
Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators Guidance for Industry

DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)**

**May 2015
Procedural**

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2 **Submitted by Sponsor-Investigators**
3 **Guidance for Industry¹**
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8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug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 create 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
17 **I. INTRODUCTION**
18

19 The purpose of this guidance is to assist sponsor-investigators in preparing and submitting
20 complete investigational new drug applications (INDs) to the Center for Drug Evaluation and
21 Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and
22 Drug Administration (FDA). Sponsor-investigators seeking to do clinical research often do not
23 have the regulatory knowledge or the resources to hire experts to help them with the IND
24 submission process. Although not an exhaustive step-by-step instruction manual, this guidance
25 highlights certain elements of this process to facilitate a sponsor-investigator's successful
26 submission of an IND. This guidance also discusses the IND review process and general
27 responsibilities of sponsor-investigators related to clinical investigations.
28

29 It is important to note that this guidance does not include discussions of all of the requirements
30 that apply to the IND submission and review process or to conducting clinical research.
31 Sponsor-investigators should review in full these requirements, which are described in the Code
32 of Federal Regulations (CFR).² Many sections of the regulations that apply to INDs are
33 described or referred to in this guidance (e.g., 21 CFR parts 50, 56, and 312). Details of the
34 informational content of an IND as well as information needed to complete required forms also
35 are provided throughout this guidance. In addition, the guidance provides useful references to
36 other IND-related information resources.
37

¹ This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

² The CFR is the codification of the general and permanent rules published in the *Federal Register* by the executive departments and agencies of the Federal government. It is divided into 50 titles that represent broad areas subject to Federal regulation. The CFR references that relate to the IND regulations are provided in parentheses in the appropriate section titles of this guidance. An electronic version of the CFR is available at <http://www.fda.gov>.

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38 This guidance is directed primarily at those sponsor-investigators who are seeking to evaluate a
39 drug that is either currently approved or is being investigated under an existing IND for a
40 different indication.³ This guidance is not intended for sponsor-investigators who are developing
41 a drug for commercial purposes (i.e., seeking market approval or licensure) and thus does not
42 focus on certain regulatory requirements that involve exchange of information or materials
43 between a sponsor and investigator. This guidance does not apply to clinical trials that do not
44 need to be conducted under an IND (i.e., that qualify for an IND exemption).⁴ This guidance
45 also is not intended to address expanded access INDs or biologic devices.⁵ Sponsor-investigators
46 should refer to available FDA regulations and guidances and/or contact the relevant CDER or
47 CBER review division to discuss and obtain additional information for preparing INDs not
48 covered by this guidance (if necessary).

49
50 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
51 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
52 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
53 the word *should* in Agency guidances means that something is suggested or recommended, but
54 not required.

55

56

57 **II. BACKGROUND (§§ 312.1 - 312.3, 312.20 - 312.23)**

58

59 Generally, FDA regulations require sponsors, including sponsor-investigators, who wish to
60 evaluate a drug or biological product in humans to submit an IND to the FDA (21 CFR part
61 312).⁶ The FDA's primary objectives in reviewing an IND are to help protect the rights and
62 safety of subjects and, in phases 2 and 3, to help ensure that the quality of the clinical trial is
63 adequate to evaluate the drug's effectiveness and safety.

64

³ Sponsor-investigators who are seeking to evaluate a marketed unapproved new drug (i.e., a drug marketed in the United States that does not have the required FDA approval for marketing) in a clinical trial should contact the relevant CDER or CBER review division.

⁴ For information about whether a trial has to be conducted under an IND, see 21 CFR 312.2, and the guidance for clinical investigators, sponsors, and IRBs *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁵ See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Qs & As*. When final, this guidance will represent the FDA's current thinking on this topic.

⁶ Part 312 applies, with certain exceptions, to all clinical investigations of drugs and biological products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)). An investigational new drug for which an IND that complies with part 312 is in effect, is exempt from the premarketing approval requirements that would otherwise apply to new drugs and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

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65 A *sponsor* takes responsibility for and initiates a clinical investigation. A sponsor can be an
66 individual or pharmaceutical company, governmental agency, academic institution, private
67 organization, or other organization.⁷ An *investigator* is the individual who actually conducts the
68 investigation (i.e., under whose immediate direction the investigational drug is administered or
69 dispensed to a subject).

70
71 A *sponsor-investigator* is an individual who both initiates and conducts an investigation, and
72 under whose immediate direction the investigational drug is administered or dispensed. The
73 term, as defined in FDA regulations, does not include any entity other than an individual.⁸ As
74 the name suggests, a sponsor-investigator assumes the responsibilities of, and must comply with,
75 FDA regulations applicable to both a sponsor and an investigator. These responsibilities include
76 the submission and maintenance of an IND.⁹

77
78 The information needed to be included in initial IND submissions falls within the broad
79 categories listed below. See section IV., Certain Information Required for an IND Submission,
80 for additional details and 21 CFR 312.23 for a comprehensive list.

- 81
- 82 • *Sponsor-investigator information*: Information on the qualifications of the sponsor-
83 investigator who intends to conduct the clinical trial. This information allows assessment
84 of whether he or she is qualified to fulfill his or her clinical trial commitments.
 - 85
86 • *Investigator's brochure* (required of sponsors, and recommended but not required of
87 sponsor-investigators): A summary of the chemical, toxicological, and pharmacokinetic
88 aspects of an investigational drug including any information on its safety and efficacy
89 obtained from any prior clinical trials, and a description of any anticipated risks, side
90 effects, precautions, and special monitoring.
- 91

⁷ A person other than an individual who uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. Not all employees or individuals who are involved in the conduct of an investigation are considered investigators. For more information, see the information sheet guidance for sponsors, clinical investigators, and IRBs *Frequently Asked Questions — Statement of Investigator (Form FDA 1572)*, section VII., 31-33, and the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*, section III.

⁸ See 21 CFR 312.3(b). Under certain circumstances, a subinvestigator can assist a sponsor-investigator in the conduct of the investigation. For more information about the use of subinvestigators, see the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*.

⁹ An individual who both initiates and conducts an investigation, and uses an investigator or investigators to conduct the investigation, is not a sponsor-investigator, but must comply with all regulations applicable to sponsors and investigators. This guidance generally refers to the roles and responsibilities of sponsor-investigators, but is also intended to be useful for certain individuals who initiate and conduct an investigation, and who also use investigators to conduct the investigation (e.g., a sponsor who is an individual and who is not developing a drug for commercial purposes but helps conduct a trial and also uses investigators to conduct the trial at multiple sites). However, because the purpose of this guidance is to assist sponsor-investigators, it does not focus on certain regulatory requirements that involve the exchange of information or materials between a sponsor and investigator. For additional information about the preparation and submission of INDs, sponsors should refer to available FDA regulations and guidances, including the references listed at the end of this guidance.

