

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

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A. Corbin

**Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is amending its regulations on 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 application for marketing approval for a drug or biological product. The final rule replaces the requirement that these studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki (Declaration) issued by the World Medical Association (WMA), specifically the 1989 version (1989 Declaration), with a requirement that the studies be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC). The final rule updates the standards for the acceptance of foreign clinical studies not conducted under an IND and helps ensure the protection of human subjects and the quality and integrity of data obtained from these studies.

**DATES:** This rule is effective [*insert date 180 days after date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:**

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**I. Background**

In the **Federal Register** of June 10, 2004 (69 FR 32467), we published a proposed rule that would revise our regulations in part 312 (21 CFR part 312) on the conditions under which we will accept non-IND foreign clinical studies

as support for an IND, a new drug application (NDA), or a biologics license application (BLA). As discussed in section III.A of this document, we revised the language used to refer to an application (other than an IND) that may be supported by non-IND foreign clinical studies from “NDA or BLA” or “marketing application” to “application for marketing approval,” which we define as an application under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), to make it clear that the regulation also applies to foreign clinical studies supporting abbreviated new drug applications (ANDAs). Previous § 312.120(a) stated that we generally accepted for review non-IND foreign clinical studies provided they were well designed, well conducted, performed by qualified clinical investigators, and conducted in accordance with ethical principles acceptable to the world community. With respect to such ethical principles, § 312.120(c)(1) stated that for a foreign clinical study not conducted under an IND to be used to support an IND or application for marketing approval, the study must have been conducted in accordance with the ethical principles stated in the 1989 Declaration or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual. Section 312.120(c)(4) set forth the text of the 1989 Declaration.

We proposed to replace the requirement that non-IND foreign clinical studies be conducted in accordance with ethical principles stated in the 1989 Declaration with a requirement that the studies be conducted in accordance with GCP. We proposed to 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 and reported

results are credible and accurate, and that the rights, safety, and well-being of trial subjects are protected. GCP also would include review and approval by an IEC before initiating a study, continuing IEC review of ongoing studies, and obtaining and documenting freely given informed consent of study subjects.

In the preamble to the proposed rule, we provided several reasons for our proposed change in requirements for non-IND foreign clinical studies. First, we noted that standards for protecting human subjects have evolved considerably over the past decade, as evidenced by revisions of the Declaration by the WMA's General Assembly and the issuance of several documents by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). We noted that the ICH document "E6 Good Clinical Practice: Consolidated Guideline" (ICH E6), which we adopted for use as guidance for industry in 1997 (62 FR 25692, May 9, 1997), includes a definition of GCP that shares many important ethical principles with the 1989 Declaration.<sup>1</sup> However, we stated that the concept of GCP in ICH E6 provides more detail and enumeration of specific responsibilities of various parties, including monitoring of the trial and reporting adverse events. Although we did not specifically incorporate ICH E6 into the proposed revision of § 312.120, we stated that the standard of GCP that we proposed for § 312.120 was consistent with that in ICH E6 and was sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical research and obtain informed consent, while helping to ensure adequate and comparable human subject protection.

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<sup>1</sup>ICH E6 and other FDA guidances adopted from the ICH are available electronically at <http://www.fda.gov/cder/guidance/index.htm>.

Another reason we stated for proposing to revise § 312.120 was that the adoption of a GCP requirement for non-IND foreign clinical studies would help provide greater assurance of the quality of the data obtained from these studies. Although the Declaration states that it is unethical to enroll human subjects in poorly designed or conducted clinical trials, it does not provide guidance on how to ensure proper conduct of trials. We proposed the GCP provisions to help ensure data quality and integrity by, among other things, specifying that GCP includes providing assurance that data are credible and accurate and requiring the submission of information on study monitoring and conformance with protocols.

Finally, we stated that deleting the reference in § 312.120 to the Declaration was necessary to eliminate the potential for confusion about the requirements for non-IND foreign clinical studies that could result from potential revisions of the Declaration. We noted that the Declaration is a document that is subject to change independent of FDA authority and, therefore, could be modified to contain provisions that are inconsistent with U.S. laws and regulations. We further noted that although revisions to the Declaration could not supersede U.S. laws and regulations, the changes might be confusing for sponsors.

We received 32 comments on the proposed rule, which we address in section III of this document.

## **II. Overview of the Final Rule, Including Changes to the Proposed Rule**

We are revising our regulations in § 312.120 on the conditions under which we will accept as support for an IND or application for marketing approval (an application under section 505 of the act or section 351 of the PHS Act) a foreign clinical study not conducted under an IND.

### *A. Acceptance of Studies*

Under revised § 312.120(a)(1), we will accept as support for an IND or application for marketing approval a well-designed, well-conducted, non-IND foreign clinical study if it was conducted in accordance with GCP and we are able to validate the data from the study through an onsite inspection, if necessary.

Under § 312.120(a)(1)(i), GCP is defined 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 and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an 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. (An IEC is defined in § 312.3 as 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.) GCP does not require informed consent in life-threatening situations under limited circumstances, as specified in § 312.120(a)(1)(i).

Section 312.120(a)(2) states that although we will not accept as support for an IND or application for marketing approval a study that does not meet the conditions in § 312.120(a)(1), we will examine data from such a study. We will do so because we require the submission of such data under applicable regulations for drugs and biologics (e.g., §§ 314.50, 314.80, 600.80, 601.2 (21

CFR 314.50, 314.80, 600.80, 601.2)) and because the data may have a bearing on the safety of a drug.

### *B. Supporting Information*

The final rule revises the regulations on the information that a sponsor or applicant who wishes to rely on a non-IND foreign clinical study to support an IND or application for marketing approval must submit to us to demonstrate that the study conformed to GCP. In response to comments, we revised § 312.120(b) to make clear that a sponsor or applicant is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the sponsor or applicant may either submit the supporting information listed in § 312.120(b) or provide a cross reference to another section of the submission where the information is located (see comment 21 of this document).

Under § 312.120(b), the sponsor or applicant must submit the information described in paragraphs (b)(1) through (b)(11). In response to comments, we changed the information requirements in § 312.120(b)(6) and (b)(11) of the proposed rule as noted in the following description. Under § 312.120(b), the sponsor or applicant must submit the following information:

- The investigator's qualifications (§ 312.120(b)(1)).
- A description of the research facilities (§ 312.120(b)(2)).
- A detailed summary of the protocol and study results and, if we request, case records or additional background data (§ 312.120(b)(3)).
- A description of the drug substance and drug product, including the components, formulation, specifications, and, if available, the bioavailability of the drug product (§ 312.120(b)(4)).

- Information showing that the study is adequate and well controlled (if the study is intended to support the effectiveness of a drug product) (§ 312.120(b)(5)).

- The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in § 312.3 (records supporting the statement, including the names and qualifications of IEC members, must be maintained by the sponsor or applicant and be available for agency review) (§ 312.120(b)(6)). (The proposed rule would have required submission to FDA of the names and qualifications of the IEC members that reviewed the study (see comment 25 of this document).)

- A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion (§ 312.120(b)(7)).

- A description of how informed consent was obtained (§ 312.120(b)(8)).

- A description of what incentives, if any, were provided to subjects to participate (§ 312.120(b)(9)).

- A description of how the sponsors monitored the study and ensured that the study was consistent with the protocol (§ 312.120(b)(10)).

- A description of how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained (any signed commitments must be maintained and available for agency review) (§ 312.120(b)(11)). (The proposed rule would have required sponsors and applicants to submit copies of any written commitments (see comment 32 of this document).)

### *C. Waivers*

The final rule includes a provision (§ 312.120(c)) under which a sponsor or applicant may request that we waive any requirement in § 312.120(a)(1) or (b).

