ACRP Regulatory Affairs Committee Review of FDA Draft Guidance

Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators

What is the guidance?
This is guidance for Sponsor-Investigators in order to facilitate in preparing and submitting INDs to CBER and CDER

Who does it impact & how?
This guidance impacts a Sponsor-Investigator, defined as an individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed.

What did ACRP RAC have to say about it?
ACRP's RAC offered extensive comments and requests for FDA to enhance clarity and readability. In brief, the RAC requested that the FDA add more guidance for scenarios that appear to be lacking in this draft document, specifically targeted advice for academic researchers and device submissions. Additionally, the RAC requested guidance and clarification from the Agency on how Sponsor-Investigators can and should proceed when they are unable to cross-reference information from commercial sponsor IND(s) when they exist.

When were the RAC's comments sent to the agency?
July 14, 2015

Where can I access this document?
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm446695.pdf

ACRP
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July 14, 2015

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In reference to docket number: **FDA-2015-D-1484-0001**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the FDA with our comments on the *Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators* Draft Guidance Document as this issue has a significant impact on our membership. The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

We applaud the FDA's efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Terri Hinkley, RN, BScN, MBA, CCRC
Interim Executive Director

FDA-2015-D-1484-0001 :Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators			
Page Number	**Text Line**	**Reference** *(if applicable)*	**Comments**
Overall	Overall	Overall	The sponsor-investigator (SI) IND guidance is MUCH NEEDED and is largely consistent with what we observe in current practice for SI submitted INDs; however, the scope may be slightly too narrow. This guidance could be particularly helpful to academic SIs who are developing new products (but are not thinking about marketing them until they hand them off to a company for further development). Universities (Harvard, Penn, etc) and the National Institutes of Health (NIH) tend to have higher than average rates of Warning Letters and closures for regulatory issues. Clarity is needed for this audience because they are not typical sponsors. For example, this guidance should address off-label drug uses (i.e., for a new indication), and explain exactly what the SI needs to do when they do not have information from the drug manufacturer and they want to do the research with the drug. The concept of requesting a waiver appears to be a new requirement; please provide the regulatory authority for this change and consider introducing this earlier in the document. ACRP would also like to offer the following comment for Agency consideration. Given the FDA is working to harmonize regulatory requirements with OHRP, please consider describing OHRP regulations that may also be applicable here and require the SI to be aware of this larger focus on Human Subject Protections.
1	19-22	Introduction	A helpful addition would be to add guidance for devices (IDE/CDRH). Also include the FDA's Office of GCP as reviewer of this document.
1	29-30	Introduction	The guidance states that it will not discuss all the requirements for completing an IND. This seems contradictory to the title and may be confusing to the reader. Could a listing of steps for submission be added at the end, like a checklist or something similar?
2	38-40	Introduction	The scope is quite narrow and is not really about INDs from Sponsor Investigators. Can the Agency please provide some more guidance regarding products not under an existing IND or currently approved? NOTE: the assumption in this guidance that the SI will be allowed to access the "pre-existing" corporate IND for a different indication may not be true – so then what? Will the FDA also be writing guidance for Sponsor Investigators who are developing a drug for commercialization, expanded access or biologic devices? Several types of