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- 92 • *Clinical trial protocol*: A detailed description of the intended investigation, depending
93 on the drug development phase.
- 94
- 95 • *Chemistry, manufacturing, and control (CMC) information*: Sufficient information that
96 ensures the proper identification, quality, purity, and strength of the investigational drug.
97
- 98 • *Pharmacology and toxicology information*: A summary of nonclinical (in vitro or
99 animal) data that is intended to support the safety of the proposed clinical trial.
- 100
- 101 • *Summary of previous human experience*: If applicable, a summary of all clinical trial
102 results intended to support the safety of the proposed clinical trial.
103

104 A sponsor-investigator may not be required to submit an IND for, for example, a study of a
105 lawfully marketed drug if the criteria for an IND exemption are met.¹⁰ Furthermore, in some
106 circumstances, even if a sponsor-investigator is required to submit an IND, the IND may not
107 need to include all of the information listed above. For example, if a sponsor-investigator is
108 proposing to evaluate a drug that is the subject of an existing IND, a sponsor-investigator can
109 seek a letter of cross-reference authorization from the sponsor of that IND (called the
110 *commercial sponsor*)^{11,12} that permits the sponsor-investigator to refer the FDA to the
111 information contained in the commercial sponsor's IND. If the sponsor-investigator is studying
112 an FDA-approved prescription or nonprescription drug, even if an IND is required, some of the
113 information needed for an IND submission can be found in the FDA-approved labeling.
114

III. ACQUIRING INFORMATION NEEDED FOR THE IND AND COMMUNICATING WITH THE FDA (§§ 312.22, 312.23)

115

116

117

118

119 After a sponsor-investigator determines that an IND needs to be submitted to the FDA, he or she
120 should acquire the relevant information for the IND related to the proposed trial. This
121 information is outlined in more depth in section IV., Certain Information Required for an IND
122 Submission. As noted above, if the drug is an FDA-approved prescription or nonprescription
123 drug, the FDA-approved labeling may provide some of the information needed for FDA review
124 of the new IND, but there may be cases in which information that the commercial sponsor has
125 collected for the drug is not part of the labeling or otherwise publicly available and may be
126 needed to support the new IND. In such cases, the commercial sponsor can provide the sponsor-
127 investigator with a letter of cross-reference authorization identifying the IND, new drug
128 application (NDA), or biologics license application (BLA) file by name, reference number,
129 volume, and page number where the information can be found and giving its permission for the

¹⁰ See the guidance for clinical investigators, sponsors, and IRBs *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*.

¹¹ In this guidance, the term *commercial sponsor* refers to a pharmaceutical company or drug manufacturer that is developing, or has developed, a drug for commercial purposes (market approval or licensure or changes to drug labeling) and has submitted an IND for the drug.

¹² A sponsor-investigator may also seek a letter of cross-reference authorization from noncommercial sponsors of INDs or holders of drug master files.

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130 sponsor-investigator to cross-reference the application. This letter of cross-reference
131 authorization should be included in the IND. The commercial sponsor also can submit a copy of
132 the letter of cross-reference authorization to its cited IND.

133
134 The letter of cross-reference authorization allows the FDA to review the specified content in the
135 referenced IND, NDA, or BLA and to rely on its previous reviews of information already
136 submitted in the commercial sponsor's application, so that the sponsor-investigator does not need
137 to provide that information again (e.g., CMC, nonclinical, and previous human experience data).
138 Sponsor-investigators should note that although a letter of cross-reference authorization allows
139 the FDA to refer to the commercial sponsor's content, it does not give sponsor-investigators the
140 right to directly access and read confidential material contained in the referenced IND, NDA, or
141 BLA. However, sponsor-investigators should have access to the commercial sponsor's current
142 investigator's brochure to help protect subjects. An IND submission that does not provide, or
143 incorporate by reference, information about adverse effects and supporting safe use (information
144 that would be found in the commercial sponsor's investigator's brochure) would be inadequate.

145
146 Acquiring the necessary information when it is not available from a commercial sponsor,
147 planning a clinical trial, and submitting a complete application for FDA review can be a complex
148 task. If a sponsor-investigator has any questions regarding preparation of the application, he or
149 she should contact the appropriate review division before submitting the application.

150
151 In CDER, the review divisions for all drugs and most biologics are located in the Office of New
152 Drugs (OND). Web sites containing CDER's and OND's organizational charts and contact
153 information can be found in the References section.

154
155 In CBER, the review divisions for the review of blood products; cellular, tissue, and gene
156 therapies; and vaccines are located in the Office of Blood Research and Review; the Office of
157 Cellular, Tissue and Gene Therapies; and the Office of Vaccines Research and Review,
158 respectively. Web sites containing CBER's organizational charts and contact information can be
159 found in the References section.

160
161 If the relevant review division is not known, the sponsor-investigator should contact CDER's
162 Division of Drug Information or CBER's Division of Manufacturer's Assistance and Training,
163 Office of Communication, Outreach and Development (both addresses and telephone numbers
164 are provided on the second title page of this guidance).

165
166 Sponsor-investigators should include accurate contact information (e.g., telephone numbers and
167 email addresses) that the FDA can use to communicate with the sponsor-investigator.
168 Communications between the sponsor-investigator and the FDA can facilitate review of a
169 submission. Therefore, the sponsor-investigator should be readily available for communications
170 with the FDA, particularly during the 30-day period after a new IND submission.

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173 **IV. CERTAIN INFORMATION REQUIRED FOR AN IND SUBMISSION**

174

175 **A. Required Forms (§§ 312.23(a)(1), 312.53(c))**

176

177 **Form FDA 1571 Investigational New Drug Application**

178

179 Under § 312.23(a)(1), a sponsor-investigator's initial IND submission must be accompanied by a
180 signed Form FDA 1571 Investigational New Drug Application (Form FDA 1571).

181

182 A signed Form FDA 1571 is required for the submission of an IND to the FDA. A signed Form
183 FDA 1571 documents the sponsor-investigator's agreement to refrain from beginning a clinical
184 trial until 30 days after the official date that the FDA receives the IND (or unless the sponsor-
185 investigator receives earlier notification from the FDA that the trial may begin), to refrain from
186 beginning or continuing a clinical trial covered by the IND if that trial is placed on clinical hold,
187 to ensure that an institutional review board (IRB) in compliance with FDA regulations will be
188 responsible for the initial and continuing review and approval of each proposed trial, and to
189 conduct the trial in accordance with all other applicable regulations. This form is largely self-
190 explanatory and contains a brief series of fill-in-the-blanks and check boxes that describe and
191 catalog the contents of the application. As such, it can serve as a road map for the sponsor-
192 investigator, a checklist, and as a cover sheet for the initial IND submission.

193

194 **Form FDA 1572 Statement of Investigator**

195

196 Before permitting an investigator to begin participation in an investigation, a sponsor is required
197 to obtain a signed investigator statement, Form FDA 1572 Statement of Investigator (Form FDA
198 1572). As an investigator, a sponsor-investigator is also required to sign Form FDA 1572. By
199 signing Form FDA 1572, the sponsor-investigator agrees to, among other things, conduct the
200 trial in accordance with the protocol, ensure that the requirements relating to obtaining informed
201 consent and IRB review are met, and comply with all requirements regarding the obligations of
202 clinical investigators (e.g., recordkeeping, reporting adverse experiences). Note that IRB
203 approval does not need to be obtained before IND submission; rather, the sponsor-investigator's
204 signature on Form FDA 1572 is a commitment to obtain IRB approval before initiating the trial.