### *D. Records*

In response to comments, we included in the final rule a provision on record retention requirements. Section 312.120(d) states that a sponsor or applicant must retain the records required by § 312.120 for 2 years after the agency's decision on an application for marketing approval for a drug or, if a study is submitted in support of an IND but not an application for marketing approval, for 2 years after the submission of the IND. The requirement to maintain appropriate records was implicit in the requirement, in proposed § 312.120(a)(1)(ii), that FDA be able to validate the data from a study through an onsite inspection if necessary, and under the proposed rule, the record retention requirements of § 312.57(c) would have applied to non-IND foreign clinical studies. However, we have concluded that it is appropriate to set forth record retention requirements specifically for these studies in § 312.120(d) (see comment 24 of this document).

## **III. Comments on the Proposed Rule**

We received 32 comments on the proposed rule. Comments were received from manufacturers, trade associations, advocacy groups, foreign bioethics organizations, and individual health care providers, researchers, and consumers. Summaries of the comments received and our responses follow:

### *A. Replacement of the Declaration With GCP*

Section 312.120(a)(1)(i) of the proposed rule stated that we would accept as support for an IND or application for marketing approval a well-designed

and well-conducted foreign clinical study not conducted under an IND if the study was conducted in accordance with GCP. The requirement for conducting a study in accordance with GCP would replace the former requirement in § 312.120(c)(1) that such a study be conducted in accordance with the ethical principles stated in the 1989 Declaration or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

At our own initiative, we revised the language used to refer to an application (other than an IND) that may be supported by non-IND foreign clinical studies to “application for marketing approval” instead of “NDA or BLA” or “marketing application.” Under § 312.120(a)(1), we further clarified that an “application for marketing approval” means “an application under section 505 of the act or section 351 of the \* \* \* PHS Act.” Applications for marketing approval under section 505 of the act include both NDAs and ANDAs. The phrase “application for marketing approval” tracks the language used in previous § 312.120. We made these revisions to avoid speculation that this final rule differed in scope from previous § 312.120, which was not our intention.

(Comment 1) Several comments expressed support for adoption of the GCP requirement and deletion of the reference to the Declaration, for the following reasons:

- The proposed changes are appropriate measures to improve public assurance of the quality of the science and ethics supporting data for non-IND studies.
- Relying on GCP reflects the adoption of ICH E6 as a global standard for the conduct of sponsored clinical research.

- The 13 principles of GCP set forth in ICH E6 are very encompassing and are in line with the guidelines used for domestic studies.
- The principles of the Declaration are within GCP and form the basis for the ethical considerations in those guidelines.
- The change from the Declaration to GCP would update the standards for the acceptance of foreign studies and help ensure the quality and integrity of data obtained from such studies.
- Applying GCP standards to foreign studies not conducted under an IND brings logical symmetry with FDA regulation of studies conducted in the United States and ends the need to comply with the strict wording of the Declaration, which lacks the detail needed to describe usefully the intended compliance.
- The proposal to rely on GCP is a more coherent approach to the multitude of complex issues that arise in overseas research than the Declaration provides.

(Response) We agree with the comments stating that the requirement to conduct studies in accordance with GCP will ensure that these foreign studies will be conducted in a manner that is comparable to that required for domestic studies conducted under an IND. We also agree that the principles of the Declaration are reflected in the concept of GCP codified in § 312.120(a)(1)(i). We also agree with the comment that application of the GCP standard will protect human subjects while also enhancing the quality and integrity of data generated in these foreign studies.

(Comment 2) One comment recommended that we give attention to the current development of international standards for the ethical review of clinical studies, including the work done by the Office for Human Research

Protections (OHRP) (of the U.S. Department of Health and Human Services), the European Forum for GCP, the World Health Organization (WHO), and the Strategic Initiative for Developing Capacity in Ethical Review.

(Response) We agree that it is important for us to monitor the development of international standards for the ethical review of clinical studies. However, for purposes of determining whether data from non-IND foreign clinical studies can be used in support of an IND or application for marketing approval under § 312.120, we have concluded that it is appropriate to require that these studies be conducted in accordance with GCP for the reasons stated in section I of this document. Although the international standards noted by the comment are important, they are not legally binding on sponsors and applicants under § 312.120, and incorporating these standards into our regulations would present the same problems as codifying a reference to the Declaration, as explained in our response to comment 4 of this document.

(Comment 3) Several comments opposed the proposal to delete the reference to the Declaration in § 312.120. Several comments stated that the Declaration represents the international standard or paradigm for the ethical conduct of clinical studies and the protection of human subjects. One comment stated that the Declaration is a living document that remains extremely influential and forms the substance of what people understand as the guiding principles of ethical research.

(Response) As stated in the preamble to the proposed rule, we believe that our GCP standard will ensure adequate protection of human subjects while providing the flexibility necessary to accommodate differences in how countries regulate clinical research and obtain informed consent. We acknowledge the prominence of the Declaration among international standards

on the treatment of human subjects in medical research, but other national and international ethical guidelines for research, such as the Belmont Report and guidelines issued by the Council for International Organizations of Medical Sciences, also are important.

The U.S. Government continues to support the Declaration's underlying principles. However, as discussed in our response to comment 7 of this document, the U.S. Government does not fully support the 2000 version of the Declaration because it contains certain statements that may be inconsistent with U.S. law and policy (e.g., concerning use of placebos in clinical trials). We believe that the requirement to conduct non-IND foreign studies in accordance with GCP, which includes a requirement to protect the rights, safety, and well-being of subjects, ensures adequate protection of subjects without a need for reference to the Declaration.

(Comment 4) Four comments stated that our statement in the proposed rule that the Declaration can be modified independent of FDA authority does not provide a basis for deleting the Declaration. These comments stated that we acknowledged that revisions to the Declaration could not supersede U.S. laws and regulations. These comments added that FDA declared in 2001 (in our guidance on "Acceptance of Foreign Clinical Studies") that the reference to the Declaration in FDA regulations was to the 1989 version. One comment stated that the possibility that the 40-year-old Declaration might become inconsistent with U.S. ethics regulations is minimal.

(Response) The comments appear to misunderstand our statements concerning the effect of modification of the Declaration. As we stated in the preamble to the proposed rule, the Declaration was not established under our authority and is subject to change independent of our control. We proposed

to remove from the regulations the 1989 Declaration, which, because it was not the most recent version approved by the WMA, had the potential to cause confusion about the requirements for non-IND foreign clinical studies. The potential for confusion may increase with each subsequent revision of the Declaration. Moreover, initiating a rulemaking to revise § 312.120 each time the Declaration is changed would be burdensome and would not be possible if the changes were inconsistent with U.S. law and policy. For these reasons, the comments' statements regarding modification of the Declaration do not support retaining a reference to the Declaration in § 312.120.

(Comment 5) One comment stated that eliminating the reference to the Declaration would damage international medical ethics and undermine the human rights approach and traditional foundations of research ethics in the Declaration, the Nuremberg Code, and the Universal Declaration of Human Rights. One comment stated that deleting the reference to the Declaration might send a message that FDA no longer supports high standards of ethics in research involving human subjects in foreign countries. One comment stated that the policy of unilaterally deciding not to rely on one of the most respected ethical documents is worrying. One comment stated that dismissing the relevance of the Declaration would encourage every other country to do the same.

(Response) We disagree with these comments. We remain firmly committed to protecting the rights, safety, and well-being of subjects in both foreign and domestic research, and this commitment is reflected in § 312.120, our IND regulations, and our guidance documents, including ICH E6. We do not believe that deleting the reference to the Declaration in § 312.120 will damage international medical ethics or result in harm to research subjects

because sponsors and applicants will need to comply with GCP, which includes protection of human subjects. It is also worth noting that the United States is not alone in declining to adopt the Declaration as the standard to apply. For example, the European Union (EU) recognizes the importance of the Declaration, noting in Directive 2001/20/EC on the implementation of GCP in the conduct of clinical trials that the “accepted basis for the conduct of clinical trials \* \* \* is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration.” Nevertheless, Directive 2001/20/EC does not incorporate the Declaration in the articles of the directive. Similarly, we do not believe that codification of the Declaration in our regulations is needed to ensure that foreign studies used to support U.S. drug applications are conducted in accordance with high ethical standards.

