
Guidance for Industry and FDA Staff

FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Office of Good Clinical Practice
March 2012**

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**Guidance for Industry and FDA Staff¹
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Not Conducted Under an IND
Frequently Asked Questions**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

On April 28, 2008, the Food and Drug Administration (FDA or Agency) amended its regulations on the acceptance of foreign clinical studies not conducted under an investigational new drug application (IND) ("non-IND foreign clinical studies") as support for an IND or a new drug application (NDA), abbreviated new drug application (ANDA), or a biologics license application (BLA) (collectively known as "marketing applications" or "applications for marketing approval").² The final rule requires that such studies be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC) and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. This final rule, which took effect on October 27, 2008, is codified at 21 CFR 312.120. It is intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies as well as the quality and integrity of the resulting data.

This guidance document is intended to clarify for sponsors and applicants how they can demonstrate compliance with the requirements of 21 CFR 312.120.³ It provides recommendations for the submission of information, whether in an IND or application for marketing approval for a drug or biological drug product,⁴ to demonstrate that a non-IND foreign clinical study was conducted in accordance with GCP.

¹ This guidance has been prepared by the Office of Good Clinical Practice (OGCP) in the Office of the Commissioner (OC) in coordination with the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² 73 Fed. Reg. 22800 (April 28, 2008).

³ This guidance is applicable to all applications submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD& C Act) (21 U.S.C. 355) or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262).

⁴ For the purposes of this guidance, all references to *drugs*, *drug products*, and *drug substances* include both human drug products and biological drug products regulated by CDER and CBER, unless otherwise specified.

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FDA's guidance documents, including this guidance, 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

Clinical research is becoming increasingly global, as detailed in reports by the Office of Inspector General (OIG) of the Department of Health and Human Services (HHS) ("OIG Reports").⁵ FDA recognizes that sponsors may choose to conduct multinational clinical studies under a variety of scenarios. Multinational studies may include domestic sites conducted under an IND, foreign sites conducted under an IND, and/or foreign sites not conducted under an IND.⁶ Sponsors may decide to use the data that is obtained from non-IND foreign sites to support clinical investigations and/or marketing approval(s) in the United States. Some sponsors may even seek to rely solely on foreign clinical data as support for an IND or application for marketing approval in the U.S.⁷ Indeed, the number of INDs and applications for marketing approval supported by foreign clinical trials has increased in recent years and will likely continue to increase in the future.

This increasing globalization of clinical trials presents challenges to both U.S. and foreign regulators, many of which are detailed in the OIG reports. Among other challenges, resource constraints limit the number of foreign clinical site inspections that can be conducted. To address these challenges, FDA has sought to leverage its resources more efficiently by: (1) encouraging sponsors to utilize data standardization in their INDs and applications for marketing approval, in order to improve review and analysis of data and facilitate implementation of a site selection model to prioritize sites for inspection; (2) engaging in collaboration and outreach with international regulatory authorities; and (3) considering alternative mechanisms of clinical trial oversight both by sponsors and FDA, such as a quality management system approach which emphasizes building quality into the research process.

This guidance document is part of FDA's overall efforts to strengthen oversight of foreign clinical trials.⁸ Specifically, FDA is issuing this guidance as part of its efforts to encourage sponsors and applicants to standardize information relating to foreign clinical trials in their INDs and applications for marketing approval (see (1), above). This guidance should help sponsors

⁵ See HHS OIG Report, *Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials* (June 2010), OEI-01-08-00510, available at <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>; HHS OIG Report, *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects* (September 2001), OEI-01-00-00190, available at <http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf>.

⁶ For information on how conducting both IND and non-IND studies affects the requirement for investigators to sign the Form FDA 1572, see FDA's Guidance, *Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)*, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf>.

⁷ Marketing approval of a new drug based solely on foreign clinical data is governed by 21 CFR 314.106.

⁸ See, for example, FDA's HSP/BIMO Modernization Initiative: Update September 2010, at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm226306.htm>.

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and applicants submit information in a consistent and standardized manner to demonstrate compliance with the requirements in 21 CFR 312.120.