205

206 **Form FDA 3674 Certification of Compliance, under 42 U.S.C. 282(j)(5)(B), with**
207 **Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. 282(j))**

208

209 The Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted on
210 September 27, 2007. Title VIII of FDAAA added new section 402(j) to the Public Health
211 Service Act (PHS Act) (42 U.S.C. 282(j)) and expanded the current National Institutes of Health
212 (NIH) data bank known as ClinicalTrials.gov. FDAAA requires the responsible party, who
213 could be the sponsor, or in certain instances, the principal investigator of particular clinical trials
214 of human drugs, biological products, and devices (referred to in FDAAA as applicable clinical
215 trials), to register the trials and to submit results information for inclusion in the

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216 ClinicalTrials.gov data bank. Sponsor-investigators may be responsible for submitting certain
217 clinical trial information to ClinicalTrials.gov.¹³

218
219 One provision of FDAAA requires that certain human drug, biological product, and device
220 applications and submissions to the FDA, including applications under section 505 of the Federal
221 Food, Drug, and Cosmetic Act, be accompanied by a certification that all applicable
222 requirements of section 402(j) of the PHS Act have been met (42 U.S.C. 282(j)(5)(B)). The
223 FDA has concluded that the statutory requirement to submit a certification also applies to INDs
224 and the submissions of new protocols to INDs.¹⁴ Where available, such certification must
225 include the appropriate National Clinical Trial numbers issued by NIH at trial registration to
226 ClinicalTrials.gov. Sponsor-investigators should use Form FDA 3674 to certify compliance with
227 42 U.S.C. 282(j). When completing Form FDA 3674, sponsor-investigators should review 42
228 U.S.C. 282(j) to determine whether the requirements of that subsection apply to any clinical
229 trial(s) referenced in the IND.

230
231 See the References section for Web sites where Forms FDA 1571, 1572, and 3674, as well as
232 instructions for filling out the forms, can be found.

B. Table of Contents (§ 312.23(a)(2))

233
234
235
236 A sponsor-investigator is required to provide a table of contents and should provide pagination
237 and tabbed breaks between sections to allow FDA reviewers to more easily navigate the
238 submission.

C. Introductory Statement and General Investigational Plan (§ 312.23(a)(3))

240
241
242 The introductory statement must include the investigational drug's name and all of its active
243 ingredients, pharmacologic class, structural formula (if known), formulation of the dosage form
244 to be used, the route of administration, and the broad objectives of the proposed clinical trial.
245 There also must be a brief summary of previous human experience with the investigational drug
246 including any investigational and marketing experience in other countries. For an investigational
247 drug under commercial development, this information can be obtained from the commercial
248 sponsor, and is most commonly submitted through a letter of cross-reference authorization to the
249 commercial IND. For an FDA-approved prescription drug, the sponsor-investigator should be
250 able to obtain all or most of this information from the drug's FDA-approved labeling, but
251 additional information may be needed if the sponsor-investigator is studying an unapproved use
252 or dose of the drug.

253
254 The general investigational plan must summarize the rationale supporting the proposed clinical
255 trial (including the dose, schedule, and patient population), the indications to be investigated, the

¹³ See <http://www.clinicaltrials.gov> for additional information about responsibilities for trial registration and results reporting.

¹⁴ See the guidance for sponsors, industry, researchers, investigators, and Food and Drug Administration staff *Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance With Section 402(j) of The Public Health Service Act, Added By Title III of the Food and Drug Administration Amendments Act of 2007*.

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256 general approach to evaluating the investigational drug, the planned trial duration, any trial plans
257 for the following year (along with an estimated number of subjects to be given the
258 investigational drug in the trial), and any risks of particular severity or seriousness anticipated on
259 the basis of toxicology. When the IND is for a single trial, the information should be directed at
260 supporting and describing that trial.

261

D. Investigator's Brochure (§§ 312.23(a)(5), 312.55)

262

263 Although an investigator's brochure is not required for sponsor-investigator investigations,¹⁵ a
264 sponsor-investigator should obtain access to an investigator's brochure when there is a
265 concurrent or otherwise related commercial investigation for which an investigator's brochure
266 was developed. A sponsor-investigator should be aware of and understand the content in the
267 commercial sponsor's investigator's brochure to the extent necessary to ensure subject safety and
268 to facilitate identification of serious and unexpected suspected adverse reactions that may require
269 expedited reporting to the FDA. The purpose of the investigator's brochure is to make
270 particularly vital information regarding the investigational drug available to the other
271 investigators involved, who may be located at different geographic locations. If a commercial
272 sponsor provides the sponsor-investigator with an investigator's brochure, including it with the
273 IND will be useful to both the sponsor-investigator and the FDA review team.

274

E. Protocols (§ 312.23(a)(6))

275

276 Sponsor-investigators must describe the trial to be conducted under the IND. IND regulations
277 allow a protocol outline, rather than a complete protocol, to be submitted for phase 1 trials with
278 the following information:¹⁶

279

- 281 • An estimate of the number of subjects involved.
- 282 • A description of safety exclusions (and of inclusion criteria).
- 283 • A description of the dosing plan including the duration, dose, dose escalation, schedule,
284 or method to be used in determining dose.
- 285 • All of the details that describe those elements of the trial that are critical to safety, such as
286 necessary monitoring of vital signs and blood chemistries. The protocol outline should
287 also include dosing escalation rules and stopping criteria. For clinical investigations of
288 cell and gene therapies, including xenogeneic cellular products, protocols may need to
289 include procedures for long-term monitoring of subjects, in accordance with FDA and
290 PHS regulations and PHS guidelines. Sponsor-investigators should contact the
291 appropriate CBER reviewing division for consultation.

292

¹⁵ Note that, under § 312.55, before an investigation begins, a sponsor must give each participating clinical investigator an investigator's brochure.

¹⁶ For drugs that may carry significant risk of toxicity, or depending on the trial population, more complete protocols for phase 1 trials may be needed. If uncertain, the investigator should contact the appropriate review division.

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297 For phase 2 and phase 3 trials, detailed protocols describing *all* aspects of the trials should be
298 submitted and must contain the following information:

- 299
- 300 • A statement of the objectives and purpose of the trial
- 301
- 302 • For a sponsor-investigator, the sponsor-investigator's name, address, and statement of
- 303 qualifications and the name of each subinvestigator (a trial team member such as a
- 304 research fellow, resident) working under the direct supervision of the investigator; the
- 305 name and address of the research facilities to be used; and the name and address of the
- 306 reviewing IRB
- 307
- 308 • The criteria for subject selection (inclusion criteria), reasons for excluding subjects
- 309 (exclusion criteria), and an estimate of the number of trial subjects
- 310
- 311 • A description of the trial design including the type of control group to be used, if any, and
- 312 a description of methods to be used to minimize bias on the part of subjects, the sponsor-
- 313 investigators, and analysts
- 314
- 315 • The method for determining the doses to be administered, the planned maximum dosage,
- 316 and the duration of individual subject exposure to the investigational drug
- 317
- 318 • A description of the observations and measurements to be made to fulfill the trial
- 319 objectives
- 320
- 321 • A description of the clinical procedures, laboratory tests, or other measures to be taken to
- 322 monitor the effects of the investigational drug in human subjects and to minimize risk
- 323

324 For phase 2 and phase 3 trials, the sponsor-investigator should include a description in the trial
325 design of plans to deviate from the original trial design should this become necessary as the
326 investigation progresses. For example, a protocol for a controlled short-term clinical trial might
327 include a plan for an early crossover of nonresponders to an alternative therapy.

