
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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Carla R. Lankford at 301-796-5203.

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

**December 2021
CMC**

IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls Recommendations Guidance for Sponsor-Investigators

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
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
<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>*

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

**December 2021
CMC**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	GENERAL CONSIDERATIONS ON CMC INFORMATION FOR AN INITIAL IND	2
A.	Regulatory Considerations.....	2
B.	Additional Considerations.....	4
III.	CMC INFORMATION FOR DRUG SUBSTANCE	5
A.	A Description of the Drug Substance, Including Its Physical and Chemical Characteristics.	5
B.	The Name and Address of the Drug Substance Manufacturer.....	5
C.	The General Method of Preparation of the Drug Substance	5
D.	Characterization	6
E.	Control of Drug Substance.....	6
1.	<i>Specification.....</i>	<i>6</i>
F.	Stability	8
IV.	CMC DATA FOR DRUG PRODUCT	8
A.	Components.....	8
B.	Quantitative Composition of the Drug Product	8
C.	Name and Address of the Drug Product Manufacturer.....	8
D.	Brief General Description of the Manufacturing and Packaging Procedures for the Product.....	8
E.	Control of Drug Product	9
F.	Container Closure System.....	9
G.	Stability	9
V.	IMMEDIATE PACKAGING LABELING	10
VI.	ENVIRONMENTAL EXCLUSION	10

1 **IND Submissions for Individualized Antisense Oligonucleotide Drug**
2 **Products for Severely Debilitating or Life-Threatening Diseases:**
3 **Chemistry, Manufacturing, and Controls Recommendations**
4 **Guidance for Sponsor-Investigators¹**
5
6

7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16 **I. INTRODUCTION**
17

18 The purpose of this guidance is to provide recommendations regarding the chemistry,
19 manufacturing, and controls (CMC) information that should be provided in an investigational
20 new drug application (IND) submitted by a sponsor-investigator² (hereafter referred to as
21 sponsor) developing an individualized antisense oligonucleotide (ASO) drug product for a
22 severely debilitating or life-threatening (SDLT) disease³ caused by a unique genetic variant
23 where only a small number of individuals are prospectively identified (typically one or two).
24 These individualized ASO drug products should be from a well-characterized chemical class for
25 which there is substantial clinical and nonclinical experience that is either publicly available or to
26 which the sponsor has a right to reference.⁴
27

28 This guidance is limited to those individualized ASO drug products, as described above, that are
29 unconjugated, manufactured using conventional methods, with formulations that are a simple
30 aqueous or a lyophilized powder to be reconstituted before administration.
31

32 This guidance provides recommendations on information to be submitted in the CMC sections of
33 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).

34
35
36
37
38
39
40
41
42

- 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

43
44
45
46
47
48
49

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).

50
51
52

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

53
54
55
56
57
58
59

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.

60
61
62

II. GENERAL CONSIDERATIONS ON CMC INFORMATION FOR AN INITIAL IND

63
64
65

A. Regulatory Considerations

66
67
68
69

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

70
71
72
73
74

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 INDs⁷ are further discussed in the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase I*

⁵ See 21 CFR 312.80.

⁶ 21 CFR part 312.

⁷ See 21 CFR 312.23.

Contains Nonbinding Recommendations
Draft — Not for Implementation

75 *Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*
76 (November 1995).⁸ That guidance includes clarification about the data that should be provided
77 in the CMC section of an initial IND submission under 21 CFR 312.23(a)(7). FDA expects
78 sponsors to submit in the CMC section of an initial IND sufficient information to ensure the
79 proper identification, quality, purity, and strength of the investigational drug product. This
80 information includes (1) data and information regarding drug substance; (2) data and information
81 regarding drug product; (3) the investigational drug immediate packaging label that includes the
82 statement “Caution: New Drug — Limited by Federal (or United States) law to investigational
83 use”;⁹ and (4) a statement requesting a categorical exclusion from an environmental assessment
84 under 21 CFR 25.30 or 25.31 or an environmental assessment under 21 CFR 25.40.¹⁰
85

86 This guidance provides recommendations about how to satisfy these general requirements for the
87 CMC content of an IND for an investigational ASO drug product within the scope of this
88 guidance and also provides specific recommendations regarding the quality (e.g., chemical
89 structure, manufacturing process, and critical quality attributes) of an individualized ASO drug
90 product that will be administered to an individual trial participant under the IND. To expedite
91 the initiation of clinical investigation of an individualized ASO drug product covered under this
92 guidance, we recommend that the sponsor first submit a pre-IND meeting request to discuss the
93 CMC plans with FDA.
94

