
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DRAFT GUIDANCE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
Procedural**

IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations Guidance for Sponsor-Investigators

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Contains Nonbinding Recommendations

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1 **IND Submissions for Individualized Antisense Oligonucleotide Drug**
2 **Products: Administrative and Procedural Recommendations**
3 **Guidance for Sponsor-Investigators¹**
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5

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7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

13
14
15 **I. INTRODUCTION**
16

17 This guidance is intended for sponsor-investigators² (hereafter referred to as sponsors)
18 developing individualized investigational antisense oligonucleotide (ASO) drug products for a
19 severely debilitating or life-threatening genetic disease.³ Most often, individuals with such
20 diseases will not have FDA-approved treatment options and their diseases will be rapidly
21 progressing, resulting in early death and/or devastating irreversible morbidity within a short time
22 frame. In these situations, drug development targeted at a larger number of patients with the
23 ASO is not anticipated because of the specificity of the mechanism of action of the ASO drug
24 product combined with the rarity of the treatment-amenable patient population.
25

26 The focus of this guidance is on administrative and procedural aspects of interacting with FDA
27 on development programs for individualized ASO drug products, such as the approach to
28 obtaining feedback from FDA and the expectations and process for making regulatory
29 submissions to FDA. The guidance provides high-level recommendations about informed
30 consent and the requirement for institutional review board (IRB) review of protocols for trials of
31 individualized ASO drug products. This guidance also addresses the initial development of these
32 individualized ASO drug products; it does not address regulatory considerations for the
33 development of these drug products for marketing and continued, long-term treatment of patients
34 with the disease for which the drug product is being developed. This guidance also does not
35 address the nonclinical data, the clinical data, or the product quality requirements that must be
36 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).

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37
38 Although the guidance is intended to help sponsors seeking to develop an individualized ASO
39 drug product, the principles and practices outlined in the guidance may also be applicable to
40 developing other types of individualized drug products (i.e., non-ASO). Sponsors who consider
41 applying the principles outlined in this guidance for non-ASO individualized drug products
42 should first consult with the appropriate review division.

43
44 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
45 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
46 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
47 the word *should* in Agency guidances means that something is suggested or recommended, but
48 not required.

49
50

51 II. BACKGROUND

52
53 Typically, a drug research and development program begins with identifying a moiety intended
54 to treat a disease or condition and subsequently evaluating that drug in animal⁴ and then human
55 studies. Clinical development programs vary considerably in size and complexity, depending on
56 disease prevalence, the heterogeneity of the condition, disease course, and many other factors.
57 Once a drug product is approved for marketing, patients other than those who participated in
58 clinical trials will have access to, and are expected to benefit from, treatment with that drug
59 product for its approved use or uses.

60
61 Advances in scientific knowledge and drug development technology, however, provide an
62 opportunity for new approaches in drug development. Contemporary approaches to genetic
63 testing and molecular diagnosis can elucidate, in certain circumstances, the precise etiology of a
64 specific patient’s genetic disease. For a patient with an extremely rare disease-causing genetic
65 variant, development of an individualized ASO drug product that is tailored to the patient’s
66 specific genetic variant may be possible.

67
68

69 III. AGENCY INTERACTIONS

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72 A. Importance of Early FDA Interaction

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75 Those participating in these development programs will have a severely debilitating or life-
76 threatening genetic disease for which there is no adequate available therapy and will generally
77 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.

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78 FDA recommends that sponsors request a pre-investigational new drug application (pre-IND)
79 meeting with the appropriate review division as soon as a participant and at least one potential
80 individualized ASO drug product (for which there are convincing proof-of-concept data) are
81 identified. Early FDA interaction will help sponsors to prepare an adequate IND submission for
82 review by the Agency and facilitate prompt administration of the investigational drug product.⁵
83

B. Established Communication Plan

84
85
86 As discussed in more detail in the guidance for industry and review staff *Best Practices for*
87 *Communication Between IND Sponsors and FDA During Drug Development* (December 2017),⁶
88 FDA recommends establishing a communication strategy with FDA.
89

90 A communication strategy can establish the preferred method (e.g., email, telephone) and
91 frequency of communications. The strategy may also set expectations related to the timing of
92 responses to inquiries and requests for information for both the sponsor and FDA. FDA staff
93 will strive to respond to sponsor questions and requests promptly and comprehensively.
94

95 FDA staff will not communicate about a sponsor's development program or IND or the progress
96 of FDA's review of the program or IND with individuals other than the sponsor (e.g., trial
97 participant, family member, or other advocate) unless the individual has been designated by the
98 sponsor as an authorized representative of the sponsor.
99

C. Confidentiality Concerns for Outside Participants

100
101
102 If a trial participant, family member, or other advocate attends a meeting between a sponsor and
103 FDA to discuss the sponsor's application, whatever the sponsor or FDA shares at a meeting
104 about the application may be considered a public disclosure of the sponsor's confidential
105 information (confidential commercial information and/or trade secret information (21 CFR
106 20.61)) unless, prior to the meeting, the sponsor and the outside participant(s) have entered into a
107 confidentiality agreement with each other. In the absence of such a confidentiality agreement,
108 under FDA's regulations on uniform access (21 CFR 20.21), any confidential information about
109 an application that is disclosed to an outside participant in this way generally is available to all
110 members of the public, including under the Freedom of Information Act.
111

112 If a sponsor informs FDA that an outside participant will be attending a scheduled meeting
113 between the sponsor and FDA, the Agency will ask the sponsor 1) to certify in writing, prior to
114 the meeting, that the sponsor understands that if an outside participant (e.g., trial participant,
115 family member, or other advocate) attends a meeting with the Agency to discuss the sponsor's
116 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>.