			submissions are footnoted at the bottom of the page but it would be more beneficial to have one larger document covering all types of IND submissions.
2	40-43	Introduction	This sentence is confusing here since an academic SI is not developing the product for marketing (at least not in the initial stages). The guidance should explain what these SI are supposed to do for a "new" drug (since the SI will not be marketing the new drug and another firm may do so at some point in the future). We believe many INDs will be from academic centers where the focus will be on unmarketed new drugs and these should be addressed in this guidance since they may form the largest percentage of the Sponsor-Investigator applications to the FDA. Please consider adding this type of guidance.
3	71-73	Footnote 8	The footnote does not indicate the SI must be an individual and not an entity (as suggested in the text). All of the info about the "subinvestigator" (including the reference to the guidance) should be removed and the appropriate text in footnote 8 should be to paraphrase 21CFR312.3(b) as follows: *"Sponsor-Investigator* means 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. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor." Alternatively, delete the entire sentence from the end of line 72 to 73 and the footnote from the text since the sentence before (lines 71-72) already makes this detail clear.
3	NA	Footnote 9	Consider deleting this footnote since it is entirely unclear and not really consistent with the stated purpose of the guidance to help SI file INDs. The footnote lacks sufficient detail to help those "certain individuals" mentioned in the footnote. As such, this may only add to the confusion. Consider simply stating how the sub-investigators are to be managed by the SI within the text.
4	104-5	Footnote 10	This information is redundant with page 2 lines 43-44 and can be deleted. (NOTE: Footnote 4 and footnote 10 needlessly cover the same info for the same reason).
4	105-113	Background	The sentence starting with "Furthermore, ..." is confusing as currently written. Perhaps this could be more clearly and affirmatively stated. For example, a sentence might be constructed to specifically answer the question: When exactly are the informational sections stated above not needed (or to be provided by someone other than the SI)? Technically, the issue is NOT that the

			information is not "needed," but rather, the information is coming from a source other than the SI (in this example, the FDA assumes the sponsor of the pre-existing IND will allow a cross reference to the info already on file with the FDA or that the needed info is in the "FDA approved labeling")
4	119	Need for IND	Footnote #10 refers the SI to the guidance document that will assist them in determining if the trial needs an IND or not. The FDA also suggests in other guidance documents that a 'pre-IND' meeting with the FDA can be helpful, maybe some similar language can be added here.
4-5	124-132	Cross-ref	The guidance might be improved by making clear statements specifying exactly when an SI is required to seek additional information from the commercial sponsor (or at least giving examples about when this cross reference is needed). In addition, the guidance might be improved by a discussion about what the SI should do when a sponsor declines or simply fails to provide the suggested "cross-ref" information to the SI. Since the language only indicates this "can" be done, one is left to assume this is not required and this nuance should be made clear so the SI will know what to do if they DO NOT secure this type of cross reference. This task can be prohibitive to the conduct of research and should be carefully explained in the guidance to ensure the needed research can occur even when sponsors are not willing to share their data as the FDA might like. Is the FDA saying that they already have the information from the sponsor of the drug being studied and that the SI does not need to get the information (especially if the sponsor does not want to share)? The relationship with the sponsor can be very diverse and more clarity on this point may be helpful (e.g., does the guidance suggest the need for "responsibility matrices" between the SI and the manufacturer (similar to the "Transfer of responsibilities" from sponsors and CROS) to ensure all responsibilities are clear and legally defined.
5	136-137	Cross-ref	NOTE: the SI did not provide the information initially, thus they are technically not providing "that information again" as stated in the sentence - please consider clarifying the sentence.
5	141-144	IB	The statement about the Investigator's brochure (IB) and the implication that an IND without an IB will be "missing" information on Adverse Effects (AE), etc. and be "inadequate" is confusing. If, as stated earlier in the guidance, INDs can be submitted by SIs without IBs, then, this paragraph should be re-worded to clarify what is considered adequate in the case where there is an IB yet the Sponsor-Investigator does not have access to it?