328

329 Each protocol submitted must be reviewed and approved by the appropriate IRB before subjects
330 can be enrolled.¹⁷ Informed consent forms frequently are included with protocols and we
331 encourage their submission.¹⁸

332

¹⁷ Certain categories of clinical investigations are exempt from the requirements for IRB review in 21 CFR part 56: (1) certain investigations that commenced before July 27, 1981; (2) emergency use of a test article provided that such use is reported to the IRB within 5 working days; and (3) taste and food quality evaluations and consumer acceptance studies, if certain conditions are met. See 21 CFR 56.104, Exemptions From IRB requirement.

¹⁸ For more information about informed consent, see 21 CFR part 50, subpart B. See also FDA information sheets and guidances for industry regarding informed consent and IRB review at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm> and <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/default.htm>, respectively.

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F. Chemistry, Manufacturing, and Control Information (§ 312.23(a)(7))

An IND must include sufficient CMC information to ensure the proper identity, strength, quality, and purity of the investigational drug. The amount of CMC information that should be provided will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available.

In all cases, the sponsor-investigator must include the following information in the IND:

- The label for the immediate packaging of the investigational drug, which must contain the statement “Caution: New Drug — Limited by Federal (or United States) law to investigational use” (§ 312.6(a))
- An environmental assessment under 21 CFR 25.40 or a statement requesting a categorical exclusion from an environmental assessment under provisions provided for in 21 CFR 25.31(e) (§ 312.23(a)(7)(iv)(e))¹⁹

The amount of CMC information that should be provided depends on the nature of the investigational drug and whether it has been lawfully marketed in the United States (or in a foreign country) or is the subject of a previously filed IND.

If the investigational drug is not lawfully marketed in the United States, and there is either no existing IND to reference or an existing IND cannot be referenced, then complete CMC information on the investigational drug must be provided. The sponsor-investigator should consult applicable guidances for industry for information on preparing the CMC section,²⁰ or contact the relevant review division.

If the investigational drug is not lawfully marketed in the United States but is being investigated under an existing IND, then the sponsor-investigator can seek a letter of cross-reference authorization from the commercial sponsor of that IND to provide to the FDA (see section II., Background). The letter of cross-reference authorization should specify the name, strength, and dosage form of the investigational drug being studied under the other IND(s).

If the investigational drug is an FDA-approved prescription or nonprescription drug, the CMC information that should be provided by the sponsor-investigator depends on how the drug will be administered. If the investigational drug will be administered using the dosage form, strength, and route of administration described in its current labeling, the sponsor-investigator should include in the IND the current drug labeling and a statement indicating that the investigational drug will be administered using the dosage form, strength, and route of administration described in its current labeling. If any change to the labeled dosage form, strength, or route of

¹⁹ See the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*.

²⁰ See the guidances for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* and *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*.

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373 administration is planned, then the sponsor-investigator should provide relevant information such
374 as release and stability data to support the proposed usage.

375
376 If the investigational drug is not lawfully marketed in the United States, but is approved and
377 marketed in a foreign country, or if the investigational drug is marketed, but not as a drug (e.g.,
378 marketed as a food, including a dietary supplement), then complete CMC information on the
379 investigational drug should be provided if it is available. However, the FDA recognizes that in
380 many such cases the sponsor-investigator will not be able to obtain all of the CMC information
381 required by 21 CFR 312.23(a)(7). In these circumstances, the sponsor-investigator can request
382 that the FDA waive the requirement for complete CMC information on the investigational drug
383 (21 CFR 312.10). The IND must include, as part of the waiver request:

- 384
- 385 • A sufficient explanation why compliance with the complete requirements of 21 CFR
386 312.23(a)(7) is unnecessary or cannot be achieved;
 - 387
 - 388 • Information that will satisfy the purpose of the requirement by helping to ensure that the
389 investigational drug will have the proper identity, strength, quality, and purity; or
 - 390
 - 391 • Other information justifying a waiver.
- 392

393 Information that is relevant to whether the investigational drug will have the proper identity,
394 strength, quality, and purity may include, for example, information indicating whether the
395 investigational drug has been licensed by a regulatory authority that has similar scientific and
396 regulatory standards as the FDA (e.g., International Conference on Harmonisation (ICH)
397 countries). This should include, to the extent possible, summary approval information and
398 current product labeling made public by the foreign regulatory authority.

399
400 In addition to the waiver request, the sponsor-investigator should include in the IND as much of
401 the CMC information required by 21 CFR 312.23(a)(7) as is available. This should include, at a
402 minimum, the following:

- 403
- 404 • The name of the manufacturer or supplier of the investigational drug.
 - 405
 - 406 • An English version of the investigational drug's labeling, including the package insert.
 - 407
 - 408 • Information on the conditions and containers that will be used to transport the drug
409 product to the U.S. clinical site(s) and information on the relabeling and repackaging
410 operations that will be used to relabel the drug product vials for investigational use. This
411 should include information on how exposure of the drug product to light and temperature
412 conditions outside of the recommended storage conditions will be prevented. A risk
413 assessment on the affect the relabeling operations may have on drug product stability
414 should also be included.
- 415

416 The sponsor-investigator should also provide, if available, the following:

- 417
- 418 • The components and composition of the investigational new drug.

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- 419
- 420
- Drug product specification and/or Certificate(s) of Analysis (COA(s)) for the specified
- 421 lot(s) of investigational drug to be used in the clinical trial. (If the specific batch numbers
- 422 and COAs are not available at the time of IND submission, they should be submitted to
- 423 the IND if they do become available.)
- 424

425 The sponsor-investigator should consult with the appropriate FDA review division regarding any

426 additional CMC information that might be warranted to support the proposed clinical trial.

427

428 For botanical drugs, as defined in the guidance for industry *Botanical Drug Products*, the

429 sponsor-investigator should refer to the guidance and consult with the FDA for special

430 considerations in requirements of CMC information. For botanical products that are marketed as

431 foods (including dietary supplements), the sponsor-investigator should obtain such information

432 from the manufacturer and provide it in the IND. If information from the manufacturer cannot

433 be obtained, the FDA may consider the specific circumstance (e.g., drug history and clinical

434 settings) and determine the CMC requirements for each individual case.

435

G. Pharmacology and Toxicology Information (§ 312.23(a)(8))

436

437

438 The sponsor-investigator must provide adequate information about the pharmacological and

439 toxicological studies of the investigational drug involving lab animals or in vitro to support the

440 sponsor-investigator's conclusion that it is reasonably safe to conduct the proposed clinical trial.