(Comment 6) Several comments stated that they preferred the Declaration over GCP (as described in ICH E6) as a standard for ethical principles. Several comments stated that the Declaration is produced by the WMA, which is comprised of 82 national medical associations, whereas ICH documents are the product of the regulatory authorities and pharmaceutical industries of the United States, the EU, and Japan. One comment stated that the Declaration is independent of any one nation and represents a consensus, albeit sometimes uneasy, between many different parties with many diverse interests. One comment stated that the ethical principles in the 2000 Declaration were produced under an international and democratic process conducted by the WMA. One comment stated that it is improper for FDA to dismiss the views

of the academicians, researchers, and clinicians who comprise the WMA and who have adopted the Declaration provisions.

(Response) Although we appreciate the significance of the Declaration, we do not agree that the manner in which it was adopted makes it the most appropriate standard for the conduct of clinical studies. In fact, our regulations do not require that studies conducted in the United States under an IND be conducted in accordance with the Declaration. Furthermore, although we have not incorporated ICH E6 into our regulations (see comment 9 of this document), we disagree with the comment's characterization of the process for developing ICH guidelines. Twenty-seven countries (the United States, Japan, and the 25 member-states of the EU) participate in the ICH process, and Canada, Switzerland, and the WHO are observers. In addition to input from regulatory authorities and drug manufacturers, there is considerable opportunity for public health organizations, consumers, researchers, academicians, and others to comment publicly on proposed ICH guidelines, both before their adoption at the international level and before they are incorporated into the regulatory framework of individual ICH countries. Finally, by deleting the reference to the Declaration, we are not dismissing the views of WMA members regarding the protection of human subjects. Instead, we simply conclude that it is most appropriate and effective to ensure that studies are properly conducted by requiring compliance with GCP, as defined in § 312.120(a)(1)(i).

(Comment 7) In objecting to the deletion of the reference to the Declaration, several comments cited the United States' objection to paragraphs 29 and 30 of the version of the Declaration adopted in 2000 (paragraphs 29 and 30). Paragraph 29 states: "The benefits, risks, burdens and effectiveness

of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.” Paragraph 30 states: “At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.” Several comments were critical of the United States’ objection to paragraphs 29 and 30 and expressed concern about its impact on research subjects. On the other hand, one comment expressed opposition to paragraphs 29 and 30.

(Response) Compliance with the GCP standard will ensure adequate protection of human subjects in foreign clinical studies while accommodating differences in local authorities’ regulation of these studies. As stated in our response to comment 3 of this document, we cannot endorse the 2000 version of the Declaration. We believe that paragraph 29 is inconsistent with U.S. law and policy because it would impose a standard for the design of clinical trials that is different from the standard of “adequate and well-controlled investigations,” which the act requires us to apply. Paragraph 30 invokes issues of health care policy that are not directly related to FDA’s mission of ensuring that medical products are safe and effective. In addition, we do not believe that this rulemaking is the proper forum for debating or resolving issues concerning particular paragraphs of the Declaration, such as use of placebo controls or continued access to therapy after a study is concluded.

(Comment 8) Several comments stated that deletion of the reference to the Declaration will have an adverse impact on the populations of developing countries, who are vulnerable to abuse, exploitation, and negligence because

of their relative poverty and lack of education. One comment stated that the proposed rule is consistent with FDA's purported purpose of weakening items in the Declaration related to protection of human subjects in developing countries. One comment stated that deletion of the Declaration would imply that FDA believes that non-U.S. study populations do not need access to study results or that non-U.S. populations could be studied and put at risk only to identify medical products that would benefit the U.S. population.

(Response) We do not agree that deleting the reference to the Declaration will have a negative impact on research subjects in developing countries or result in less protection for subjects in foreign studies. Human subject protection is essential to GCP as defined in revised § 312.120, which, among other things, requires the protection of the rights, safety, and well-being of trial subjects, and review and approval of studies by an IEC. We do not believe that referencing the Declaration in our regulations would provide additional protection to the populations of developing countries beyond the protections set forth in revised § 312.120.

(Comment 9) Several comments stated that ICH E6 is concerned primarily with procedural and technical issues, not overarching ethical issues. One comment stated that GCP does not encompass the range of concerns about the protection of human subjects that is provided for in the Declaration. One comment stated that while the Declaration focuses on researchers' ethical conduct and the primacy of patient welfare, ICH E6 focuses on the relations between researchers and pharmaceutical sponsors. One comment stated that ICH E6 is designed to improve data quality but is unconcerned with ethics.

(Response) We disagree with the comments. Most importantly, we note that the definition of GCP contained in § 312.120 is the standard that will apply

to these studies, rather than the procedures set forth in ICH E6. The regulation requires, among other things, that the rights, safety, and well-being of subjects be protected, that an IEC review and approve (or provide a favorable opinion on) each study before initiation, and that subjects give informed consent.

As for ICH E6 itself, protecting the interests of human subjects is one of its two fundamental purposes, along with helping to ensure the quality of data from clinical studies. The first paragraph of the introduction to ICH E6 states that compliance with GCP “provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible” (p. 6). In addition, the first principle of GCP listed in ICH E6 (section 2.1) is that “[c]linical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)” (p. 8). Sections 3.1 and 4.3/4.8 of ICH E6 address the responsibilities of institutional review boards (IRBs)/IECs and investigators, respectively, concerning matters related to the care and treatment of research subjects,<sup>2</sup> including provisions on informed consent and medical care of subjects. Thus, although ICH E6 does address procedural issues, ethical issues are another principal focus of the document.

(Comment 10) Several comments recommended that FDA simply add to the regulations a requirement to comply with GCP rather than delete the reference to the Declaration. One comment stated that it understood the need for data standardization and urged us to add GCP requirements without eliminating the reference to the Declaration. One comment stated that

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<sup>2</sup>ICH E6 at pp. 10–11, 14–15, 17–21.

international studies, as they have been conducted in the past, can comply with both documents. Another comment stated that adherence to both documents would not cause the quality of these foreign studies to suffer. Several comments stated that the GCP guidance does not address conflict of interest or the need to publish results, which are both included in the Declaration. These comments stated that the two documents are complementary and that the regulations could require that affected studies comply with both documents.

(Response) For the reasons stated previously in this document, it is no longer appropriate for § 312.120 to require compliance with the Declaration, either the 1989 version, the current (2000) version, or some other future or past version. Moreover, we believe that because of the requirement in § 312.120 that acceptable foreign studies be conducted in accordance with GCP, which includes ensuring that the rights, safety, and well-being of trial subjects are protected, a specific reference to the Declaration will not enhance protection of human subjects. Nor do we believe that § 312.120 should address conflicts of interest or the need to publish study results. Other FDA regulations address conflicts of interest in these foreign studies (for example, the provisions on financial disclosure by clinical investigators in part 54 (21 CFR part 54) are applicable to studies submitted in support of an NDA, ANDA, or BLA under § 314.50(k), 21 CFR 314.94(a), and § 601.2(a), respectively). With respect to the publication of study results, we note that section 801 of the Food and Drug Administration Amendments Act of 2007 (42 U.S.C. 282(j)(3)) provides for publication in a results data bank of the results of “applicable clinical trials” under certain circumstances. In addition, we strongly encourage sponsors to seek publication in peer-reviewed journals.

*B. Definition of Independent Ethics Committee*

We proposed to add, under § 312.3, a definition for IEC. We proposed to define IEC to mean 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. An IRB, as defined in § 56.102(g) (21 CFR 56.102(g)) of this chapter and subject to the requirements of part 56 (21 CFR part 56), is one type of IEC.

(Comment 11) Several comments stated that the proposed definition of IEC differed from the definition in ICH E6, and requested that we provide clarification of the term “adequately constituted” in the definition of IEC. One comment suggested either defining “adequately constituted” as “if its composition and membership complies with [part] 56, subpart B of this chapter,” or omitting “adequately constituted” from the definition of IEC, making it consistent with the definition in ICH E6. Other comments suggested defining IEC as in section 1.27 or 3.2 of ICH E6.