5	146-172	Contact info	This information about the various CDER and CBER review divisions seems out of place here. Can this section be shortened to one sentence (or removed) and the contact info for the FDA be kept in one section at the end of the guidance? The last paragraph (166-170) seems unnecessary and can be discussed elsewhere (e.g. correct phone number in Form 1571; review times and communications in section VI under review procedures).
6	182	Signed 1571	The sentence "A signed ...FDA." is redundant with the sentence above.
6	196-198	1572	The TWO sentences "Before permitting...1572." are confusing. These 2 sentences can probably be deleted and replaced with the simpler statement "The Sponsor-Investigator is required to sign Form FDA 1572 as both the sponsor and the investigator for the IND." The rest of the paragraph appears to cover the appropriate info.
8	264	Footnote 15	Please clarify what happens if the SI does not have an IB? Please clarify if the reference is intended to inform the SI if they decide to have a sub investigator then they need to provide them with an IB (or at least as much of the information as they can gather).
8	280	Footnote 16	The info about significant risk of toxicity needing a "more complete" protocol, does not appear to be supported by the statutes – please provide the regulatory requirement for this footnote or remove it. If this is FDA's way of asking for more information in order to make an informed decision on the IND submissions, then maybe it could be reworded more as an FYI? Also, no reference is provided to the SI to help them determine the phase of their trial. Would it be helpful to have an explanation here or a further reference?
9	330-331	Informed Consent	The statement "Informed consent forms frequently are included with protocols and we encourage their submission" is confusing, it sounds like a consent form may not be needed for the study. This might be misconstrued by the SI. Could this sentence be changed to state that although a consent form is needed for the trial the investigator does not need to submit a version with the IND but it is helpful to do so?
10	360-364	Cross reference	Please clarify what the SI should do if they are not able to secure a letter of cross reference to the commercial sponsor IND. For example, consider introducing the information about the request to waive the requirement for CMC info much earlier in this document.
13	482-489	Cross reference	Please clarify what the SI should do if they are not able to secure a letter of cross reference to the commercial sponsor human experience data.
14	520-528 542-3	Contact the review division	This guidance advises, in many places, a requirement for the SI to contact the review division to discuss areas needing clarification. One example in this section seems particularly onerous related to the use of a device to deliver a drug and the requirement to contact the review division. One option would be to have ONE place in the guidance stating that the SI can (and

			should) call the FDA with questions (e.g. in the reference) rather than stating this same suggestion many times in the document.
14	547-549	Numbering system	Please provide more information about the numbering of the IND. The FDA assigns a number to the IND and then each communication sent by the SI to the FDA needs to be numbered. A couple of different designations are currently used depending on the type of submission, i.e. S001 was a supplemental submission for a protocol update and R001 was for a deviation from the protocol.
15	555-557	Mailing address	Please provide the actual mailing address in the guidance and refer to the web address for any updated address information (with explanation regarding the potential for the address to change).
16	589	Figure 1	The box "Safe to proceed" in the center of the figure should be edited to add "or 30 days has elapsed since submission" to correctly reflect the ability of a SI to start the trial after 30 days. Also, a box "FDA sends a letter to the SI with date of receipt" might be helpful to remind the SI that the 30 days begins with the date of receipt from FDA. Also between "safe to proceed" and "drug may be shipped" should there be "obtain IRB/EC approval?" Also, please clarify if the SI is ok to ship investigational product when a contract and an agreement not to dispense until all hurdles have been met are in place.
18	615-617	Clinical Hold	We suggest that lines 619-620 be moved to the paragraph directly above this.
18	654-656	IND changes	The word "must" in this sentence is confusing since, presumably, no such IND changes would be required if the protocol does not need changes. This sentence should be reworded to state that the SI should make updates to the IND as needed to ensure clinical investigations are conducted according to protocols included in the application. Also, this may be the only place discussing the potential for more than one protocol to exist under the IND.
18	656-658	Essential Information	To assist with understanding the intent of this sentence, could the Agency please provide an example of information that is not provided in a protocol amendment, IND safety report or IND annual report?
18	676-678	New IND	Examples would be helpful here to illustrate when a new IND would be required (this section appears to be a new regulatory requirement that is not clear in the statutes and the appropriate regulation should be cited here to support this requirement).
19	697	Footnote 24	We recommend that the first and last sentences of footnote 24 be removed altogether and the remaining content of footnote 24 be moved to the text of the document. Since this guidance document is for Sponsor-Investigators, the reference to non-Sponsor-Investigator requirements may cause undue confusion.