441 The sponsor-investigator should include a discussion of the rationale for the investigational

442 drug's intended dose, duration, schedule, and route of administration in the proposed trial. This

443 rationale, particularly for phase I trials, is best supported by in vitro and available animal data, as

444 described in the guidance for industry *Content and Format of Investigational New Drug*

445 *Applications (INDs) for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic,*

446 *Biotechnology-Derived Products.*

447

448 If an FDA-approved drug will be used at the same dose, duration, and route of administration as

449 described in its current labeling, then the sponsor-investigator should include a statement to this

450 effect and include a copy of the current label.

451

452 If the drug has not been approved by the FDA, but is being studied under a cross-referenced

453 IND, then the sponsor-investigator should provide a letter of cross-reference authorization to

454 cross-reference the drug's pharmacology and toxicology data.

455

456 If the drug is not approved by the FDA but is approved and marketed in a country listed in

457 section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act or is marketed as a food (such

458 as a dietary supplement), additional toxicological information is dependant on the trial

459 (population, dose, duration), the extent of foreign use, current labeling, published information,

460 and any information available from foreign regulatory authorities. The sponsor-investigator

461 should provide any appropriate documentation and/or a summary of this information.

462

463 For trials that involve doses, durations, or changes in the routes of administration (e.g.,

464 intravenous to oral) that have not been tested or for which inadequate safety information exists,

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465 the sponsor-investigator should consult with the review division as to the appropriate toxicology
466 studies necessary to support the proposed use.

467
468 A justification for the use of any drug combinations to be studied should be provided in the IND.
469 The factors to consider are possible pharmacokinetic or toxicological interactions that may affect
470 the combination's safety profile. If interactions are expected, then some consideration should be
471 given to dose reduction of either one or more of the compounds in the investigational
472 combination. For additional discussion of this topic, see the guidance for industry *Nonclinical*
473 *Safety Evaluation of Drug or Biologic Combinations*.

474
475 Additional nonclinical studies may be needed for studies in pediatric patients where inadequate
476 data exist to support the safety of either an FDA-approved or unapproved drug in that patient
477 population. For additional discussion of this topic, see the guidance for industry *Nonclinical*
478 *Safety Evaluation of Pediatric Drug Products*.

H. Previous Human Experience With the Investigational Drug (§ 312.23(a)(9))

481
482 If there has been previous human experience with the investigational drug, the sponsor-
483 investigator is required to provide a summary of this information. As noted previously, it may be
484 necessary for the commercial sponsor to give permission via a letter of cross-reference
485 authorization to cross-reference all INDs in which the investigational drug is being studied.

486
487 If the investigational drug has been investigated or marketed previously, either in the United
488 States or other countries, detailed information relevant to the safety of the proposed trial or the
489 trial's rationale must be provided.

490
491 Any published material relevant to the safety of the proposed trial or to an assessment of the
492 drug's effectiveness for its proposed investigational use should be provided. A reference list and
493 copies of significant supportive published literature related to previous human experience with
494 the investigational drug should be included in the submission. Although a reference list and
495 copies of published literature are useful, a consolidated assessment of the available information
496 and how it applies to the current investigation would help to justify the sponsor-investigator's
497 proposed dose, duration, drug combination, populations, and other trial information.

498
499 The sponsor-investigator should contact the review division if he or she has specific questions,
500 especially if the drug or drug combination has not been investigated previously.

I. Other Important Information (§ 312.23(a)(10)(i) – (iii))

503
504 In certain circumstances, a sponsor-investigator may be required to provide other types of
505 important information on special topics as noted below, especially if the investigational drug is
506 not approved.

- 507
508 • **Drug dependence and abuse potential** — If the investigational drug is a psychotropic
509 substance or otherwise has abuse potential, then information describing related clinical
510 trials and experience as well as any appropriate animal data must be submitted.

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- **Radioactive drugs** — Sufficient data from animal studies or human clinical trials must be submitted to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to human subjects. Phase 1 trials of radioactive drugs must include trials that will obtain sufficient data for dosimetry calculations.

J. Relevant Information (§ 312.23(a)(11))

If a device is to be used in conjunction with the investigational drug (e.g., a nebulizer for an inhaled drug or a pump for continuous infusion for home use), the FDA may require under 21 CFR 312.23(a)(11) other relevant information on the manufacturer and model of the device to be employed and a general description of relevant conditions of use (e.g., carrier gas, flow rate, temperature), and whether the device is FDA-approved or cleared for its intended use in the trial. If the sponsor-investigator intends to use the device other than for its cleared or approved intended use and/or indication, he or she should contact the review division in CDER or CBER and then the Center for Devices and Radiological Health, or alternatively, the Office of Combination Products.

V. SUBMISSION INFORMATION (§ 312.22(D))

After all the needed information has been acquired, the IND is ready for submission to the FDA. Even though the FDA is moving toward requiring electronic submission of an IND in the electronic common technical document format, paper submissions are acceptable. Sponsor-investigators who wish to submit INDs electronically to CDER can submit the documents in portable document format and any data in statistical analysis system transport files either by email to the review division project manager or on a CD accompanying the paper copies. Sponsor-investigators who wish to submit INDs electronically to CBER should refer to the guidance for industry *Providing Regulatory Submissions to CBER in Electronic Format — Investigational New Drug Applications (INDs)* and/or should contact the appropriate review division in CBER to determine the procedures for submitting INDs to CBER in electronic format.

Paper submissions of the initial IND and each subsequent amendment must be provided in triplicate (the original and two photocopies are acceptable). Each submission related to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND should be numbered “000”; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

For INDs reviewed in CDER, there are two different mailing addresses depending on whether the IND submission is related to: (1) therapeutic biological products, which include monoclonal antibodies, proteins intended for therapeutic use (e.g., cytokines, interferons, enzymes), and immunomodulators; or (2) not related to therapeutic biological products (i.e., for a drug)

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555 regardless of delivery method (e.g., overnight mail and courier or U.S. Postal Service).²¹ For
556 INDs reviewed in CBER, refer to the Information on Submitting an Investigational New Drug
557 Application Web site for the mailing address.²²
558

559

560 **VI. THE IND PROCESS AND REVIEW PROCEDURES (§§ 312.30, 312.31, 312.40 –** 561 **312.42, 312.110)**

562

563 After the FDA receives the IND, an *IND Acknowledgement Letter* will be sent to the sponsor-
564 investigator. The letter includes important information such as the assigned review division,
565 IND number, division contact, and the official FDA date of receipt. The latter is important
566 because by regulation the proposed trial may not be initiated until 30 calendar days after official
567 FDA receipt. This time period allows the division's multidisciplinary review team, comprised of
568 clinical reviewers, chemists, toxicologists, clinical pharmacologists, and project managers (along
569 with a microbiologist and/or statistician depending on the indication and development phase), to
570 review the proposed clinical trial materials. This review generally includes, for example, the
571 proposed investigational drug's formulation, toxicity, nonclinical pharmacology and toxicology,
572 and any previous human experience information provided. In addition, many teams also may
573 consider other proprietary studies and clinical trials in similar drugs and may perform literature
574 searches.