(Response) The requirement in § 312.3 that the IEC be “adequately constituted” emphasizes the importance of the IEC having appropriate expertise to perform its critical role in the protection of human subjects. As described in the preamble to the proposed rule, we would 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 (see, e.g., section 3.2.1 of the Good Clinical Practice guidance [ICH E6])” (69 FR 32467 at 32468). Such an “adequately constituted” IEC is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. Although the definition of an IEC in ICH E6 does

not include the term “adequately constituted,” ICH E6 defines an IEC as being “constituted of medical/scientific professionals and nonmedical/nonscientific members whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects” (section 1.27). We view our proposed definition of IEC as consistent with the definition of IEC in ICH E6 but at the level of specificity and detail appropriate for regulation. We recognize that the organization and membership of IECs may differ among countries because of the local needs of the host country, but we believe that such variation should not affect an IEC’s ability to perform its functions. Our regulations must be sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical research, including the composition of an IEC. Therefore, we will not specifically define IEC membership in the regulations or require that an IEC comply with the requirements in subpart B of part 56, or with the recommendations for membership in ICH E6. However, we would consider an IEC that is constituted to comply with part 56 or with ICH E6 to be “adequately constituted.” In fact, the definition of IEC in § 312.3 clarifies that an IRB, as defined in § 56.102(g) and subject to the requirements of part 56, is one type of IEC. For these reasons, we decline to omit “adequately constituted” from the definition of IEC in § 312.3.

### *C. Local Laws and Regulations*

(Comment 12) Some comments stated that the proposed rule would delete the provision in former § 312.120(c)(1) requiring that foreign clinical research be conducted according to the laws and regulations of the country in which the research was conducted, when such laws provided for greater protection of human research subjects than the principles of the Declaration. Some comments stated that deleting the reference to compliance with local laws of

the host country supported the notion that FDA could accept data collected in violation of those laws.

(Response) We do not agree that deletion of this provision will lead to FDA accepting studies not conducted in accordance with local laws. Sponsors, IECs, investigators, and research sites and/or institutions are all responsible for complying with the local requirements for conducting research, including any requirements that may be more stringent than the requirements in § 312.120. A host country may deny a sponsor's request to conduct research in the country if the sponsor does not comply with local requirements, or may stop a study that is in progress in violation of the host country's laws. New § 312.120 sets forth U.S. standards for acceptance of foreign clinical studies in support of an IND or application for marketing approval, including that the study be conducted in accordance with GCP. We are confident that these standards provide for the protection of human subjects, and we will accept a study only if these standards are met. In addition, sponsors or applicants that currently conduct clinical trials in accordance with ICH E6 would comply with local requirements because ICH E6 states that one of the principles of GCP is that clinical trials be conducted consistent with the applicable regulatory requirements (i.e., any laws and regulations addressing the conduct of clinical trials of investigational products of the jurisdiction where a trial is conducted).

(Comment 13) One comment stated that although proposed § 312.120 referenced general GCP standards, it did not clarify whether GCP as interpreted by the host country was at all relevant to acceptance of data or whether the ethics committee that must be used was one approved by the host country.

(Response) The host country's interpretation of GCP is relevant to these non-IND foreign clinical studies because the host country requires the sponsor to comply with its laws. However, we will only accept data from studies that we determine were conducted in accordance with GCP as described in § 312.120(a)(1)(i). As to whether the IEC must be approved by the host country, if a host country requires by law that the host country approve the IEC, the sponsor would need to comply with that requirement. However, we will not specifically require in § 312.120 that an adequately constituted IEC be approved by the host country. We do not believe that such approval is essential to ensuring the quality of data or the protection of human subjects. Therefore, this matter is left to the discretion of the host country.

(Comment 14) One comment recommended including a provision in § 312.120 to continue to allow a sponsor to document that the study was conducted in a country where the laws and regulations already provide for strict adherence to the principles of GCP, which would clearly provide for the assurance of protection of human research subjects and quality of clinical data. As support for this approach, the comment stated that clinical trials conducted in Europe must now meet the requirements of the EU Clinical Trials Directive and its implementing guidance for the conduct of clinical trials under GCP.

(Response) We believe that the supporting documentation required under § 312.120(b), combined with an onsite inspection if necessary, will provide us with the ability to determine if a foreign clinical investigation was conducted in accordance with GCP. If the country adheres to the principles of GCP and the study complied with those principles, this should be reflected in the documentation submitted to us. Therefore, it is not necessary to add a provision as suggested by the comment.

*D. Acceptance of Studies*

(Comment 15) One comment stated that the proposed rule should be consistent with FDA's 1998 guidance "FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products" (New Cancer Treatment Guidance). The comment stated that section III.B of the New Cancer Treatment Guidance allows certain data to be submitted to us without additional data collection, auditing, or analyses by a pharmaceutical company submitting a marketing application, depending on the quality and credibility of the institutions providing such data.

(Response) We do not agree that this rule and the New Cancer Treatment Guidance concern the same issues. Although the guidance addresses the submission of certain data without the applicant being subject to auditing, this is applicable only to data from studies conducted by independent cancer clinical trials organizations that have well-established and publicly available procedures for research data management, monitoring, and auditing, and a track record of high-quality research (e.g., U.S. National Cancer Institute-sponsored cooperative cancer research groups and other highly credible organizations that have no commercial interest in study outcomes). The guidance does not address the submission of foreign clinical data and is limited in scope to drugs for treating cancer. We will not accept foreign clinical studies in support of an IND or application for marketing approval except as set forth in § 312.120.

(Comment 16) One comment recommended including the following statement in § 312.120 to reduce the potential regulatory burden: "The information to be provided in support of the IND does not need to be submitted to FDA throughout the study. The supporting information may be provided

at the time the clinical study report is filed to the FDA in support of an NDA and/or made available upon request.”

(Response) We do not agree that including such a statement in § 312.120 is necessary because the submission and reporting requirements are already clear. Information required under § 312.120 to be submitted in support of an IND or application for marketing approval would be submitted at the time the application is submitted to the agency. Once an application is pending before the agency, the applicable reporting requirements for INDs, NDAs, ANDAs, or BLAs under part 312, 314, or 601 (21 CFR parts 314 and 601), apply.

#### *E. Definition of Good Clinical Practice*

For the purposes of § 312.120, we proposed, in § 312.120(a)(1)(i), to 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 and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. We also proposed to require that GCP include oversight by an IEC and obtaining informed consent of subjects.

The final rule clarifies the limited circumstances in which GCP would not require informed consent. The proposed rule stated that GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds that the conditions present are consistent with those described in §§ 50.23 or 50.24(a) (21 CFR 50.23 or 50.24(a)), or when the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects and ensure compliance with applicable regulatory requirements. We explained in the preamble that this provision would be consistent with the GCP guidance, which recommends that a legally authorized

representative provide informed consent or that the requirement of informed consent be waived under such circumstances. In the final rule, we have made more explicit two conditions that were implicit in the proposed rule: The IEC review must occur before initiation of the study and the IEC must find that informed consent is not feasible.

In addition, we deleted the provision referring to the IEC ensuring compliance with applicable regulatory requirements. Upon reconsideration, we recognized that the reference to “applicable regulatory requirements” was not clear. We had not described the requirements we considered to be applicable, and without additional clarity, the phrase did not provide additional protections for subjects in the study. Therefore, we decided that the provision would be clearer without this phrase.

(Comment 17) Several comments requested confirmation that compliance with ICH E6 would be adequate to assure compliance with § 312.120 and questioned whether citing compliance with ICH E6, rather than submitting the supporting documentation required under 312.120(b), would be acceptable. One comment requested that we waive requirements in the proposed rule for any study conducted in EU member states, provided the member can submit a EudraCT (a database of clinical trials in the EU) number, and for any studies that have been conducted in Japan under Japanese Good Clinical Practices. One comment stated that the rule should explicitly require following ICH E6 because imposing a U.S. standard “consistent with” an international standard seemed insufficient. One comment recommended that if § 312.120 does not specifically require following ICH E6, we should acknowledge in the final rule or subsequent guidance that ICH E6 should be taken into account as one GCP

standard that we find acceptable, and describe in what ways the standard set forth in § 312.120 differs from that in ICH E6.