95 For drug products, including drug products administered under an IND, section 501(a)(2)(B) of
96 the Federal Food, Drug, and Cosmetic Act and FDA’s implementing regulations require that the
97 methods used in or the facilities or controls used for their manufacturing, processing, packing, or
98 holding comply with current good manufacturing practice (CGMP) (21 U.S.C. 351(a)(2)(B); 21
99 CFR parts 210 (general) and 211 (finished pharmaceuticals)). However, in general, the
100 production of an investigational drug product for use in a phase 1 clinical trial is exempt under
101 21 CFR 210.2(c) from compliance with the regulations in part 211. As described in the preamble
102 to the final rule amending 21 CFR 210.2(c),¹¹ the rationale for exempting phase 1 IND products
103 from compliance with 21 CFR part 211 is based on many factors, including that such studies are
104 conducted to establish the basic safety, rather than efficacy, of the drug product; are designed to
105 determine the metabolism and pharmacologic actions of the drug product in humans; and are
106 limited in the total number of trial participants.
107

108 In addition, the manufacturing and control conditions for the production of investigational drug
109 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).

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

115
116 Individualized ASO drug products are not expected to follow the traditional investigational
117 phases of drug development (i.e., clinical trial phases 1 through 3) as described in 21 CFR
118 312.21. As such, the applicability of 21 CFR part 211 for manufacturing individualized ASO
119 drug product batches for clinical investigation under an IND (e.g., first clinical batch versus
120 subsequent clinical batches) requires further clarification. Because the rationale used to exempt
121 phase 1 drug products from complying with 21 CFR part 211 is generally applicable to the
122 initiation of clinical investigation of an individualized ASO drug product, in general it would be
123 acceptable for the first clinical drug product batch to be manufactured consistent with the CGMP
124 recommendations in the guidance for industry *CGMP for Phase 1 Investigational Drugs*.
125 However, if additional batches of the individualized ASO drug product are needed for continued
126 administration to a subject, then to ensure consistent quality, safety, and efficacy of the
127 individualized ASO drug product, FDA generally expects that sponsors would manufacture
128 subsequent batches of the individualized ASO drug products in compliance with 21 CFR part
129 211 and follow the recommendations in the guidance for industry *Preparation of Investigational*
130 *New Drug Products (Human and Animal)* (November 1992).

131 **B. Additional Considerations**

132
133
134 To expedite the initiation of clinical investigations of these individualized ASO drug products,
135 we recommend that, when possible, the same batch of drug product used for the nonclinical
136 studies be used for initial clinical investigations.¹² If different batches of the drug product are
137 intended for nonclinical studies and clinical investigations, the sponsor should provide
138 information to support a conclusion that the batch used in the nonclinical studies is representative
139 of the batch intended for use in the clinical investigations, from a quality perspective. This
140 information should include a description of any differences in the manufacturing processes
141 between the nonclinical and clinical batches, as well as analytical data establishing that the
142 nonclinical batch is representative of the batch to be administered to the subject(s).

143
144 In some cases, CMC information can be incorporated by reference from another application or a
145 drug master file (DMF).¹³ This should be discussed with FDA at the pre-IND meeting. The pre-
146 IND meeting package, therefore, should include a description of the CMC information that will
147 be provided in the sponsor's IND for the individualized ASO drug product, as well as a list of
148 cross-referenced applications (e.g., other INDs, including INDs for other individualized ASO
149 products) and DMFs, including a list of the information that will be incorporated by reference
150 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.

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

155
156 The CMC data that sponsors of individualized ASO drug products within the scope of this
157 guidance should submit in their IND applications are described in the sections below.

158
159

160 **III. CMC INFORMATION FOR DRUG SUBSTANCE¹⁴**

161

162 **A. A Description of the Drug Substance, Including Its Physical and Chemical** 163 **Characteristics**

164

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

172

173 **B. The Name and Address of the Drug Substance Manufacturer**

174

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

178

179 **C. The General Method of Preparation of the Drug Substance**

180

181 In addition to the information described in the guidance for industry *Content and Format of*
182 *Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-*
183 *Characterized, Therapeutic, Biotechnology-derived Products*,¹⁵ the submission should include a
184 flow diagram and a full narrative description of the manufacturing process, including purification
185 steps. The flow diagram should contain all representative coupling/chain elongation and
186 deprotection steps, as well as any purification, impurity reduction, or removal steps (e.g.,
187 chromatography, lyophilization or solvent removal, desalting tangential flow filtration).