575

576 By the end of this 30-day review period, if the division makes the determination that it is safe to
577 proceed with the clinical trial, the FDA may (e.g., to convey any comments regarding the
578 submission) or may not contact the sponsor-investigator about its determination. Unless notified
579 by the FDA within 30 days that a clinical hold has been placed, the trial can proceed as long as
580 IRB approval has been obtained. If the division makes the determination within the 30-day
581 review period that the trial should be placed on clinical hold, the FDA will notify the sponsor-
582 investigator as soon as possible after making that determination (usually by telephone) to not
583 initiate the trial. Likewise, the sponsor-investigator will be notified promptly if the FDA makes
584 the determination that a trial that has been initiated needs to be suspended, as further described in
585 Figure 1, The IND Review Process, and section VI.A., Clinical Holds and Requests for
586 Modifications.
587

²¹ For the relevant mailing addresses, see
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm>.

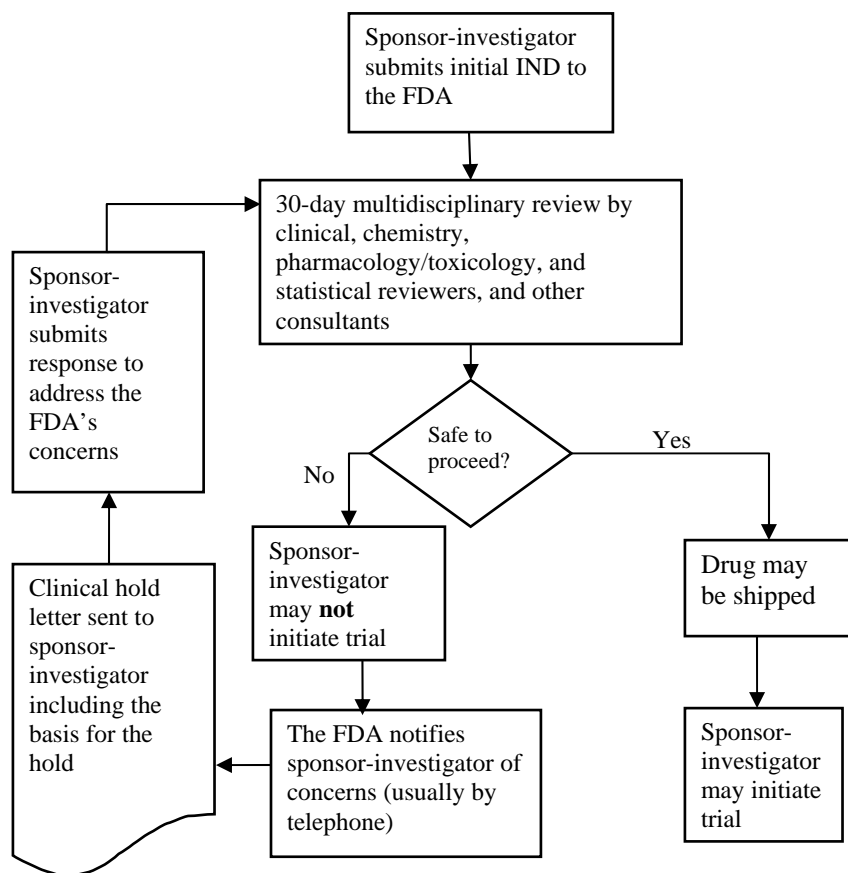
²² See
<http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEPProcess/ucm094309.htm>.

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588 **Figure 1: The IND Review Process**

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591

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A. Clinical Holds and Requests for Modifications (§ 312.42)

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594

The FDA may place a proposed or ongoing trial on **clinical hold** if the FDA makes certain findings, including that:

595

596

597

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
- The sponsor-investigator is not qualified, by reason of his or her scientific training and expertise to conduct the trial
- The investigator's brochure is misleading, erroneous, or incomplete (where applicable)
- The IND contains insufficient information for the FDA to assess the risks to subjects of the proposed trial
- The IND is for the study of a drug intended to treat certain diseases or conditions and limits the eligibility of prospective subjects because of the risk or potential risk of reproductive toxicity

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- 612 • For phase 2 or 3 trials, the plan or protocol for the investigation is clearly deficient in
613 design to meet its stated objectives

614
615 Under certain circumstances, the FDA may also place on clinical hold a proposed or ongoing
616 trial that is not designed to be adequate and well-controlled, or if the criteria for a trial involving
617 an exception from informed consent, as described in 21 CFR 50.24,²³ are not met.

618
619 Sponsor-investigators should familiarize themselves with the clinical hold provisions in the
620 regulations to avoid this potential outcome.

621
622 Whenever the FDA concludes that a deficiency exists in a clinical investigation that may be
623 grounds for imposing a clinical hold, the FDA will, unless subjects are exposed to immediate and
624 serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor-investigator
625 before issuing the clinical hold order.

626
627 The FDA will contact the sponsor-investigator to impose a clinical hold, usually by telephone, on
628 or before day 30 after the submission of the IND; however, the FDA may place the trial on
629 clinical hold after the 30-day period if the FDA finds the criteria for imposing a clinical hold are
630 met. The FDA will, as soon as possible, and within no more than 30 days of imposition of the
631 clinical hold, send a letter to the sponsor-investigator that provides the sponsor-investigator a
632 written explanation of the basis for the hold. The letter may also describe the specific issues and
633 deficiencies that led to the hold, what the sponsor-investigator must do for the FDA to remove
634 the clinical hold, and other pertinent comments.

635
636 The clinical hold means that the sponsor-investigator may not initiate or continue (if the trial has
637 already begun but new safety concerns have been identified) the trial or trials subject to this
638 action, and the clinical hold remains in force until the sponsor-investigator adequately addresses
639 the deficiencies that led to the clinical hold, or otherwise satisfies the FDA that the trial or trials
640 can proceed, and is told by the FDA that the clinical hold has been lifted. The sponsor-
641 investigator should address these deficiencies in writing to the division with any requested data.
642 If a sponsor-investigator of an IND that has been placed on clinical hold requests in writing that
643 the clinical hold be removed and submits a complete response to the issues identified in the
644 clinical hold letter, the FDA will respond in writing to the sponsor-investigator within 30
645 calendar days of receipt of the complete response. The FDA's response will remove, maintain,
646 or modify the clinical hold, and the letter will state the reasons for such determination.

647
648 Notwithstanding the 30-calendar-day response time, a sponsor-investigator may not proceed with
649 a clinical trial on which a clinical hold has been imposed until the sponsor-investigator has been
650 notified by the FDA that the hold has been lifted.

651

²³ Note that, if an investigation involves an exception from informed consent under 21 CFR § 50.24, the sponsor-investigator must prominently identify on Form 1571 that the investigation is subject to the requirements in § 50.24 (21 CFR 312.23(f)).

