs*. However, if additional batches of the individualized ASO drug product are needed for continued administration to a subject, then to ensure consistent quality, safety, and efficacy of the individualized ASO drug product, FDA generally expects that sponsors would manufacture subsequent batches of the individualized ASO drug products in compliance with 21 CFR part 211 and follow the recommendations in the guidance for industry *Preparation of Investigational New Drug Products (Human and Animal*) (November 1992).

B. Additional Considerations

To expedite the initiation of clinical investigations of these individualized ASO drug products, we recommend that, when possible, the same batch of drug product used for the nonclinical studies be used for initial clinical investigations.[12] If different batches of the drug product are intended for nonclinical studies and clinical investigations, the sponsor should provide information to support a conclusion that the batch used in the nonclinical studies is representative of the batch intended for use in the clinical investigations, from a quality perspective. This information should include a description of any differences in the manufacturing processes between the nonclinical and clinical batches, as well as analytical data establishing that the nonclinical batch is representative of the batch to be administered to the subject(s).

In some cases, CMC information can be incorporated by reference from another application or a drug master file (DMF).[13] This should be discussed with FDA at the pre-IND meeting. The pre-IND meeting package, therefore, should include a description of the CMC information that will be provided in the sponsor's IND for the individualized ASO drug product, as well as a list of cross-referenced applications (e.g., other INDs, including INDs for other individualized ASO products) and DMFs, including a list of the information that will be incorporated by reference from those applications and/or DMFs in the IND. If a cross-referenced application or DMF is

[12] The acceptability of this approach will depend on FDA's assessment of the CMC information and the results of the toxicology studies provided in the IND.

[13] See 21 CFR 314.420 and the draft guidance for industry *Drug Master Files* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic.

submitted by a firm other than the sponsor, the IND for the individualized ASO drug product must contain a letter of authorization from the DMF holder or sponsor of the cross-referenced application authorizing FDA to review the relevant information referenced in the cross-referenced application or DMF.

The CMC data that sponsors of individualized ASO drug products within the scope of this guidance should submit in their IND applications are described in the sections below.

III. CMC INFORMATION FOR DRUG SUBSTANCE[14]

A. A Description of the Drug Substance, Including Its Physical and Chemical Characteristics

The sponsor must provide a description of the drug substance, which should include the structure, nomenclature, structural formula, molecular formula, molecular weight, and molecular weight of the salt form (if applicable). In addition, the sponsor should provide a statement regarding the nature of base moieties and backbone, carbohydrate moieties, internucleoside linkages, and counter ions (if applicable) that constitute the structure of the individualized ASO drug substance. The sponsor should provide information about the physical properties such as hygroscopicity, solubility in aqueous media, and the melting temperature (T_m) (if relevant).

B. The Name and Address of the Drug Substance Manufacturer

The sponsor should submit the full street address of the manufacturer (including any contract manufacturer or test laboratory) of the individualized ASO drug substance used to manufacture batches of drug product that will be used in the clinical trial.

C. The General Method of Preparation of the Drug Substance

In addition to the information described in 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*,[15] the submission should include a flow diagram and a full narrative description of the manufacturing process, including purification steps. The flow diagram should contain all representative coupling/chain elongation and deprotection steps, as well as any purification, impurity reduction, or removal steps (e.g., chromatography, lyophilization or solvent removal, desalting tangential flow filtration).

The narrative description should contain the chemical structures and configurations, including stereochemical information for the starting materials, intermediates (either in situ or isolated), and, when feasible, significant side products. Furthermore, a manufacturing step should be described in detail if it is unique or critical to the synthesis or manufacturing process. In general, FDA does not expect the sponsor to identify a column or equipment model number or

[14] See 21 CFR 312.23(a)(7)(iv)(*a*).

[15] See section III., F., 2., c. of the guidance.

manufacturer, but the IND should include a clear description of process controls that ensure quality of the drug substance (e.g., process steps ensuring impurity clearance).[16]

The sponsor should provide a list of materials used in the manufacture of the ASO drug substance (e.g., starting materials, reagents, solvents, auxiliary materials).

For sterile drug substances, the sponsor should submit a description of the sterilization process (e.g., moist or dry heat terminal sterilization, aseptic filtration), but submission of information related to sterilization process validation is not necessary.