			Perhaps this can be clarified to explain why a NON SI needs to meet the sponsor responsibilities if they are neither the sponsor nor the SI? Also the last sentence of this footnote seems unnecessary and irrelevant to the topic of the footnote.
19	710	GCP	This "...for a Web site..." information is unclear. Suggest to strike the parenthetical and replace with a footnote linking to the applicable website.
19	712	Footnote 26/27	Simply put the (21CFR50) and (21CFR56) in the text at the spot where the ref occurs. This should make the text more direct, with fewer unnecessary footnotes and a tiny bit shorter.
19	716-722	Monitoring	The "brief summary" referenced in the monitoring section is unclear. What exactly should be included in the "brief summary" to ensure the monitoring will be "adequate," etc? Consider adding a reference to the guidance "Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects" or "Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring".
19	726-727	Charging for Drug	Consider adding more explanation for this topic. Billing issues can be very confusing especially if the investigational product/drug is usually prescribed but is just being used for research.
20	743	Retention of records	What is the guidance for SIs who are not doing marketing applications? The idea of the SI keeping records for 2 years after a *marketing application* is approved is confusing, since the SI may not be conducting the IND with the goal of marketing it.
20	752-756	Serious risks	Why is the sponsor separated out in the parenthetical, can this just be one sentence with the changed language underlined: "The sponsor-investigator must also notify the FDA and all participating investigators in an IND safety report of potential serious risks..." This compound sentence could use some clarification.
21	777	Anniversary Date	Within 60 days of the anniversary date, does this mean 30 days before to 30 days after or is it 60 days before or 60 days after? Suggest re-wording to +/- 30 or +/- 60 days for clarity.
21	796-797	Reporting	Last bullet point, should there be an "if applicable" added to the foreign marketing developments?
21	802	Footnote 30	Consider adding info to text and removing ref 30 since it refers to some prior note and is confusing here. Note 13 simply lists the website for clinicaltrials.gov to seek more info. Can this section be clarified to state specifically which SI are required to post exactly what information on this website as a result of the IND annual report? Providing this information would be helpful.

22	818; 833	Footnote 31/32	Please move these footnotes as references and include them in the text – consider this as one statement, for example, add the sentence to the end of the first paragraph on the page (and remove both footnotes on this page): “As stated in 21CFR312.66, The Sponsor Investigator is responsible to promptly report all changes to the research activities to the IRB.”
24	892; 895	Footnote 34/35	The information in these two footnotes seems unnecessary since the title of the document is a “DRAFT” guidance

Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators

Guidance for Industry

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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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 (CDER) Amalia Himaya at 301-796-0700 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-7800.

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

Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators

Guidance for Industry

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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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Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators Guidance for Industry[1]

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

I. INTRODUCTION

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

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

[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.

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

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

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

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

[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.

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

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, as defined in FDA regulations, does not include any entity other than an individual.[8] As the name suggests, a sponsor-investigator assumes the responsibilities of, and must comply with, FDA regulations applicable to both a sponsor and an investigator. These responsibilities include the submission and maintenance of an IND.[9]

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

- *Sponsor-investigator information*: Information on the qualifications of the sponsor-investigator who intends to conduct the clinical trial. This information allows assessment of whether he or she is qualified to fulfill his or her clinical trial commitments.

- *Investigator's brochure* (required of sponsors, and recommended but not required of sponsor-investigators): A summary of the chemical, toxicological, and pharmacokinetic aspects of an investigational drug including any information on its safety and efficacy obtained from any prior clinical trials, and a description of any anticipated risks, side effects, precautions, and special monitoring.

[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.

- *Clinical trial protocol*: A detailed description of the intended investigation, depending on the drug development phase.

- *Chemistry, manufacturing, and control (CMC) information*: Sufficient information that ensures the proper identification, quality, purity, and strength of the investigational drug.

- *Pharmacology and toxicology information*: A summary of nonclinical (in vitro or animal) data that is intended to support the safety of the proposed clinical trial.

- *Summary of previous human experience*: If applicable, a summary of all clinical trial results intended to support the safety of the proposed clinical trial.

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

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

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

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

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

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

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

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

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

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

IV. CERTAIN INFORMATION REQUIRED FOR AN IND SUBMISSION

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

Form FDA 1571 Investigational New Drug Application

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

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

Form FDA 1572 Statement of Investigator

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

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

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

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

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

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

B. Table of Contents (§ 312.23(a)(2))

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

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

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

The general investigational plan must summarize the rationale supporting the proposed clinical 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*.

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

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

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

E. Protocols (§ 312.23(a)(6))

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

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

[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.