(Response) As noted in the preamble to the proposed rule, we have already incorporated many of the principles of GCP into our existing regulations. However, we have not specifically incorporated all of ICH E6 into our regulations, and we will not do so in § 312.120, for several reasons. First, for one of the same reasons that we deleted the reference to the Declaration from § 312.120, we do not believe that it is appropriate to reference in a regulation a document that is subject to change independent of our control. Second, although we adopted ICH E6 in 1997 for use as guidance for industry, there are other international documents that provide acceptable standards for GCP. Specific incorporation of ICH E6 into § 312.120 would constrain our ability to accept data from non-IND foreign clinical studies from countries that use other comparable GCP standards. Finally, ICH E6 contains a level of detail and specificity that is not appropriate for regulations. We believe that the GCP standard in § 312.120 is appropriate because it provides sufficient flexibility to accommodate differences in how countries regulate the conduct of clinical research, while still ensuring adequate and comparable human subject protection. Therefore, we do not require that sponsors or applicants follow ICH E6, but a study conducted in compliance with ICH E6 would meet the GCP requirements in § 312.120. However, for the agency to evaluate such a study, the information required under § 312.120(b) must be submitted. It would not be adequate to simply submit a statement that ICH E6 or Japanese GCP were followed, or to provide only a EudraCT number.

### *F. IEC Review and Approval*

Proposed § 312.120(a)(1)(i) stated that GCP includes review and approval (or provision of a favorable opinion) by an IEC before initiating a study and continuing review of an ongoing study by an IEC.

(Comment 18) One comment stated that the requirement for review and approval by an IEC does not guarantee protection of the participants unless the guidelines that the IEC must follow are stated explicitly and are not weaker than the Declaration.

(Response) We disagree. Although § 312.120(a)(1)(i) requires review and approval of a clinical study before initiation, the regulation does not specify the procedures that the IEC must follow because different procedures offering equivalent human subject protection may be followed in different countries. As previously stated, we believe that the GCP standards in § 312.120, including the requirement for review and approval by an IEC, are and should be sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical research, while ensuring adequate and comparable human subject protection.

### *G. Onsite Inspection*

Proposed § 312.120(a)(1)(ii) would have required, as a condition of acceptance of a study submitted under this section, that we be able to validate the data from the study through an onsite inspection if we deem it necessary.

(Comment 19) One comment recommended that we give attention to the current development of national and regional (e.g., European Medicines Agency) inspections outside the United States and the role they might play in providing public assurance for the quality of data and the protection of human subjects.

(Response) Although this rule does not address the process for conducting inspections outside the United States, we can review and consider information from inspections by foreign authorities. However, if deemed necessary, we are also able, under § 312.120(a)(1)(ii), to conduct an onsite inspection to validate the data from a study.

#### *H. Data From Studies Not Conducted in Accordance With GCP*

Proposed § 312.120(a)(2) stated that although we will not accept as support for an IND, NDA, or BLA a study that does not meet the conditions of § 312.120(a)(i), we will examine data from such a study.

(Comment 20) One comment requested that we clarify the meaning of proposed § 312.120(a)(2). The comment asked if this provision means that a sponsor should submit studies conducted on the investigational product but differentiate studies that comply for FDA review of safety and efficacy, or that we will review noncompliant studies as supportive.

(Response) The provision states that we “will not accept as support” for an IND or application for marketing approval a study that does not meet the conditions of § 312.120(a)(1) (i.e., a “noncompliant” study). Nonetheless, a sponsor or applicant of an IND or application for marketing approval must submit all studies and other information required under applicable FDA regulations for drugs and biologics, including “noncompliant” studies. We would review information from “noncompliant” studies because they might have bearing on the safe use of the product. In the application, a sponsor or applicant should identify any studies that do not meet the conditions of § 312.120(a)(1).

## *I. Supporting Information*

Proposed § 312.120(b) would have required a sponsor or applicant submitting a non-IND foreign clinical study in support of an IND, NDA, or BLA to submit, in addition to information required elsewhere in parts 312, 314, or 601, supporting information that describes the actions taken to ensure that the research conformed to GCP.

### 1. General Comments

(Comment 21) Some comments stated that certain of the proposed requirements for submission of supporting information in § 312.120(b) are not entirely consistent with guidance provided in other relevant ICH documents. One comment requested that we confirm that conducting a study in accordance with ICH E6 and reporting and submitting the study according to ICH E3 (“Structure and Content of Clinical Study Reports”), ICH M4 (“Common Technical Document for the Registration of Pharmaceuticals for Human Use”), and FDA’s corresponding guidance documents satisfies all the requirements of proposed § 312.120(b). In addition, the comment requested that in cases where the requirements in § 312.120(b) differed from ICH E3 and M4 standards, we consider modifying the requirements, thereby allowing sponsors to submit IND and non-IND studies according to a single standard.

(Response) Conducting a study in accordance with ICH E6 and reporting and submitting the study according to ICH E3, ICH M4, and FDA’s corresponding guidance documents would not satisfy all the requirements of § 312.120(b). The supporting documentation required in § 312.120(b) must describe the actions the sponsor or applicant took to ensure that the research conformed to GCP. This supporting documentation will supplement information required elsewhere in parts 312, 314, or 601. If any of the

supporting information is already included in another section of the IND or application for marketing approval, the sponsor or applicant would not be required to submit this information more than once. We revised § 312.120(b) to clarify that, in submitting the description of the actions taken to ensure that research conformed to GCP, the sponsor or applicant is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the description submitted must provide either the supporting information required in § 312.120(b)(1) through (b)(11) or a cross-reference to another section of the submission where the information is located.

In some cases, it would be necessary to supplement studies submitted according to ICH E3 and M4 with additional information to adequately describe the actions the sponsor or applicant took to ensure that research conformed to GCP. ICH E3 provides advice on structuring and reporting data from a clinical trial, and ICH M4 provides advice on the organization of information in an application. These documents, unlike ICH E6, were not developed to address GCP.

## 2. Investigator Qualifications and Description of Research Facilities

Proposed § 312.120(b)(1) would have required submission of the investigator's qualifications, and proposed § 312.120(b)(2) would have required submission of a description of the research facilities.

(Comment 22) One comment stated that we were imposing an additional regulatory burden by requiring a description of the investigator's qualifications and a description of the research facilities. The comment stated that the information provided should be similar to that currently provided to FDA by sponsors for studies conducted under an IND.

(Response) We do not agree that the rule would impose any additional regulatory burden related to investigator's qualifications and description of research facilities. Section 312.120(b)(1) and (b)(2) of the final rule are unchanged from previous § 312.120(b)(1) and (b)(2), so there is no greater or lesser regulatory burden compared to what was previously required. In addition, we believe that assessment of the qualifications of the investigators and the adequacy of the research facilities are important factors in determining the reliability of the data generated by the study. IND sponsors are required to submit information about investigator qualifications and the name and address of the research facilities (whether domestic or foreign) to be used for each protocol (§ 312.23(a)(6)(iii)(b)). This rule does not require more information about investigator qualifications from sponsors of non-IND foreign studies. However, we generally are less likely to be familiar with the research facilities in which those studies are conducted. Therefore, we believe that it is appropriate to require a description of the research facilities for these studies to help us determine the adequacy of the facilities and to prioritize the need for an onsite inspection.

### 3. Detailed Summary of Protocol and Results of the Study

Proposed § 312.120(b)(3) would have required submission of a detailed summary of the protocol and results of the study. In addition, the sponsor or applicant would have been required to submit case records maintained by the investigator or additional background data, such as hospital records or other institutional records, if requested by FDA.

(Comment 23) One comment recommended that we modify the requirement in proposed § 312.120(b)(3) to allow sponsors to follow ICH E3,

in which annex I, “Synopsis,” provides the template for the detailed summary of the protocol.