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

D. Secure Email and Faxes

126
127
128
129 Outside of regulatory submissions to a sponsor’s application, communication between a sponsor
130 and FDA will often be conducted via email. Communication via unsecured email should not
131 include confidential commercial information, trade secret information, or trial participant
132 information (21 CFR 20.21; 21 CFR 20.63). Accordingly, FDA recommends that sponsors
133 establish a secure email with FDA to allow for communications that may include such
134 information. Sponsors can contact the Office of Information Management and Technology to
135 request secure email.⁷

136
137 Faxes may be used for communication between sponsors and FDA when secure email has not
138 been established. Before transmitting faxes, sponsors and FDA regulatory project managers
139 should contact their counterparts to arrange for confirmation of receipt of the fax.

140
141 Communications via fax or secure email do not substitute for formal regulatory submissions,
142 which are required, for example, for submitting original IND applications and amendments to an
143 IND (21 CFR 312.23, 312.30, 312.31).

IV. SUBMISSION EXPECTATIONS

A. General

144
145
146
147
148
149
150 Complete and well-organized submissions, in a format conducive to scientific review, can help
151 increase the efficiency of FDA’s review and prevent delays in FDA responses to requests for
152 information. All IND submissions should include overall summaries with enough detail to allow
153 FDA staff to understand the regulatory and developmental context of the submission.

154
155 Although it is not required that research INDs⁸ for developing individualized ASO drug
156 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*.

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

160
161 Under FDA's IND regulations at 21 CFR 312.23(b), a sponsor ordinarily is not required to
162 resubmit information previously submitted to FDA but instead may incorporate the information
163 by reference. If the information is in an existing IND application, the sponsor should identify the
164 IND number, type of submission in which the information is located (e.g., nonclinical
165 information amendment), the date of submission, page number(s), and, if applicable, volume
166 number. If a sponsor seeks to reference information submitted to the Agency by a person other
167 than the sponsor, the sponsor should include a written statement authorizing such reference that
168 is signed by the person who submitted the information. However, in either instance, depending
169 on when the information was submitted and its format (e.g., paper versus electronic), voluntarily
170 resubmitting the information may facilitate and expedite FDA's review.

171
172 Formal submissions in paper or non-eCTD electronic format should be mailed to the CDER
173 Central Document Room located at 5901-B Ammendale Road in Beltsville, Maryland. Sponsors
174 submitting in paper format are expected to send their applications in triplicate, with one original
175 and two copies of the submission.

B. Pre-IND Meeting Package

1. Content

176
177
178
179
180
181 The package should include information to justify the proposal to develop an individualized
182 ASO drug product. Generally, the content of a pre-IND meeting package should also include
183 information to support proof of concept, initial dosing in humans, and safety monitoring plans
184 for initial human dosing, as well as the proposed clinical protocol. Furthermore, the package
185 should include the nonclinical, bioinformatic (information related to the design of the
186 oligonucleotide), and product quality data that the sponsor intends to submit with its IND.

2. Format

187
188
189
190 The content of a meeting package, including for pre-IND meetings, should be organized
191 according to the proposed meeting agenda.¹⁰ The package should be a sequentially paginated
192 document with a table of contents, appropriate indices, appendices, and cross references.

193
194 The questions for discussion with FDA should be grouped by FDA review discipline and
195 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.

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

198

C. Application

199

200
201 When the sponsor has gathered the recommended information, the sponsor should submit a
202 research IND to FDA. To aid FDA in understanding the proposed development context and
203 related benefit-risk considerations, the sponsor should include in the initial IND submission the
204 justification for developing an individualized ASO drug product. During the pre-IND meeting,
205 or at some other point before submitting the IND, the sponsor should discuss expectations for the
206 content of the IND submission with the relevant FDA review division, since some of the content
207 and format requirements at 21 CFR 312.23 may not be relevant for this type of application.

208

1. Nonclinical Report Format

209

210
211 Because the proposed study will be first in humans, it is unlikely that human data will be
212 available at the time of the initial IND submission. Thus, only product manufacturing and quality
213 information, bioinformatic (information related to the design of the oligonucleotide), and
214 nonclinical data will support the safety of initiating administration to a participant. It is critical
215 that the nonclinical data be adequately presented and documented.

216

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

220

221 • A statement of the purpose of the study

222

223 • A detailed description of the control and test article (e.g., purity, stability), study design
224 (e.g., control, dose levels, number of animals per sex per group), animal species or
225 model, methodology used, and parameters assessed

226

227 • Complete data sets for all parameters evaluated (e.g., individual animal line listings and
228 summary data tables)

229

230 • Analysis and interpretation of the results

231

232 • Conclusions

233

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

237

2. Chemistry, Manufacturing, and Controls Report Format

238

239
240 The guidance for industry *Content and Format of Investigational New Drug Applications (INDs)*
241 *for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived*

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

246

247 Drug Substance

248

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

254

255 Drug Product

256

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

267

268 3. *Safety and Annual Reports*

269

270 a. Safety reports

271

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

275

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

278

279 b. Annual reports

280

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

283

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.

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284 **D. Ethical and Human Subject Protection Considerations**

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

289

290 *1. IRB Review*

291

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

300

301 *2. Informed Consent*

302

303 Under FDA regulations, informed consent must be obtained under circumstances that provide
304 prospective participants, or their legally authorized representatives, sufficient opportunity to
305 consider whether to participate and that minimize the possibility of coercion or undue influence
306 (21 CFR 50.20). The sponsor should include a copy of the informed consent document in the
307 original IND submission.

308

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