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652 **B. IND Amendments (§§ 312.30, 312.31)**

653
654 After the initial IND is submitted and is in effect, a sponsor-investigator must make changes to
655 the IND as needed to ensure that the clinical investigations are conducted according to protocols
656 included in the application. Sponsor-investigators also need to provide essential information on
657 the IND that is not within the scope of any protocol amendment, IND safety report, or annual
658 report. All these written communications to the FDA are called **amendments** to the IND. The
659 division will review these amendments as they are received.

660
661 It is important to identify in the amendment whether a reply from the FDA is expected. If the
662 sponsor-investigator wants the FDA to comment on the submission, the amendment must include
663 a request for an FDA reply (e.g., a specific request to review new information and respond by a
664 certain proposed date), which can be included in a cover letter of an amendment. In addition to
665 including this request in the amendment, the sponsor-investigator can also contact the review
666 division directly (e.g., for an informal discussion or to request a teleconference).

667
668 In contrast to the initial IND submission, if the IND is not on clinical hold, the sponsor-
669 investigator may implement changes to the IND immediately after sending the amendment to the
670 FDA, without waiting 30 days (though new protocols and protocol changes to ongoing trials still
671 require prior approval by an IRB unless the change to the protocol is necessary to eliminate
672 apparent immediate hazards to human subjects). Note that the FDA reserves the right to suspend
673 an ongoing trial (by placing it on clinical hold, as noted in section VI.A., Clinical Holds and
674 Requests for Modifications) at any time a suspension is warranted.

675
676 In some situations, it may be unclear whether a change to an existing protocol or a new protocol
677 should be communicated as an amendment to an existing IND or under a new IND, or if a new
678 30-day review period at the FDA is warranted. In such situations, the sponsor-investigator
679 should seek case-by-case guidance from the relevant CDER or CBER review division to
680 minimize the chance of an unexpected clinical hold.

681 682 **C. Import and Export Requirements (§ 312.110)**

683
684 Sponsors importing an investigational new drug under an IND must comply with 21 CFR
685 312.110(a). An investigational new drug offered for import into the United States complies with
686 the requirements of this part if it is subject to an IND that is in effect for it under § 312.40 and:
687 (1) the consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified
688 investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is
689 responsible for the control and distribution of the investigational drug, and the IND identifies the
690 consignee and describes what, if any, actions the consignee will take with respect to the
691 investigational drug. For details on export requirements, see § 312.110(b).

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694 **VII. OTHER SPONSOR-INVESTIGATOR RESPONSIBILITIES**

695
696 Sponsor-investigators conducting trials under an IND must comply with both the sponsor and
697 investigator responsibilities specified in 21 CFR parts 312, 50, and 56.²⁴ Sponsor-investigators
698 should read these regulations in their entirety and become familiar with all of their
699 responsibilities. Some but not all of the responsibilities discussed in these regulations are
700 summarized below with references to more comprehensive discussions.

701 702 **A. Good Clinical Practice, Including Human Subject Protection and IRB** 703 **Review and Approval (§ 312.40, 21 CFR Parts 50 and 56)**

704
705 In general, the sponsor-investigator should conduct trials according to good clinical practice
706 (GCP). GCP is an international ethical and scientific quality standard for designing, conducting,
707 recording, and reporting trials that involve the participation of human subjects.²⁵ GCP includes
708 human subject protection as afforded by adherence to requirements for review and approval of
709 the trial by an IRB and requirements to obtain informed consent from each clinical trial subject
710 (see General Information in the References section for a Web site that contains a summary of
711 these standards). Sponsor-investigators must conduct trials in compliance with FDA regulations
712 about the protection of human subjects²⁶ and about IRB review and approval of studies.²⁷

713 714 **B. Monitoring Ongoing Investigations (§ 312.50)**

715
716 Sponsor-investigators are responsible for ensuring proper monitoring of the investigation. We
717 recommend that sponsor-investigators submit a brief summary to the IND to demonstrate that
718 there is adequate monitoring of the clinical investigation to demonstrate the trial(s) are conducted
719 in accordance with regulatory requirements, GCPs, and the protocol; that the rights and well-
720 being of human subjects are protected; that data reporting, including safety reporting to the
721 sponsor-investigator and the IRB, is accurate and complete; and that the sponsor-investigator has
722 adequate oversight over the clinical investigation, as outlined in 21 CFR part 312, subpart D.²⁸

723

²⁴ As noted above, a person who both initiates and conducts an investigation, and uses an investigator or investigators to conduct the investigation, is not a sponsor-investigator, but must also comply with both sponsor and investigator responsibilities. Because the purpose of this guidance is to assist sponsor-investigators, who are single individuals, it does not focus on certain regulatory requirements that involve the exchange of information or materials between a sponsor and investigator (e.g., sponsors' responsibilities to select qualified investigators, provide them with the information they need to conduct an investigation properly, and ensure proper monitoring of the investigation). For additional information about the preparation and submission of INDs, sponsors should refer to available FDA regulations and guidances, including the references listed at the end of this guidance.

²⁵ See the ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*.

²⁶ See 21 CFR part 50, Protection of Human Subjects.

²⁷ See 21 CFR part 56, Institutional Review Boards.

²⁸ For additional information regarding responsibilities of sponsor-investigators in clinical trials (including monitoring), see the ICH document on GCPs at <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>.

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C. Promotion of or Charging for Investigational Drug (§§ 312.7, 312.8)²⁹

Promoting the investigational drug is not permitted. Charging for the investigational drug is only permitted in rare circumstances, and then only with prior written approval by the FDA.

D. Records and Reports (§§ 312.57, 312.58, 312.62, 312.68)

A sponsor-investigator must maintain adequate and accurate case histories. Case histories include case report forms (CRFs) and supporting data, including, for example, signed and dated informed consent forms, and any medical or clinical trial records that serve as source documents to support the information recorded on the CRFs. A sponsor-investigator must also maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. Records of drug disposition must include the dates of administration, quantity, and use by subjects.

The FDA may periodically inspect trial sites to ensure that a sponsor-investigator is properly capturing and storing this critical data. Failure to adhere to the investigational plan and inadequate records (particularly, subject case histories) are among the most frequently cited GCP deficiencies at FDA inspections. Sponsor-investigators are required to retain records and reports for 2 years after a marketing application is approved for a drug or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been notified (21 CFR 312.57(c)).

E. IND Safety Reports (§ 312.32)

A sponsor-investigator is responsible for promptly reviewing all information relevant to the safety of the investigational drug and notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but no later than 7 calendar days after receipt of the information. The sponsor-investigator must also notify the FDA (and sponsors must notify all participating investigators) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

The IND safety reports can be submitted using Form FDA 3500A or in a narrative format, but must be marked as “IND Safety Report” (see the References section for the Web site where Form FDA 3500A can be found). Additional information may be requested by the review division.

If other IND safety reports have been previously submitted concerning a similar suspected adverse reaction, then the sponsor-investigator must identify these reports and analyze the significance of this event in light of the previous, similar reports or any other relevant information.

²⁹ See the draft guidance for industry *Charging for Investigational Drugs Under an IND — Qs & As*. When final, this guidance will represent the FDA’s current thinking on this topic.