188

189 The narrative description should contain the chemical structures and configurations, including
190 stereochemical information for the starting materials, intermediates (either in situ or isolated),
191 and, when feasible, significant side products. Furthermore, a manufacturing step should be
192 described in detail if it is unique or critical to the synthesis or manufacturing process. In general,
193 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.

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

196
197 The sponsor should provide a list of materials used in the manufacture of the ASO drug
198 substance (e.g., starting materials, reagents, solvents, auxiliary materials).

199
200 For sterile drug substances, the sponsor should submit a description of the sterilization process
201 (e.g., moist or dry heat terminal sterilization, aseptic filtration), but submission of information
202 related to sterilization process validation is not necessary.

203
204 **D. Characterization**

205
206 The sponsor should confirm the chemical structure of the drug substance using physical and
207 chemical techniques, including nucleotide sequencing, T_m, and mass spectral analysis. The
208 sponsor should provide the sequence determination of an ASO drug substance; however, if the
209 sequence determination is not provided in the initial IND, the sponsor should include an
210 adequate justification in the IND and submit the sequence in an amendment as soon as possible.
211 The sponsor should provide information on impurities in the ASO drug substance. The sponsor
212 should summarize the actual and potential impurities most likely to arise during manufacture,
213 purification, and storage of the drug substance. FDA recommends that sponsors list ASO-related
214 impurities and, when appropriate, group them based on their structural class or relative retention
215 times.

216
217 The sponsor should provide a discussion related to the occurrence of non-ASO related impurities
218 (e.g., elemental impurities, residual solvents, protecting groups) and how control of these
219 impurities is ensured. The submission should include specifications for observed non-ASO
220 related impurities or a scientific justification for why such testing would not be required (e.g.,
221 description of the step(s) included in the manufacturing process to remove certain non-ASO
222 related impurities).

223
224 If the clinical batch is different from the batch used for nonclinical studies, the sponsor should
225 provide data (such as high-performance liquid chromatography (HPLC) chromatograms of the
226 drug substance) to compare the quality of these batches (e.g., homogeneity and purity of the
227 nonclinical and clinical ASO drug substance batches).

228
229 **E. Control of Drug Substance**

230
231 *I. Specification*

232
233 This section should include a table of all elements of the specification to which the batch of drug
234 substance should conform, including the test, associated acceptance criteria, and references to the
235 analytical procedures that will be used to perform each test. In this section, the sponsor should
236 provide a brief description of the analytical methods. In addition to considering the
237 recommendations provided in the guidance for industry *Content and Format of Investigational*
238 *New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized,*

¹⁶ See 21 CFR 312.23(a)(7)(iv)(a).

Contains Nonbinding Recommendations
Draft — Not for Implementation

239 *Therapeutic, Biotechnology-Derived Products*,¹⁷ sponsors should include the following in the
240 specifications:

- 241
- 242 • The identity of the ASO drug substance. FDA recommends using a combination of two
243 or more methods to establish the identity of the ASO drug substance. Common methods
244 include sequencing and molecular weight determination. Other methods, such as the
245 determination of T_m, chromatographic retention time using HPLC, may also be
246 acceptable;
 - 247
 - 248 • A test for the salt form (if applicable);
249
 - 250 • A strength assay, which should include reporting of the full-length drug product content,
251 with exclusion of the P=O impurity (if present);
252
 - 253 • The determined quantities of each specified impurity or grouped impurities;
254
 - 255 • The quantities of individual unidentified impurities;¹⁸
256
 - 257 • The total impurities content;
258
 - 259 • Residual solvents;¹⁹
260
 - 261 • Moisture content;
262
 - 263 • Microbiological testing (e.g., microbial limits (United States Pharmacopeia (USP)
264 General Chapter <61> and General Chapter <62> or equivalent) or sterility (USP General
265 Chapter <71> or equivalent))²⁰; and
266
 - 267 • Bacterial endotoxins (USP General Chapter <85> or equivalent).
268

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

271

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.

272 **F. Stability**

273
274 The sponsor should provide information relating to the stability of the synthetic ASO drug
275 substance. This should include available stability data and the protocol that will be used to
276 monitor ongoing drug substance stability. Preliminary data should be provided in tabular format.
277 The sponsor should also provide a description of the container closure system.

278
279
280 **IV. CMC DATA FOR DRUG PRODUCT**²¹

281
282 **A. Components**

283
284 The sponsor must provide a list of all components used in the manufacture of the investigational
285 drug product,²² including those components intended to appear in the drug product and those
286 which may not appear, but which are used in the manufacturing process. The sponsor should cite
287 quality of the inactive ingredients by reference to a compendial monograph (e.g., USP and the
288 National Formulary²³) (if applicable), or the IND should contain the supplier's CoA.