Much of the information in this guidance comes from the preamble to the final rule, 73 Fed. Reg. 22800 (April 28, 2008). It is organized in a question and answer format that tracks the regulatory provisions. In addition to addressing the substantive requirements of the final rule, this guidance addresses organization and submission procedures. Specifically, as described in Section III.B, when sponsors or applicants submit information about a non-IND foreign clinical study, they should clearly identify in the cover letter (a) that the material is being submitted in accordance with 21 CFR 312.120, and (b) where in the submission the information required by 21 CFR 312.120(b) can be located.

Although FDA will not accept as support for an IND or application for marketing approval any study that does not meet the conditions of 21 CFR 312.120, FDA will examine the data from such a study because the data may have a bearing on the safe use of the product.⁹ Sponsors and applicants are reminded that they must submit all studies and other information as required under the applicable regulations for drugs,¹⁰ including studies that do not comply with the requirements of 21 CFR 312.120.

III. DISCUSSION

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived.¹¹ When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with the requirements in 21 CFR 312.120 in order to use the study as support for an IND or application for marketing approval. Under 21 CFR 312.120, FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application for marketing approval if the study was conducted in accordance with GCP and if FDA is able to validate the data from the study through an onsite inspection, if necessary.¹² Note that marketing approval of a new drug based solely on foreign clinical data is governed by 21 CFR 314.106.

The GCP requirements at 21 CFR 312.120 help protect human subjects and enhance the quality and integrity of the resulting clinical data.¹³ They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.¹⁴ Many of the requirements at 21 CFR 312.120 are already incorporated into the IND regulations at 21 CFR part 312, as well as 21 CFR parts 50 and 56,¹⁵ and are consistent with certain international ethical and policy standards for clinical trials (e.g., International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) “Good

⁹ 21 CFR 312.120(a)(2); 73 Fed. Reg. at 22807.

¹⁰ See, for example, 21 CFR 314.50, 314.80, 600.80, and 601.2.

¹¹ 21 CFR part 312.

¹² 73 Fed. Reg. at 22801.

¹³ *Ibid.*

¹⁴ 73 Fed. Reg. at 22802.

¹⁵ 73 Fed. Reg. at 22807.

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Clinical Practice: Consolidated Guideline” (ICH E6), which FDA adopted for use as guidance for industry in 1997).¹⁶

A. ACCEPTANCE OF STUDIES (21 CFR 312.120(a))

FDA regulations define GCP as “a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.”¹⁷

GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study.

As defined at 21 CFR 312.3(b), an IEC is “a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation, and is adequately constituted to provide assurance of that protection.” We consider an IEC to be “adequately constituted” if it includes a reasonable number of members with the qualifications and experience to perform the IEC’s functions. One type of IEC is an institutional review board (IRB) as defined in 21 CFR 56.102(g) and subject to the requirements of 21 CFR part 56. Another type of IEC is one that adheres to section 3.2.1 of ICH E6. Compliance with 21 CFR part 56 or ICH E6 is not required, however, for an IEC to be considered “adequately constituted” under 21 CFR 312.120. We have expressly allowed for flexibility in how to meet the requirements of this regulation in recognition that the organization and membership of IECs may differ among countries because of local needs.¹⁸ For more information on IEC membership, see Section III.B.6 of this guidance document, below.

ICH E6 defines informed consent as “a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.”¹⁹ Informed consent is “documented by means of a written, signed, and dated informed consent form.”²⁰ In obtaining and documenting informed consent, an investigator should comply with the applicable regulatory requirement(s) and should adhere to principles of GCP.²¹ Prior to the beginning of the trial, the investigator should obtain the IEC’s written approval of the informed consent form and any additional written information that will be provided to study subjects.²²

¹⁶ ICH E6 and other FDA guidance documents adopted from the ICH are available electronically at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

¹⁷ 21 CFR 312.120(a)(1)(i).

¹⁸ 73 Fed. Reg. at 22805.

¹⁹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>.

²⁰ Ibid.

²¹ Ibid.

²² For additional information concerning the informed consent process, refer to ICH E6, section 4.8.