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

- A statement of the objectives and purpose of the trial
- For a sponsor-investigator, the sponsor-investigator's name, address, and statement of qualifications and the name of each subinvestigator (a trial team member such as a research fellow, resident) working under the direct supervision of the investigator; the name and address of the research facilities to be used; and the name and address of the reviewing IRB
- The criteria for subject selection (inclusion criteria), reasons for excluding subjects (exclusion criteria), and an estimate of the number of trial subjects
- A description of the trial design including the type of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, the sponsor-investigators, and analysts
- The method for determining the doses to be administered, the planned maximum dosage, and the duration of individual subject exposure to the investigational drug
- A description of the observations and measurements to be made to fulfill the trial objectives
- A description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the investigational drug in human subjects and to minimize risk

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

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

[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.

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*.

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

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

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

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

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

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

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

- The components and composition of the investigational new drug.

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

The sponsor-investigator should consult with the appropriate FDA review division regarding any additional CMC information that might be warranted to support the proposed clinical trial.

For botanical drugs, as defined in the guidance for industry *Botanical Drug Products*, the sponsor-investigator should refer to the guidance and consult with the FDA for special considerations in requirements of CMC information. For botanical products that are marketed as foods (including dietary supplements), the sponsor-investigator should obtain such information from the manufacturer and provide it in the IND. If information from the manufacturer cannot be obtained, the FDA may consider the specific circumstance (e.g., drug history and clinical settings) and determine the CMC requirements for each individual case.

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

The sponsor-investigator must provide adequate information about the pharmacological and toxicological studies of the investigational drug involving lab animals or in vitro to support the sponsor-investigator's conclusion that it is reasonably safe to conduct the proposed clinical trial. The sponsor-investigator should include a discussion of the rationale for the investigational drug's intended dose, duration, schedule, and route of administration in the proposed trial. This rationale, particularly for phase 1 trials, is best supported by in vitro and available animal data, as described in the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*.

If an FDA-approved drug will be used at the same dose, duration, and route of administration as described in its current labeling, then the sponsor-investigator should include a statement to this effect and include a copy of the current label.

If the drug has not been approved by the FDA, but is being studied under a cross-referenced IND, then the sponsor-investigator should provide a letter of cross-reference authorization to cross-reference the drug's pharmacology and toxicology data.

If the drug is not approved by the FDA but is approved and marketed in a country listed in section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act or is marketed as a food (such as a dietary supplement), additional toxicological information is dependant on the trial (population, dose, duration), the extent of foreign use, current labeling, published information, and any information available from foreign regulatory authorities. The sponsor-investigator should provide any appropriate documentation and/or a summary of this information.

For trials that involve doses, durations, or changes in the routes of administration (e.g., intravenous to oral) that have not been tested or for which inadequate safety information exists,

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

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

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

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

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

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

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

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

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

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

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

- **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)