D. Characterization

The sponsor should confirm the chemical structure of the drug substance using physical and chemical techniques, including nucleotide sequencing, T_m, and mass spectral analysis. The sponsor should provide the sequence determination of an ASO drug substance; however, if the sequence determination is not provided in the initial IND, the sponsor should include an adequate justification in the IND and submit the sequence in an amendment as soon as possible. The sponsor should provide information on impurities in the ASO drug substance. The sponsor should summarize the actual and potential impurities most likely to arise during manufacture, purification, and storage of the drug substance. FDA recommends that sponsors list ASO-related impurities and, when appropriate, group them based on their structural class or relative retention times.

The sponsor should provide a discussion related to the occurrence of non-ASO related impurities (e.g., elemental impurities, residual solvents, protecting groups) and how control of these impurities is ensured. The submission should include specifications for observed non-ASO related impurities or a scientific justification for why such testing would not be required (e.g., description of the step(s) included in the manufacturing process to remove certain non-ASO related impurities).

If the clinical batch is different from the batch used for nonclinical studies, the sponsor should provide data (such as high-performance liquid chromatography (HPLC) chromatograms of the drug substance) to compare the quality of these batches (e.g., homogeneity and purity of the nonclinical and clinical ASO drug substance batches).

E. Control of Drug Substance

1. Specification

This section should include a table of all elements of the specification to which the batch of drug substance should conform, including the test, associated acceptance criteria, and references to the analytical procedures that will be used to perform each test. In this section, the sponsor should provide a brief description of the analytical methods. In addition to considering the recommendations provided in the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized,*

[16] See 21 CFR 312.23(a)(7)(iv)(*a*).

Therapeutic, Biotechnology-Derived Products,[17] sponsors should include the following in the specifications:

- The identity of the ASO drug substance. FDA recommends using a combination of two or more methods to establish the identity of the ASO drug substance. Common methods include sequencing and molecular weight determination. Other methods, such as the determination of T_m, chromatographic retention time using HPLC, may also be acceptable;

- A test for the salt form (if applicable);

- A strength assay, which should include reporting of the full-length drug product content, with exclusion of the P=O impurity (if present);

- The determined quantities of each specified impurity or grouped impurities;

- The quantities of individual unidentified impurities;[18]

- The total impurities content;

- Residual solvents;[19]

- Moisture content;

- Microbiological testing (e.g., microbial limits (United States Pharmacopeia (USP) General Chapter <61> and General Chapter <62> or equivalent) or sterility (USP General Chapter <71> or equivalent))[20]; and

- Bacterial endotoxins (USP General Chapter <85> or equivalent).

The certificate of analysis (CoA) for the proposed clinical batch as well as the nonclinical batches, if any, should be included.

[17] See section III., F., 2., d. of the guidance.

[18] See the International Council for Harmonisation (ICH) guidance for industry *Q3A Impurities in New Drug Substances* (June 2008).

[19] For details about residual solvents, consult the ICH guidance for industry *Q3C Impurities: Residual Solvents* (December 1997).

[20] Sterility testing is recommended if the drug substance is sterile and additional sterilization steps are not included during drug product manufacturing. In addition, if the drug substance is sterile, a description of the sterilization steps (e.g., membrane filtration, terminal sterilization) implemented to manufacture the sterile drug substance should be provided. Otherwise, drug substance specifications should include bioburden testing.

F. Stability

The sponsor should provide information relating to the stability of the synthetic ASO drug substance. This should include available stability data and the protocol that will be used to monitor ongoing drug substance stability. Preliminary data should be provided in tabular format. The sponsor should also provide a description of the container closure system.

IV. CMC DATA FOR DRUG PRODUCT [21]

A. Components

The sponsor must provide a list of all components used in the manufacture of the investigational drug product,[22] including those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process. The sponsor should cite quality of the inactive ingredients by reference to a compendial monograph (e.g., USP and the National Formulary[23]) (if applicable), or the IND should contain the supplier's CoA.

B. Quantitative Composition of the Drug Product

The sponsor should submit a brief summary, preferably a table, of the composition of the individualized ASO drug product. For processing aid or aids that are removed during manufacture (e.g., Water for Injection used to formulate a lyophilized product), the submission should include the amount(s) of aid or aids used and amount of aid or aids removed.

C. Name and Address of the Drug Product Manufacturer

The sponsor should submit the full street address of the manufacturer (including any contract manufacturer, packing facility, or test laboratories) of the individualized ASO drug product batches intended to be used in the clinical trial.