(Response) We do not agree that submitting only the Synopsis from annex I of ICH E3 would be adequate to meet the requirements in § 312.120(b)(3) because the synopsis would not provide sufficient detail about the study protocol or results. Therefore, we have not modified the requirement as suggested by the comment. Although following ICH E3 is not required, an integrated, full clinical study report submitted in accordance with ICH E3 would be acceptable for meeting the requirements for providing summaries of the study protocol and results in § 312.120(b)(3). In addition, sponsors and applicants must submit information required elsewhere in parts 312, 314, or 601.

(Comment 24) One comment indicated that the reference to “hospital records” in § 312.120(b)(3) suggests that we could request hospital records instead of a description of medical records maintained by an investigator, which might lead to data privacy concerns. One comment stated that the requirements for recordkeeping by investigators described in ICH E6, which it said were comparable to the requirements for investigator recordkeeping in § 312.62, should be included in the final rule.

(Response) Proposed § 312.120(b)(3) was unchanged from previous § 312.120(b)(3). If we need source documents such as hospital records to verify data, these records must be available during an onsite inspection or provided upon request. If the necessary records are not available, we might not accept the study as support for an IND or application for marketing approval. We believe that informed consent documents should notify subjects that regulatory authorities will have direct access to the subject’s original medical records for

verification of clinical trial procedures and data, which is consistent with ICH E6, section 4.8.10(n). However, if a sponsor or applicant cannot disclose foreign records because it is prohibited by foreign law, the sponsor or applicant and FDA would need to agree upon an alternative validating procedure if the agency is to rely on the data.

With respect to investigator recordkeeping, this rule does not address individual investigator responsibilities, but rather describes the requirements for sponsors or applicants who are submitting non-IND foreign clinical studies in support of an IND or application for marketing approval. Sponsors or applicants are responsible for ensuring that their investigators meet their responsibilities. As originally proposed, the retention requirements in § 312.57(c) for records and reports required under part 312 would have applied to records required under this rule. However, we decided to clarify the record retention requirements applicable to records required under this rule and incorporate the provision directly into § 312.120. Accordingly, we have added the following provision at § 312.120(d): A sponsor or applicant must retain the records required by this section for a foreign clinical study not conducted under an IND as follows: (1) If the study is submitted in support of an application for marketing approval, retain records for 2 years after an agency decision on that application; (2) if the study is submitted in support of an IND but not an application for marketing approval, retain records for 2 years after the submission of the IND. This record retention provision is similar to the requirements set forth in § 312.57(c).

#### 4. Names and Qualifications of IEC Members

Proposed § 312.120(b)(6) would have required submission of the names and qualifications for the members of the IEC that reviewed the study.

(Comment 25) One comment stated that although the requirement to provide names and qualifications of IEC members is in current § 312.120(c)(3), the regulation should allow for situations where it is impossible for a sponsor or clinical investigator to obtain this information. One comment stated that because of privacy concerns, some IECs only provide sponsors with letters to confirm that the constitution of the IEC is in agreement with GCP. The comment stated that ICH E6 requires that the investigator files include the IEC composition to document that the IEC is so constituted, and that this information is available in sponsor files. The comment recommended that as an alternative we consider requiring the name and address of each IEC that approved a study. One comment requested allowing a statement from the IEC that it is properly constituted within the applicable laws that they must follow. Another comment suggested that we change the requirement to “information on the composition (preferably names and qualifications, but at a minimum qualifications) of the IEC that reviewed the study to ensure that the IEC is duly constituted.” Another comment recommended that we only require a statement from the IEC that it is organized and operates according to ICH E6 and the applicable laws and regulations, which the comment stated was consistent with ICH E6, section 5.11.1(b). Two comments stated that the proposed requirement deviated from ICH E3, which includes a list of IECs or IRBs (plus the name of the committee chair, if required by the regulatory authority). The comments recommended that the requirement be revised to be consistent with ICH E3.

(Response) Because oversight by an adequately constituted IEC is an essential component of human subject protection, it is critical that there be adequate documentation of the IEC composition. We believe that submission

of the names and qualifications of the members of the IEC that reviewed the study, as proposed, is one way to document the adequacy of the committee. Nevertheless, in response to concerns raised by some of the comments, we have developed an alternative approach that provides comparable assurance. As revised, § 312.120(b)(6) requires submission of the name and address of the IEC that reviewed the study and a statement that the IEC meets the definition of IEC in § 312.3. Section 312.120(b)(6) also states that the sponsor or applicant must maintain records supporting the statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request. We specify that the retained records must include records of the names and qualifications of IEC members because we do not believe it is possible to verify that an IEC is adequately constituted without knowing about the IEC members. Because sponsors or applicants were already required under previous § 312.120(c)(3) to submit the names and qualifications of IEC members, this change lessens the burden on sponsors and applicants. In addition, sponsors or applicants who comply with ICH E6 would also obtain and retain records on the information required in § 312.120(b)(6) (see sections 3.4 and 5.5.11 of ICH E6).

(Comment 26) One comment recommended that we clarify the type of information that must be provided to document the qualifications of the IEC because it will be difficult to assess meaningfully the true qualifications of IEC members simply by review of their formal professional qualifications. One comment recommended that FDA clarify that “qualifications” means not only formal academic certifications but also evidence that the members of the IEC, individually and as a group, are competent to protect clinical trial participants and ensure that the study is conducted in compliance with GCP. The comment

suggested that the sponsor be required to provide evidence that the IEC members received training in bioethics and the principles of GCP or provide evidence that the IEC was accredited.

(Response) We believe that submitting a statement that the IEC meets the definition in § 312.3 and maintaining the records specified in § 312.120(b)(6) will provide sufficient documentation that the committee is adequately constituted to provide assurance that the rights, safety, and well-being of human subjects are protected. We believe that it is appropriate to allow flexibility in the composition and training of the IEC. If we deem it necessary in a particular case, we will inspect the sponsor's or applicant's records. Therefore, we will not require sponsors and applicants to provide evidence of training or IEC accreditation.

#### 5. Summary of the IEC's Decision

Proposed § 312.120(b)(7) would have required submission of a summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion.

(Comment 27) One comment requested clarification of the requirement to provide "a summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion." The comment asked if it would be acceptable to provide a general statement that the IEC approved the study protocol prior to its conduct, noting any modifications required by the IEC (along with such items as amendments and consent forms). One comment recommended that IEC review and approval should continue to be documented by receipt of the approval letter from the committee. The comment stated that these letters are usually issued in the local language of the country in which the study is conducted and official translations could be provided. If approval

letters are acceptable, the comment requested clarification on whether we would expect approval letters for only the original protocol or for all protocol amendments as well. One comment recommended that the requirement under § 312.120(b)(7) also account for documenting continuing review by the IEC under § 312.120(a)(1)(i).

(Response) We agree that it would be sufficient to provide a brief summary of the IEC's actions to approve or modify and approve the study, prior to the initiation of the study. For example, it would be acceptable to provide the name of the IEC and a list of IEC actions and dates (e.g., initial approval date, date of approval of modification to study (if any)). Alternatively, it would be acceptable to provide approval letter(s) from the IEC, including those for protocol amendments. Although continuing review by the IEC is required under § 312.120(a)(1)(i), documentation of such review does not need to be submitted under § 312.120(b)(7).

## 6. Description of Informed Consent Process

Proposed § 312.120(b)(8) would have required submission of a description of how informed consent was obtained.

(Comment 28) Two comments recommended that we modify the requirement in § 312.120(b)(8) so that it is acceptable to follow ICH E3, section 5.3, which calls for a description of how and when consent was obtained (the representative written information for the research subject (if any), and the sample informed consent are provided in accordance with appendix 16.1.3). One comment stated that the proposed rule requests more stringent supporting information on how informed consent was obtained than what is currently required in part 314 for studies conducted under an IND and submitted in an NDA.