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B. SUPPORTING INFORMATION (21 CFR 312.120(b))

A sponsor or applicant submitting non-IND foreign data in support of an IND or an application for marketing approval for a drug must include a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP. Because the description is not required to duplicate information already submitted in the IND or the application for marketing approval, the sponsor or applicant may indicate the location of the required information by providing cross-references (and/or hyperlinks) to relevant sections of the IND application, to relevant sections of an application for marketing approval, or to relevant sections of previously submitted materials.

The location of all information required by 21 CFR 312.120 should be clearly delineated in the submission. FDA recommends that the sponsor or applicant clearly indicate the following:

1. whether each clinical study was conducted at both foreign and domestic sites or only foreign sites;
2. whether each foreign site was under an IND or was subject to the requirements of 21 CFR 312.120; and
3. for each clinical study subject to 21 CFR 312.120, where in the submission or in previously submitted materials the following information can be found:
 - a. each of the elements required under 21 CFR 312.120(b) (e.g., “Information showing that the study is adequate and well controlled, 21 CFR 312.120(b)(5) -- See IND Application, Section X.1, pp. y-z”); and
 - b. any waiver requests as applicable under 21 CFR 312.120(c) (e.g., “Waiver request for certain requirements applicable to Study [X] -- see IND Application, Section X.6, pp. y-z”).

Clearly delineating where the required information can be found will facilitate FDA’s review of the IND or marketing application by enabling Agency confirmation of the sponsor’s/applicant’s compliance with the requirements of 21 CFR 312.120.

Within an eCTD format of an application (for marketing approval or an IND), FDA recommends that a sponsor or applicant list the studies subject to the requirements of 21 CFR 312.120 in Section 5.2 of Module 5. The listing can be part of an overall tabular listing or be constructed as an accompanying table and appropriately identified as such. A sponsor or applicant might also use a submission’s cover letter, particularly in the case of an IND, to indicate whether the submission contains studies subject to 21 CFR 312.120. Whether in Module 5 or in a cover letter, the submission should contain page references and/or links to the respective individual full Clinical Study Reports (CSRs) for the identified studies.

Within a CSR of a study, using an ICH E3 format as an example, FDA recommends that a sponsor or applicant identify on the Title Page that the study is being submitted in accordance with 21 CFR 312.120. The Title Page should contain a reference and/or a

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link to a section or an appendix which specifically addresses the sponsor's compliance with 21 CFR 312.120. (In ICH E3 format, such an Appendix would be in addition to the kind of Appendices already listed in the ICH E3 Guidance, e.g. 16.5). FDA further recommends identifying specific foreign non-IND clinical sites using Appendix 16.1.4 ("List and Description of Investigators") in ICH E3 format or a similarly designated section.

The section or appendix specifically intended to address compliance with 21 CFR 312.120 should include a brief statement describing actions the sponsor has taken and should provide supporting information in accordance with all the required elements as listed in the regulations (see below). FDA anticipates that for each such element the sponsor would provide the necessary information or provide reference and/or links to other sections of the study report which contain the information. FDA strongly advises against duplicating information provided elsewhere in the application.

The regulation allows for flexibility in how the requirements are to be met. For example, a full CSR prepared in accordance with ICH E3 "Structure and Content of Clinical Study Reports"²³ may meet many of the requirements under 21 CFR 312.120, but adherence to ICH E3 is not required. The same holds for ICH E6: a sponsor or applicant may choose but is not required to meet many of the requirements of this rule through adherence to ICH E6. Note, however, that even if studies are submitted according to ICH E3 or E6, in some cases it may be necessary to provide additional information to FDA to meet the requirements of 21 CFR 312.120, as well as other applicable requirements in 21 CFR parts 312, 314, or 601.²⁴

Below, we discuss in more detail each of the required elements of 21 CFR 312.120(b) ("Supporting Information"). Although we make reference throughout these answers to relevant portions of ICH E3 and E6, we remind sponsors and applicants that they may choose to meet the requirements of 21 CFR 312.120 through other means. FDA encourages sponsors and applicants to discuss any questions or concerns they may have about the format and content of the required information during pre-submission meetings with FDA (e.g., pre-IND and pre-NDA/BLA meetings).

1. Investigator Qualifications (Section 312.120(b)(1))

What documentation should the sponsor or applicant provide regarding investigator qualifications?