289
290 **B. Quantitative Composition of the Drug Product**

291
292 The sponsor should submit a brief summary, preferably a table, of the composition of the
293 individualized ASO drug product. For processing aid or aids that are removed during
294 manufacture (e.g., Water for Injection used to formulate a lyophilized product), the submission
295 should include the amount(s) of aid or aids used and amount of aid or aids removed.

296
297 **C. Name and Address of the Drug Product Manufacturer**

298
299 The sponsor should submit the full street address of the manufacturer (including any contract
300 manufacturer, packing facility, or test laboratories) of the individualized ASO drug product
301 batches intended to be used in the clinical trial.

302
303 **D. Brief General Description of the Manufacturing and Packaging Procedures**
304 **for the Product**

305
306 The sponsor should submit a flow diagram and a brief written description of the manufacturing
307 process, including any bioburden reduction and sterilization steps used (e.g., membrane
308 filtration, terminal sterilization). The description should include the air classification of the
309 rooms used in the manufacture of the drug product (e.g., Class 100, Grade A, ISO 5).

310

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.

311 **E. Control of Drug Product**

312
313 The IND should include specifications with corresponding test methods.²⁴ The sponsor should
314 test the drug product for identity, strength, impurities/degradation products (including identity,
315 quality, and a justification for acceptable level of any new impurity present only in the drug
316 product), foreign and particulate matter, sterility, bacterial endotoxins, and any specific tests
317 applicable to the dosage form. As detailed in Table 1 below, the acceptance criterion for bacterial
318 endotoxins should be established based on the maximum proposed dose and route of
319 administration (i.e., intrathecal, intravitreal, or subcutaneous).

320
321 **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

323
324 The sponsor should describe noncompendial analytical methods for the drug product, if different
325 from the drug substance analytical methods, at the same level of detail as for the drug substance.

326
327 **F. Container Closure System**

328
329 The sponsor should provide a description of the container closure system for the individualized
330 ASO drug product, including the identity of materials of construction of each primary packaging
331 component (e.g., USP Type 1 glass vial, bromobutyl rubber stopper, flip-off seal). The sponsor
332 should provide specifications for each component or the manufacturer’s CoA. The sponsor
333 should describe methods for depyrogenation and sterilization for any components that are not
334 supplied as sterile.

335
336 **G. Stability**

337
338 The sponsor should monitor the stability of the individualized ASO drug product packaged in the
339 proposed container closure system under the proposed storage conditions. The sponsor should
340 provide the stability protocol for the clinical batch, including a brief description of the stability
341 study and the test methods, with a commitment to monitor stability of the drug product
342 throughout its use. If initial stability data for the clinical batch are available, the sponsor should
343 provide the data in tabular format. If stability data for the clinical batch are not available, the
344 sponsor should provide any available supportive stability data (e.g., data from the nonclinical
345 batch, if different from the clinical batch; data from a laboratory batch).

346
347 If the individualized ASO drug product is modified before use (e.g., reconstituted or diluted for
348 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.

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

351
352 However, if extended storage conditions are necessary, the sponsor should conduct
353 microbiological studies supporting the postconstitution/postdilution storage time (as stated in the
354 proposed product labeling) as recommended in the ICH guidances for industry *Q8(R2)*
355 *Pharmaceutical Development* (November 2009)²⁵ and *Q1A(R2) Stability Testing of New Drug*
356 *Substances and Products* (November 2003).²⁶ The submission should include a description of
357 the test methods and results of studies that are designed using a minimum countable inoculum
358 (less than or equal to 100 colony forming units (CFU)/ milliliter (mL)) to simulate potential
359 microbial contamination that may occur during drug product constitution or dilution.
360 Additionally, the sponsor should justify the selected test conditions and/or diluents as necessary.
361 Challenge organisms can include strains described in USP General Chapter <51> in addition to
362 typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. The
363 sponsor should provide a positive control that demonstrates the viability of the organisms over
364 the duration of the test period.

365
366

367 **V. IMMEDIATE PACKAGING LABELING**

368

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

372
373

374 **VI. ENVIRONMENTAL EXCLUSION**

375

376 The IND sponsors should either include a claim for categorical exclusion of environmental
377 analysis requirements under 21 CFR 25.30 or 25.31 or provide an environmental assessment
378 under 21 CFR 25.40.²⁹ For an individualized ASO drug product under an IND, we recommend
379 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).