(Response) We do not believe it is necessary to modify the requirement as suggested. The requirement to provide a description of how informed consent was obtained allows for flexibility regarding the manner in which this information can be submitted. For example, ICH E6, section 4.8, provides standards for the informed consent process, including who obtains informed consent, as well as how and when it should be obtained. Submitting documentation of this process would be acceptable to meet the requirement in § 312.120(b)(8). Likewise, it would be acceptable for sponsors or applicants to follow the relevant provisions in ICH E3 to meet the requirements. We do not agree that § 312.120(b)(8) is more stringent than the corresponding requirements in part 314 for studies conducted under an IND. Sponsors conducting studies under an IND would have to meet the requirements in parts 50, 56, and 312, which include detailed requirements for obtaining informed consent.

#### 7. Description of Incentives to Subjects

Proposed § 312.120(b)(9) would have required submission of a description of what incentives, if any, were provided to subjects to participate in the study.

(Comment 29) Two comments recommended that we clarify the requirements of § 312.120(b)(9). One comment stated that it should be acceptable to provide a general statement in the protocol, study report, and sample consent that subjects were reimbursed for their time and travel costs or that subjects were paid for participation. Two comments stated that it should be adequate to follow ICH E3 (appendix 16.1.3), which includes providing a sample or model informed consent form, since it would describe any incentives.

(Response) We believe that there should be some flexibility in how sponsors or applicants comply with § 312.120(b)(9). If the sponsor or applicant follows ICH E6, informed consent would include an explanation of any incentives provided to subjects (section 4.8.10), so a sponsor or applicant could submit a model consent form to meet § 312.120(b)(9). Alternatively, we agree that following ICH E3 and providing a sample or model informed consent form that describes any incentives provided, as specified in appendix 16.1.3 of ICH E3, would be sufficient to satisfy § 312.120(b)(9). A sponsor or applicant could also satisfy § 312.120(b)(9) by submitting a brief description of any incentives provided to subjects to participate in the study.

#### 8. Description of Study Monitoring

Proposed § 312.120(b)(10) would have required submission of a description of how the sponsor monitored the study and ensured that the study was carried out consistent with the study protocol.

(Comment 30) Two comments asked that we modify the requirements to state that it is acceptable to follow ICH E3, section 9.6, Data Quality Assurance, which would mean providing a description of any steps taken at the investigational sites or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data; steps might include training sessions, monitoring of investigators, use of centralized testing, and data audits. One comment recommended that the proposed rule be revised to allow the submission of a general description of what activities were used to ensure the quality of data (e.g., monitoring, investigator training), in keeping with part 314.

(Response) As with the other requirements for submission of supporting information, we believe that there should be some flexibility in how sponsors

or applicants meet the requirements in § 312.120(b)(10). We agree that following ICH E3, section 9.6, would be acceptable to meet these requirements. Alternatively, sponsors or applicants could provide a description of how the study was monitored as specified in ICH E6, section 5.18. Although it is acceptable to follow these sections of ICH E3 or E6 to comply with § 312.120(b)(10), we will not require that they be followed, and a sponsor or applicant might use an alternative approach to comply with this provision.

#### 9. Description of Investigator Training and Signed Written Commitments

Proposed § 312.120(b)(11) would have required submission of a description of how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol. In addition, the sponsor or applicant would have been required to submit copies of written commitments, if any, by investigators to comply with GCP and the protocol.

(Comment 31) Some comments requested that we clarify the requirements in § 312.120(b)(11). One comment asked if submission of a general statement in the study report that investigators were trained at an investigators meeting and/or during site initiation visits would be acceptable. Two comments stated that investigator training was included in ICH E3, section 9.6, and recommended that we modify the requirement so that it is acceptable to reference this section of the clinical study report.

(Response) We agree that 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), would be an acceptable means of complying with § 312.120(b)(11), provided that the description included how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol. As previously stated with

respect to other supporting documentation requirements, a sponsor or applicant might use an alternative approach to meet this requirement.

(Comment 32) Several comments recommended that we eliminate the proposed requirement to submit copies of written commitments, if any, by investigators to comply with GCP and the protocol. Three comments stated that written investigator commitments are usually included on the investigator signature page of the study protocol. Under ICH E3, appendix 16.1.1, a blank copy of this page is provided with the protocol. In addition, ICH E6, section 8.2.2, advises sponsors to archive individual investigators' signature pages in the sponsor's trial master file. The comments stated that to comply with this part of § 312.120(b)(11), it should suffice to submit a description of how the investigator commitment to comply with GCP and the protocol was obtained, and we should eliminate the proposed requirement to submit an individual form for each participating investigator. Two comments requested that the proposed rule be revised to require that the signed investigator agreements be available in the sponsor's files, to be provided to us upon request. One comment stated that there is no need to submit an individual form for each investigator because this information has already been obtained by the sponsor. One comment recommended that we require sponsors to obtain written commitments from investigators to comply with GCP and the study protocol.

(Response) We agree that submitting individual copies of signed investigator agreements is unnecessary. We recognize that, for those sponsors following ICH E3 and E6, these documents would be either submitted with the clinical study report or kept on file with the sponsor. We believe that it would be acceptable to 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. Therefore, we revised § 312.120(b)(11) to require submission of such a statement instead of copies of signed investigator commitments. We believe that evaluation of the statements regarding commitments, combined with the availability of the signed commitments (if any) for our inspection, provides adequate assurance that investigators received GCP training and minimizes the burden on sponsors and the agency. We disagree with the comment that recommended requiring signed investigator commitments. Although we encourage sponsors to obtain written commitments, such commitments may not be required in all countries, and we do not want to preclude submission of ethically conducted foreign clinical studies solely because a written commitment was not obtained.

#### *J. Waivers*

Proposed § 312.120(c) would have permitted sponsors or applicants to request that FDA waive any applicable requirements under § 312.120(a)(1) and (b). Under proposed § 312.120(c)(2), we could have granted a waiver if we found that doing so would be in the interest of the public health.

(Comment 33) One comment stated that proposed § 312.120(c)(2) could be construed as placing the interest of public health ahead of the need to protect trial participants in foreign countries. The comment recommended that we clarify the provision to indicate that a waiver would not be granted if this would compromise the sponsor's obligation to show that trial participants had been protected at all times, even though the waiver might be in the interest of public health.

(Response) In providing for this waiver, we are giving the agency a measure of discretion to avoid inappropriate results. We envision that we

might use this provision to allow us to accept a non-IND foreign clinical study conducted before the effective date of this rule, if the study is in compliance with the provisions of § 312.120 prevailing at the time it was conducted, but out of technical compliance with the terms of this rule. Section 312.120(c)(2) allows us to decide whether to grant or deny waivers on a case-by-case basis, taking into account all appropriate circumstances.

#### **IV. Implementation**

The proposed effective date would have applied the rule, when final, to foreign clinical studies for which the first subject is enrolled 180 days after the date of publication of the final rule. As proposed, a clinical trial that is currently ongoing, which might not be completed and for which the results might not be submitted to FDA (in an IND or application for marketing approval) for several years, would be submitted under previous § 312.120.

We have determined that it is appropriate to make the rule effective 180 days after the date of publication in the **Federal Register** and applicable to foreign clinical studies regardless of the status of subject enrollment (e.g., ongoing, completed, not yet initiated). We have made this change to decrease the potential for confusion about which version of § 312.120 (new or previous) is applicable to ongoing clinical studies. We do not believe that this change will affect the ability of most sponsors or applicants to comply with § 312.120 because most foreign clinical trials are currently being conducted in accordance with GCP principles. If necessary, we can use the waiver provision under § 312.120(c) to accept studies initiated before the effective date of the rule if doing so would be in the interest of the public health.

#### **V. Legal Authority**

We are issuing this rule under the authority of the provisions of the act that apply to drugs (section 201 *et seq.* (21 U.S.C. 321 *et seq.*)) and section

351 of the PHS Act. These laws authorize the agency<sup>3</sup> to issue regulations to ensure the following: (1) Data that we review are of adequate quality to enable us to make appropriate regulatory decisions; (2) clinical investigators involved in developing data submitted to us are qualified to conduct such clinical investigations and are otherwise reliable; and (3) clinical investigations generating data submitted in support of applications are well designed and well conducted in a manner supporting the reliability of study results.