Answer: FDA requires documentation to show that the investigator is qualified to serve as a study investigator based on their training and experience specifically related to the proposed clinical investigation.²⁵

²³ This guidance and other ICH guidance documents are available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm>.

²⁴ 73 Fed. Reg. at 22808.

²⁵ 21 CFR 312.120(b)(1).

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Such documentation generally includes a curriculum vitae or summary of training. If this information is already included as part of the CSR, referencing the appropriate section within the CSR is acceptable. For research involving novel technologies and/or the potential for increased risk of morbidity and/or mortality, the sponsor or applicant may wish to include additional documentation identifying the clinical investigator's specific experience in this field (e.g., as demonstrated by recent presentations or publications) and with the test article.

2. Description of the Research Facilities (Section 312.120(b)(2))

Is the name and address of the research facility a sufficient description to address this requirement?

Answer: No, the name and address of the research facility is generally not a sufficient description to meet the requirement in 21 CFR 312.120(b)(2). Because FDA is generally less likely to be familiar with the research facilities in which foreign non-IND studies are conducted, greater detail is usually needed. For example, it would generally be adequate to identify and briefly describe the academic medical center, hospital, physician's office, clinical research unit or other type of facility at which the research is being conducted. The description should include enough information to enable FDA to determine the adequacy of the facilities to execute the protocol requirements (e.g., whether the site is appropriately staffed and equipped to conduct the proposed research and is able to provide the appropriate emergent or specialized care, if required).

3. Detailed Summary of the Protocol and Study Results and, If Requested, Case Records or Additional Background Data (Section 312.120(b)(3))

- a. *Would a study report "Synopsis" (as shown in ICH E3, Annex I)²⁶ provide a sufficiently detailed summary of the protocol and study results?*

Answer: No, as stated in the preamble to the final rule, submitting only the Synopsis from Annex I of ICH E3 would not be adequate to meet the requirement in 21 CFR 312.120(b)(3), because the Synopsis would not provide sufficient detail about the study protocol or results.²⁷ By contrast, submitting an integrated, full CSR in accordance with ICH E3 would meet this requirement, although alternative approaches are also acceptable.

Integrated, full CSRs are commonly submitted for clinical and human pharmacology investigations that contribute to the evaluation of effectiveness for the proposed indication or that otherwise support

²⁶ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>

²⁷ 73 Fed. Reg. at 22808.

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information included in proposed labeling for the product.²⁸ Sponsors and applicants are reminded that, even if they submit such integrated, full CSRs, they must also submit any additional information that is required by 21 CFR parts 312, 314, or 601.

- b. *Will FDA need access to case records maintained by the investigator or additional background data such as hospital or other institutional records?*

Answer: Yes, FDA may need to review source documents such as hospital records to verify data, whether during an on-site inspection or upon request.²⁹ For example, a review division within FDA may request submission of investigator, hospital, or institutional records outside of an inspectional context. If so, these records must be made available to the Agency for FDA to rely on the data.³⁰ In addition, FDA believes that informed consent documents should notify subjects that international regulatory authorities may need to have direct access to the subjects' original medical records for verification of clinical study procedures and data.³¹ This position is consistent with ICH E6, section 4.8.10(n).³²

If the necessary records are not available, FDA may not accept the study data in support of an IND or application for marketing approval. If the records exist but a sponsor or applicant cannot disclose them to FDA because such disclosure is prohibited by applicable foreign law, the sponsor or applicant may seek a waiver of this requirement, as described below in Section III.C. For FDA to rely on such data that cannot be disclosed, the sponsor and FDA would need to agree on an alternative validation procedure.³³

4. Description of the Drug Substance and Drug Product, Including the Components, Formulation, Specifications, and, If Available, the Bioavailability of the Drug Product (Section 312.120(b)(4))

What information should the sponsor or applicant provide to meet the requirement in 21 CFR 312.120(b)(4)?

Answer: In general, the description of the drug required under 21 CFR 312.120(b)(4) would already be included in other sections of the IND or

²⁸ For more information, see FDA's Guidance, *Submission of Abbreviated Reports and Synopses in Support of Marketing Applications*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072053.pdf>.

²⁹ 21 CFR 312.120(a)(ii) and (b)(3).