D. Brief General Description of the Manufacturing and Packaging Procedures for the Product

The sponsor should submit a flow diagram and a brief written description of the manufacturing process, including any bioburden reduction and sterilization steps used (e.g., membrane filtration, terminal sterilization). The description should include the air classification of the rooms used in the manufacture of the drug product (e.g., Class 100, Grade A, ISO 5).

[21] See 21 CFR 312.23(a)(7)(iv)(*b*).

[22] Ibid.

[23] Reference to a foreign compendium that provides for equivalent quality (e.g., European Pharmacopeia, Japanese Pharmacopeia) is acceptable.

E. Control of Drug Product

The IND should include specifications with corresponding test methods.[24] The sponsor should test the drug product for identity, strength, impurities/degradation products (including identity, quality, and a justification for acceptable level of any new impurity present only in the drug product), foreign and particulate matter, sterility, bacterial endotoxins, and any specific tests applicable to the dosage form. As detailed in Table 1 below, the acceptance criterion for bacterial endotoxins should be established based on the maximum proposed dose and route of administration (i.e., intrathecal, intravitreal, or subcutaneous).

Table 1: USP Endotoxin Limits

U.S. Pharmacopeia (USP) Reference	Type of Administration	Endotoxin Limits
USP General Chapter <85>	Subcutaneous	5 EU/Kg/Hour
	Intrathecal	0.2 EU/Kg/Hour
USP General Chapter <771>	Intraocular (e.g., intravitreal)	2.0 EU/Dose/Eye

The sponsor should describe noncompendial analytical methods for the drug product, if different from the drug substance analytical methods, at the same level of detail as for the drug substance.

F. Container Closure System

The sponsor should provide a description of the container closure system for the individualized ASO drug product, including the identity of materials of construction of each primary packaging component (e.g., USP Type 1 glass vial, bromobutyl rubber stopper, flip-off seal). The sponsor should provide specifications for each component or the manufacturer's CoA. The sponsor should describe methods for depyrogenation and sterilization for any components that are not supplied as sterile.

G. Stability

The sponsor should monitor the stability of the individualized ASO drug product packaged in the proposed container closure system under the proposed storage conditions. The sponsor should provide the stability protocol for the clinical batch, including a brief description of the stability study and the test methods, with a commitment to monitor stability of the drug product throughout its use. If initial stability data for the clinical batch are available, the sponsor should provide the data in tabular format. If stability data for the clinical batch are not available, the sponsor should provide any available supportive stability data (e.g., data from the nonclinical batch, if different from the clinical batch; data from a laboratory batch).

If the individualized ASO drug product is modified before use (e.g., reconstituted or diluted for infusion), the drug product, ready for administration (e.g., in the infusion bag), should not be

[24] Where applicable, testing should be performed using the official compendial methods referenced in USP General Chapter <1> Injections and Implanted Drug Products (Parenterals) — Product Quality Tests.

stored at room temperature for longer than 4 hours or under refrigerated conditions for longer than 24 hours to minimize the risk for excessive growth of adventitious microbial contamination.

However, if extended storage conditions are necessary, the sponsor should conduct microbiological studies supporting the postconstitution/postdilution storage time (as stated in the proposed product labeling) as recommended in the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009)[25] and *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).[26] The submission should include a description of the test methods and results of studies that are designed using a minimum countable inoculum (less than or equal to 100 colony forming units (CFU)/ milliliter (mL)) to simulate potential microbial contamination that may occur during drug product constitution or dilution. Additionally, the sponsor should justify the selected test conditions and/or diluents as necessary. Challenge organisms can include strains described in USP General Chapter <51> in addition to typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. The sponsor should provide a positive control that demonstrates the viability of the organisms over the duration of the test period.

V. IMMEDIATE PACKAGING LABELING

The sponsor must submit in the IND a copy of the proposed immediate packaging label.[27] The immediate packaging label must include the statement "Caution: New Drug — Limited by Federal (or United States) law to investigational use."[28]

VI. ENVIRONMENTAL EXCLUSION

The IND sponsors should either include a claim for categorical exclusion of environmental analysis requirements under 21 CFR 25.30 or 25.31 or provide an environmental assessment under 21 CFR 25.40.[29] For an individualized ASO drug product under an IND, we recommend that the sponsor provide a claim for categorical exclusion under 21 CFR 25.31(e).

[25] See section II., E. of the guidance.

[26] See 2.2.7 (section II., B., 7.) of the guidance.

[27] 21 CFR 312.23(a)(7)(iv)(*d*).

[28] 21 CFR 312.6(a).

[29] See 21 CFR 312.23(a)(7)(iv)(*e*).