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768 For more information about safety reporting requirements for INDs, and for information about
769 sponsor-investigator obligations to follow up on safety information, see the guidance for industry
770 and investigators *Safety Reporting Requirements for INDs and BA/BE Studies*.

771
772 A sponsor-investigator is also responsible for promptly notifying the IRB of all unanticipated
773 problems involving risk to human subjects or others (see § 312.66).

774

F. IND Annual Reports (§ 312.33)

776

777 Within 60 days of the anniversary date that an IND went into effect, a sponsor-investigator must
778 submit a brief annual report of the progress of the trial. The annual report is intended to update
779 the review division as to all relevant developments over the preceding year. This annual report
780 must contain certain information, including, but not limited to, the following:

781

- 782 • Individual trial progress (i.e., enrollment, dropouts) with results, if the trial has been
783 completed or if interim results are known
- 784
- 785 • A narrative or tabular summary showing the most frequent and most serious adverse
786 events by body system
- 787
- 788 • A summary of all IND safety reports submitted during the previous year
- 789
- 790 • A list of subjects who dropped out because of adverse events and a description of the
791 adverse events
- 792
- 793 • New information regarding the investigational drug's actions (e.g., dose response),
794 completed nonclinical studies, and any CMC changes, if available
- 795
- 796 • A general investigational plan for the coming year, significant foreign marketing
797 developments
- 798

799

800 If a trial is completed, the final report should be submitted to the FDA, as should a list of any
801 publications that result from the clinical trial. In addition to the submissions to the FDA, the
802 sponsor-investigator should consider any responsibilities under Title VIII of FDAAA related to
803 submission of data for applicable clinical trials to the NIH ClinicalTrials.gov data bank.³⁰

804 Responsible parties have a statutory obligation to update clinical trial registration information on
805 ClinicalTrials.gov (42 U.S.C. 282(j)(4)(C)). In addition, for certain applicable clinical trials that
806 have been completed, summary trial results must be submitted (42 U.S.C. 282(j)(3)).

807

³⁰ See note 13, *supra*.

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808 **VIII. WITHDRAWING, TERMINATING, INACTIVATING, OR REACTIVATING AN** 809 **IND (§§ 312.38, 312.44, 312.45)**

810
811 In general, a sponsor-investigator may withdraw an IND at any time (e.g., after the trial has been
812 completed) by notifying the review division. If an IND is withdrawn, all clinical trials conducted
813 under the IND must be ended. If the sponsor-investigator is withdrawing the IND for safety
814 reasons, the FDA and the IRB must be promptly informed.

815
816 Under certain circumstances, the FDA may terminate an IND. If an IND is terminated, the
817 sponsor-investigator must end all clinical investigations conducted under the IND, notify the
818 IRB,³¹ and recall or otherwise provide for the disposition of all unused supplies of the drug. A
819 termination action may be based on deficiencies in the IND or in the conduct of an investigation
820 under an IND. In general, the FDA will only initiate an action to terminate an IND under
821 § 312.44 after first attempting to resolve differences informally or, when appropriate, through the
822 clinical hold procedures described earlier in this guidance.

823
824 A sponsor-investigator can request that an IND be placed on inactive status if no subjects are
825 entered into clinical trials for a period of 2 years or more under an IND, or if all investigations
826 under an IND remain on clinical hold for 1 year or more. The inactive status of an IND has the
827 benefit of relieving the sponsor-investigator from the obligation of submitting annual reports to
828 the FDA.

829
830 In contrast to a withdrawal, the sponsor-investigator can seek to reactivate the inactive IND by
831 submitting a request to reactivate the inactive IND including a protocol amendment containing
832 the proposed general investigational plan for the coming year and appropriate protocols with IRB
833 approval.³² If the protocol amendment relies on information previously submitted, the plan
834 should reference such information. Additional information supporting the proposed
835 investigation, if any, should be submitted in an information amendment. The submitted
836 information will be subject to a new 30-day safety review as described in section VI., The IND
837 Process and Review Procedures. A trial under an IND on inactive status can only proceed 30
838 days after the FDA receives the protocol amendment, unless the FDA notifies the sponsor-
839 investigator that the investigation described in the amendment is subject to a clinical hold, or on
840 earlier notification by the FDA that the clinical investigations described in the protocol
841 amendment may begin.

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843

³¹ See 21 CFR 312.66.

³² See 21 CFR 312.66.

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REFERENCES

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Contact Information

Contact the FDA: <http://www.fda.gov/AboutFDA/ContactFDA/default.htm>

CDER Ombudsman contact information:

<http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/contactcder/cderombudsman/default.htm>

CDER and OND organizational charts:

<http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm347877.htm>

OND contact information:

<http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm184426.htm>

CBER Ombudsman contact information:

<http://www.fda.gov/aboutfda/centersoffices/oc/officeofscientificandmedicalprograms/ucm2005612.htm>

CBER organizational chart and contact information:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/default.htm>

Office of Combination Products:

<http://www.fda.gov/CombinationProducts/default.htm>

CDRH:

<http://www.fda.gov/MedicalDevices/default.htm>

General Information

The IND process and useful links:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>

FDA-approved drugs listed in The Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations: <http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>

Forms 1571, 1572, 3674, and 3500A

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>

Good clinical practice standards related to FDA-regulated clinical trials:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

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- 890 **Guidances for Industry**³³
891
892 Draft guidance for industry *Charging for Investigational Drugs Under an IND — Qs & As*³⁴
893
894 Draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Qs*
895 *& As*³⁵
896
897 Guidance for clinical investigators, sponsors, and IRBs *Investigational New Drug Applications*
898 *(INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*
899
900 Guidance for FDA reviewers and sponsors *Content and Review of Chemistry, Manufacturing,*
901 *and Control (CMC) Information for Human Gene Therapy Investigational New Drug*
902 *Applications (INDs)*
903
904 Guidance for FDA reviewers and sponsors *Content and Review of Chemistry, Manufacturing,*
905 *and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug*
906 *Applications (INDs)*
907
908 Guidance for industry *Botanical Drug Products*
909
910 Guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for*
911 *Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived*
912 *Products*
913
914 Guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*
915
916 Guidance for industry *IND Exemptions for Studies of Lawfully Marketed Drug or Biological*
917 *Products for the Treatment of Cancer*
918
919 Guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and*
920 *Controls Information*
921
922 Guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare*
923 *of Study Subjects*
924
925 Guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*
926
927 Guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products*
928

³³ These guidances can be found on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

³⁴ When final, this guidance will represent the FDA's current thinking on this topic.

³⁵ When final, this guidance will represent the FDA's current thinking on this topic.

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- 929 Guidance for industry *Providing Regulatory Submissions to CBER in Electronic Format —*
930 *Investigational New Drug Applications (INDs)*
931
- 932 Guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE*
933 *Studies*
934
- 935 Guidance for sponsors, industry, researchers, investigators, and Food and Drug Administration
936 staff *Certifications to Accompany Drug, Biological Product, and Device*
937 *Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act,*
938 *Added By Title VIII of The Food and Drug Administration Amendments Act of 2007*
939
- 940 ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*
941
- 942 ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric*
943 *Population*
944