³⁰ Ibid.

³¹ Note that the submission of case report forms (CRF) as specified by 21 CFR 314.50 are required for submission of an application for marketing approval.

³² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>

³³ 73 Fed. Reg. at 22808.

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application for marketing approval.³⁴ This requirement can therefore generally be met through cross-references to other sections of the submission.

5. Information Showing that the Effectiveness Study is Adequate and Well Controlled Under 21 CFR 314.126 (Section 312.120(b)(5))

What information should the sponsor or applicant submit to FDA to show that the study is adequate and well controlled under 21 CFR 314.126?

Answer: As an example, integrated, full CSRs in accordance with ICH E3 generally provide appropriate detail to show that the study is adequate and well-controlled as described in 21 CFR 314.126. Note: the sponsor or applicant should also explain how the foreign data are applicable to the U.S. population and U.S. medical practice.³⁵

6. The Name and Address of the IEC that Reviewed the Study and a Statement that the IEC Meets the Definition in 21 CFR 312.3(b) (Section 312.120(b)(6))

a. What does FDA consider an “adequately constituted” IEC?

Answer: FDA regulations at 21 CFR 312.3(b) define an IEC as a “review panel that is responsible for ensuring the protections of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.” FDA believes an “adequately constituted” IEC is one that consists of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed trial. As provided in ICH E6, section 3.2, an IEC includes at least five members, including at least one member whose primary area is in a nonscientific area and at least one member who is independent of the institution where the research will be conducted (i.e., not otherwise affiliated with the institution and not part of the immediate family of a person who is affiliated with the institution). FDA recommends that every nondiscriminatory effort be made to ensure that the IEC composition is not limited to only one gender and that it reflects the social and cultural diversity of the community(ies) from which research participants are most likely to be drawn.³⁶ It is further advised that only those members who are independent of the investigator and the sponsor of the trial vote on trial-related matters.³⁷

³⁴ 21 CFR 312.23, 21 CFR 314.50, 21 CFR 314.94, and 21 CFR 601.2.

³⁵ See 21 CFR 314.106.

³⁶ See 21 CFR 56.107(b).

³⁷ ICH E6, section 3.2.

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FDA recognizes that the organization and membership of IECs may differ among countries because of local needs of the host country. Such variation is acceptable as long as the IEC can assure the protection of the rights, safety, and well-being of human subjects involved in the clinical investigation.

- b. *What information must the sponsor or applicant provide to FDA and what information must the sponsor or applicant maintain with respect to the names and qualifications of all IEC members?*

Answer: The sponsor or applicant is required by 21 CFR 312.120(b)(6) to provide only the name and address of the IEC that reviewed the study and a statement that the IEC meets the definition of an IEC in 21 CFR 312.3(b). However, as provided in 21 CFR 312.120(b)(6), the sponsor or applicant must maintain records supporting the statement, including the names and qualifications (e.g., occupation, training, and experience) of all IEC members, and must make these records available for Agency review upon request. If that is not possible because of governing law relating to privacy concerns, FDA recommends that sponsors and applicants clearly document the attempts made to obtain IEC member names along with an explanation as to why the IEC member names cannot be obtained or disclosed. Such information can then be submitted to FDA in a waiver request, as described below in Section III.C.

7. Summary of the IEC's Decision to Approve or Modify and Approve the Study, or to Provide a Favorable Opinion (Section 312.120(b)(7))

- a. *How much detail should the sponsor or applicant provide regarding the IEC's decisions?*

Answer: In most cases, a brief summary of the IEC actions to approve or modify and approve the clinical investigation would be sufficient. For example, it may suffice to provide FDA with the name of the IEC and a list of IEC actions and dates (e.g., initial approval date, date of approval of modification, etc.), or alternatively to provide FDA with the approval letters from the IEC (including those for protocol amendments). If FDA determines that additional information is necessary to understand the IEC's decisions on the clinical investigation, the Agency will request this information from the sponsor or applicant.

- b. *After submitting this required documentation in the IND/NDA/BLA, is the sponsor required to submit IEC actions on continuing review to FDA?*

Answer: No, although continuing review by the IEC is required under 21 CFR 312.120(a)(1)(i), documentation of such review need not be

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submitted under 21 CFR 312.120(b)(7). However, such continuing review information should be maintained and available to FDA upon request.