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

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

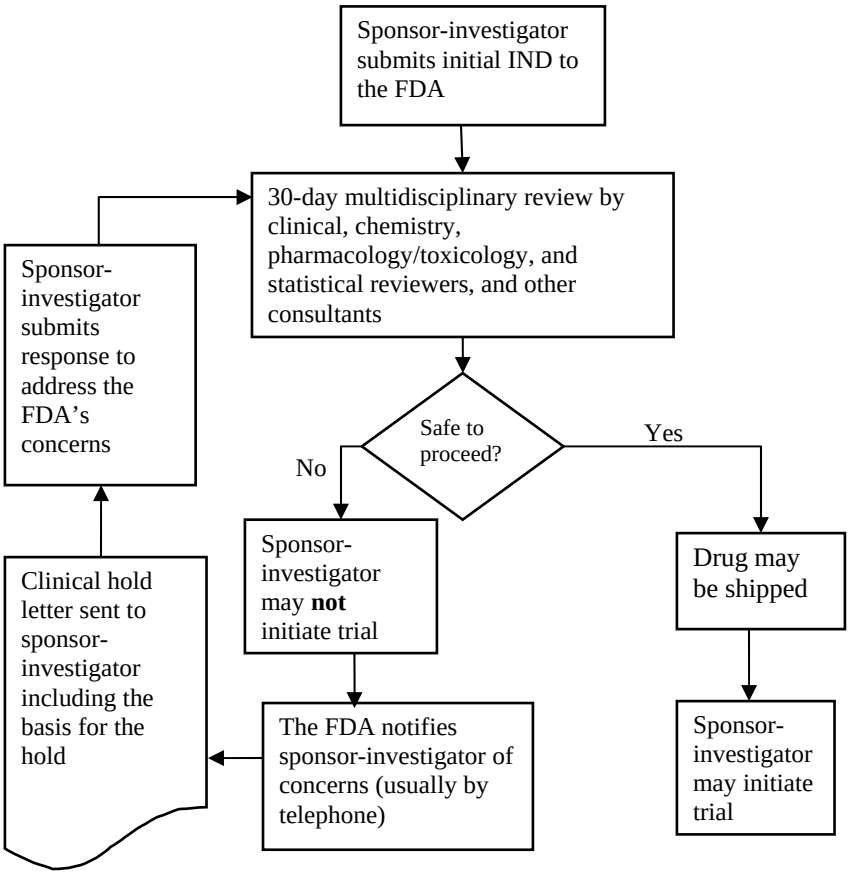
After the FDA receives the IND, an *IND Acknowledgement Letter* will be sent to the sponsor-investigator. The letter includes important information such as the assigned review division, IND number, division contact, and the official FDA date of receipt. The latter is important because by regulation the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

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

[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/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/ucm094309.htm.

Figure 1: The IND Review Process



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

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

- 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

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

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

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

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

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

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

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

[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)).

B. IND Amendments (§§ 312.30, 312.31)

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

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

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

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

C. Import and Export Requirements (§ 312.110)

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

VII. OTHER SPONSOR-INVESTIGATOR RESPONSIBILITIES

Sponsor-investigators conducting trials under an IND must comply with both the sponsor and investigator responsibilities specified in 21 CFR parts 312, 50, and 56.[24] Sponsor-investigators should read these regulations in their entirety and become familiar with all of their responsibilities. Some but not all of the responsibilities discussed in these regulations are summarized below with references to more comprehensive discussions.

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

In general, the sponsor-investigator should conduct trials according to good clinical practice (GCP). GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.[25] GCP includes human subject protection as afforded by adherence to requirements for review and approval of the trial by an IRB and requirements to obtain informed consent from each clinical trial subject (see General Information in the References section for a Web site that contains a summary of these standards). Sponsor-investigators must conduct trials in compliance with FDA regulations about the protection of human subjects[26] and about IRB review and approval of studies.[27]

B. Monitoring Ongoing Investigations (§ 312.50)

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

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[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.

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.

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

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

F. IND Annual Reports (§ 312.33)

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

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

If a trial is completed, the final report should be submitted to the FDA, as should a list of any publications that result from the clinical trial. In addition to the submissions to the FDA, the sponsor-investigator should consider any responsibilities under Title VIII of FDAAA related to submission of data for applicable clinical trials to the NIH ClinicalTrials.gov data bank.[30] Responsible parties have a statutory obligation to update clinical trial registration information on ClinicalTrials.gov (42 U.S.C. 282(j)(4)(C)). In addition, for certain applicable clinical trials that have been completed, summary trial results must be submitted (42 U.S.C. 282(j)(3)).

[30] See note 13, supra.

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

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

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

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

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

[31] See 21 CFR 312.66.

[32] See 21 CFR 312.66.

REFERENCES

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/ucm200612.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

Guidances for Industry[33]

Draft guidance for industry *Charging for Investigational Drugs Under an IND — Qs & As*[34]

Draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Qs & As*[35]

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

Guidance for FDA reviewers and sponsors *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*

Guidance for FDA reviewers and sponsors *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)*

Guidance for industry *Botanical Drug Products*

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

Guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*

Guidance for industry *IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*

Guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*

Guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*

Guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*

Guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products*

[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.

Guidance for industry *Providing Regulatory Submissions to CBER in Electronic Format — Investigational New Drug Applications (INDs)*

Guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies*

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 VIII of The Food and Drug Administration Amendments Act of 2007*

ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*

ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*