8. Description of How Informed Consent Was Obtained (Section 312.120(b)(8))

What level of detail is needed in this description?

Answer: Submitting documentation of the informed consent process detailed in ICH E6, section 4.8, and/or relevant sections of ICH E3 is one acceptable means of meeting the requirement in 21 CFR 312.120(b)(8) to describe how informed consent was obtained.

9. Description of What Incentives, If Any, Were Provided to Subjects to Participate (Section 312.120(b)(9))

What information should sponsors or applicants provide to address this requirement?

Answer: FDA believes that there should be some flexibility in how sponsors or applicants comply with 21 CFR 312.120(b)(9). The sponsor or applicant may follow ICH E6 or ICH E3, providing a sample or model informed consent form that describes any incentives provided (section 4.8.10 of ICH E6 and appendix 16.1.3 of ICH E3), to satisfy 21 CFR 312.120(b)(9). Alternatively, a sponsor or applicant may satisfy this requirement by submitting a brief narrative description of any incentives provided to subjects who participate in the study.³⁸

10. Description of How the Sponsor Monitored the Study and Ensured that the Study Was Carried Out Consistently with the Study Protocol (Section 312.120(b)(10))

What documentation fulfills the requirement for a description of how the sponsor monitored the study and ensured that the study was conducted consistent with the protocol?

Answer: Following ICH E3, section 9.6, is one acceptable way to meet this requirement. The sponsor or applicant should describe the methods used to oversee the conduct of and reporting of data from clinical investigations. The sponsor or applicant should also provide a cross-reference to audit-related information for the investigations, as applicable (e.g., audit certificates).³⁹

³⁸ 73 Fed. Reg. at 22810.

³⁹ 21 CFR 314.50(d)(5)(xi).

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11. Description of How Investigators were Trained to Comply with GCP and to Conduct the Study in Accordance with the Study Protocol, and Written Commitments by Investigators to Comply with GCP and the Protocol (Section 312.120(b)(11))

a. What documentation fulfills this requirement?

Answer: Submitting a statement in accordance with ICH E3, section 9.6 (i.e., whether investigator meetings or other steps were taken to prepare investigators and standardize performance), is one acceptable means of complying with 21 CFR 312.120(b)(11), provided that the description includes how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol.⁴⁰

b. Is a sponsor required by 21 CFR 312.120(b)(11) to obtain signed commitments from investigators to comply with GCP and the protocol?

Answer: No, although FDA encourages sponsors to obtain written commitments from investigators, such commitments may not be required or may even be prohibited in some countries, and FDA does not want to preclude submission of well-designed and ethically conducted foreign clinical studies solely because a written commitment was not obtained.⁴¹ To meet the requirement in 21 CFR 312.120(b)(11), sponsors or applicants must submit a statement indicating whether written commitments by investigators to comply with GCP and the protocol were obtained and, if so, to maintain such commitments on file to be provided upon the Agency's request.⁴² For those sponsors following ICH E3 and E6, these documents would be either submitted with the CSR or kept on file with the sponsor or applicant.

C. WAIVERS (21 CFR 312.120(c))

FDA believes that many sponsors and applicants will be able to comply with 21 CFR 312.120, and therefore will not request waivers, because many foreign clinical investigations are conducted in accordance with GCP principles. For this reason, when publishing the rule, FDA anticipated relatively few waiver requests. Experience to date has confirmed that waiver requests are rare.

Sponsors or applicants may nonetheless ask FDA to waive any applicable requirements under 21 CFR 312.120(a)(1) and (b) by submitting a waiver request

⁴⁰ 73 Fed. Reg. at 22810.

⁴¹ For more on this issue, see FDA's Guidance, *Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)*, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf>.

⁴² 73 Fed. Reg. at 22810-22811.

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under 21 CFR 312.120(c). FDA will decide whether to grant or deny waivers on a case-by-case basis, taking into account all appropriate circumstances.⁴³

FDA anticipates that waivers may be sought, for example, in the following circumstances:

- To allow for acceptance of a non-IND foreign clinical study conducted before the effective date of the revised 21 CFR 312.120 (April 28, 2008). The sponsor or applicant may submit a request for waiver if the study was in compliance with the provisions of 21 CFR 312.120 at the time it was conducted but was out of technical compliance with the terms of the revised 21 CFR 312.120.
- If FDA requests case records maintained by the investigator or additional background data, such as hospital or other institutional records, but these documents cannot be provided as required by 21 CFR 312.120(b)(3) because disclosure is prohibited by governing law. In this case, the sponsor or applicant should document this disclosure prohibition by the foreign entity (e.g., the countries that prohibit such disclosure, the nature of the prohibitions, and the extent to which these prohibitions may impede sponsors in carrying out other obligations requiring record access). The sponsor or applicant can then submit such information in a waiver request to FDA. For FDA to rely on the affected data, the sponsor and FDA would need to agree on an alternative validation procedure.⁴⁴
- If the sponsor or applicant cannot obtain IEC member names as required by 21 CFR 312.120(b)(6), because of governing law relating to privacy concerns. In this instance, FDA recommends that the sponsor or applicant clearly document attempts made to obtain the names along with an explanation as to why the names cannot be obtained. Such information can be submitted to FDA in a waiver request.

1. Required Contents and Submission of a Waiver Request (Section 312.120(c)(1))

a. What are the criteria for a waiver?

Answer: Pursuant to 21 CFR 312.120(c)(1), a waiver request is required to contain at least one of the following:

- (i) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;
- (ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or
- (iii) Other information justifying a waiver.

⁴³ 73 Fed. Reg. at 22811.

⁴⁴ 73 Fed. Reg. at 22808.

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b. When and how should a waiver request be submitted?

Answer: Waiver requests may be submitted as a part of an original IND or application for marketing approval, a supplemental application, or an amendment to an application submitted under 21 CFR Parts 314 and 601.⁴⁵ The affected application should use the waiver section of Module 1 in eCTD format and/or include a cover letter that clearly states that a waiver under 21 CFR 312.120(c) is being requested. The waiver section or the cover letter should identify the affected studies and the relevant sections of the application. If a waiver has already been requested and granted by FDA, the previously submitted materials that include the waiver request should be referenced in the cover letter (or in Module 1).

In addition, FDA recognizes that there may be certain circumstances where, before submitting a waiver request, sponsors may wish to discuss with FDA concerns regarding their ability to meet all of the regulatory requirements under 21 CFR 312.120. Depending on the circumstances, these issues may be discussed with FDA during a pre-IND or pre-NDA/BLA meeting. For example, a sponsor who is considering locating sites in a foreign country where privacy laws would prohibit them from obtaining IEC member names may wish to discuss their concerns during the early stages of planning a study.

c. Should a sponsor or applicant expect a response to a waiver request?

Answer: FDA will notify the sponsor or applicant in writing as to whether the waiver request is granted or denied.

d. What if the sponsor or applicant does not hear back from FDA regarding a waiver request?

Answer: The sponsor or applicant should contact the FDA review division to which the waiver was submitted to inquire about the status of the waiver request. Although specific timelines cannot be provided, the FDA will attempt to respond to waiver requests as quickly as possible. The sponsor or applicant should not assume that no response means that the request for waiver has been granted.

⁴⁵ 21 CFR 312.120(c)(1).

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2. Public Health Implications of Waiver Requests (Section 312.120(c)(2))

Under what circumstances would a waiver be granted?

Answer: FDA may grant a waiver if it finds that doing so would be in the interest of the public health.⁴⁶ The regulation allows the Agency to decide on a case-by-case basis whether to grant or deny a waiver, taking into account all appropriate circumstances.

D. RECORDS (21 CFR 312.120(d))

How long must a sponsor or applicant retain records required under 21 CFR 312.120?

Answer: A sponsor or applicant must retain the required records for a foreign clinical study not conducted under an IND for at least 2 years after an Agency decision on the supporting marketing application or, if the study is submitted in support of an IND but not a marketing application, for 2 years after submission of the IND.⁴⁷

⁴⁶ 21 CFR 312.120(c)(2).

⁴⁷ 21 CFR 312.120(d).