Section 505 of the act requires us to weigh evidence of effectiveness and safety to determine whether the evidence supports drug approval, whether data are adequate to permit a clinical investigation to proceed under the IND regulations, and/or whether a product is appropriately labeled, and to weigh evidence of bioequivalence for generic drug approvals. Section 505(d) of the act provides that we may approve an NDA only after finding substantial evidence “consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

When we review INDs, section 505(i) of the act requires us to determine whether the reports submitted in support of an application are “adequate to justify the proposed clinical testing” and whether the sponsor has submitted

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<sup>3</sup>In light of section 903(d) of the act (21 U.S.C. 393(d)) and the Secretary of Health and Human Services’ (the Secretary’s) delegations to the Commissioner of Food and Drugs, statutory references to “the Secretary” in the discussion of legal authority have been changed to “FDA” or the “agency.”

“adequate reports of basic information \* \* \* necessary to assess the safety of the drug for use in clinical investigation.”

The act also requires us to determine whether adequate and reliable studies are sufficient to support a drug’s labeling. Under section 505(d)(5), evidence from clinical investigations of a drug’s safety and effectiveness must support the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Section 505(j)(2)(A)(iv) of the act further requires us to assess information submitted in an ANDA demonstrating, among other things, that the ANDA drug is either bioequivalent to an already approved new drug which is the subject of an approved NDA, or can be expected to have the same therapeutic effect as such a drug, as determined by a petition submitted under section 505(j)(2)(C) of the act.

Section 701(a) of the act (21 U.S.C. 371(a)) authorizes the agency to issue regulations for the efficient enforcement of the act.

Section 351(a)(2)(C)(i)(I) of the PHS Act authorizes the agency to approve a BLA only if the applicant demonstrates that the product is safe, pure, and potent. Section 351(a)(2)(A) of the PHS Act authorizes the agency to establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.

These statutory provisions authorize us to issue regulations describing when we may consider foreign clinical studies not conducted under the IND regulations as reliable evidence supporting an IND or application for marketing approval.

## **VI. Paperwork Reduction Act of 1995**

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the

Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting and recordkeeping burden. The estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

*Title:* Foreign Clinical Studies Not Conducted Under an IND

*Description:* Previous § 312.120 stated that we generally accept foreign clinical studies not conducted under an IND provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles. It further stated that such studies must be conducted in accordance with the 1989 Declaration or the laws of the country in which the research is conducted, whichever provides greater protection to subjects.

The final rule replaces the requirement that non-IND foreign studies be conducted in accordance with the 1989 Declaration with a requirement to conduct such studies in accordance with GCP, including review and approval by an IEC. We are making this change for the following reasons: (1) We want to provide greater assurance of the quality of data obtained from non-IND foreign studies; (2) standards for protecting human subjects have evolved considerably over the past decade and include the adoption of GCP; and (3) we want to eliminate the reference to the Declaration because that document is subject to change, independent of FDA authority, in a manner that might be inconsistent with U.S. laws and regulations, and referring to a superseded

version of the Declaration could create the potential for confusion about the requirements for non-IND foreign studies.

Under revised § 312.120(a), we will accept as support for an IND or application for marketing approval a well-designed and well-conducted foreign clinical study not conducted under an IND if the study is conducted in accordance with GCP and we are able to validate the data from the study through an onsite inspection if necessary. GCP includes review and approval by an 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 before initiating a study.

Previous § 312.120(b) required a sponsor of a non-IND foreign study who wanted to rely on that study as support for an IND or application for marketing approval to provide certain data to FDA. Revised § 312.120(b) requires this same information as well as the following: (1) The name and address of the IEC and a summary of its decision to approve, or modify and approve, the study; (2) a description of how informed consent was obtained and what incentives, if any, were provided to subjects to participate in the study; (3) a description of how the sponsor monitored the trial and ensured that it was carried out consistently with the study protocol; and (4) a description of how investigators were trained to comply with GCP and to conduct the trial in accordance with the protocol, as well as a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained.

Revised § 312.120(c) specifies how sponsors or applicants can request a waiver for any of the requirements under § 312.120(a)(1) and (b). By permitting a waiver of certain requirements, this provision is not likely to increase the

burden on a sponsor or applicant. Under revised § 312.120(c)(1), a waiver request must contain at least one of the following: (1) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved; (2) a description of an alternative submission or course of action that satisfies the purpose of the requirement; or (3) other information justifying a waiver. Under revised § 312.120(c)(2), FDA may grant a waiver if doing so would be in the interest of the public health.

*Description of Respondents:* Businesses.

*Burden Estimate:* Table 1 of this document provides an estimate of the annual reporting burden associated with the rule:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN<sup>1</sup>

21 CFR Section	No. of Respondents	Frequency of Responses	Total Annual Responses	Hours per Response	Total Hours
312.120	115	5	575	32	18,400
Total					18,400

<sup>1</sup>There are no capital costs or operating and maintenance costs associated with this collection of information.

We estimate that, each year, 115 companies submit a total of approximately 575 non-IND foreign clinical studies in support of an IND or application for marketing approval for a drug or biological product. We conducted consultations with seven large and small companies that had submitted non-IND foreign clinical studies to us during 1998 through 2001. All respondents indicated that they currently conduct non-IND foreign clinical studies in conformance with GCP and generally document all the items listed in revised § 312.120(b). Sponsors often plan to obtain marketing approval in more than one country and often conduct studies with the intention to submit data for review in multiple countries that may require compliance with GCP. Companies previously were required (under previous § 312.120(b)(1) through (b)(5) and (c)(3)) to document the items in revised § 312.120(b)(1) through (b)(7) as well as to document how the research conformed to the ethical principles

contained in the 1989 Declaration or the foreign country's standards, whichever represented the greater protection of the individual (previous § 312.120(c)(2)).

Hour burden estimates will vary due to differences in size, complexity, and duration across studies, because each of these factors affects the amount and intricacy of data collected. For example, the applicant of a study that involves five research sites, each with its own IEC, must submit documentation of review by all five committees. However, if the same study is performed with one IEC overseeing all five sites, the hour burden estimate would be less.

As previously stated in this document, the general position among the sponsors that we interviewed was that documenting their compliance with GCP would take between 18 and 32 hours annually for each non-IND foreign clinical trial. To provide a liberal estimate of costs to industry, we assumed that no companies currently document compliance with any component of GCP and that the documentation required under revised § 312.120(b) would require 32 hours to complete for each study submitted for a total of 18,400 annual burden hours (575 x 32 hours).

In addition to the reporting requirements set forth in table 1 of this document, the final rule includes a provision, § 312.120(d), stating how long sponsors and applicants must retain records required by § 312.120. Under the proposed rule, the retention requirements in § 312.57(c), for records and reports required under part 312, would have applied to these records. However, we decided to clarify the recordkeeping requirements applicable to records required under this rule by establishing § 312.120(d). Under § 312.120(d), if a study is submitted in support of an application for marketing approval, records must be retained for 2 years after an agency decision on that

application; if a study is submitted in support of an IND but not an application for marketing approval, records must be retained for 2 years after the submission of the IND. The recordkeeping requirements for studies under part 312 are approved under OMB control number 0910–0014 until May 31, 2009.

In compliance with the PRA (44 U.S.C. 3507(d)), we submitted a copy of this rule to OMB for its review and approval of these information collections.

The reporting requirements of this final rule have been approved under OMB control number 0910–0622. This approval expires on April 11, 2011. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the information collection displays a currently valid OMB control number.

## **VII. Environmental Impact**

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## **VIII. Federalism**

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the final rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## IX. Analysis of Economic Impacts

We have examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is not an economically significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of the rule on small entities. Because the estimated impact of the final rule is not substantial and, in any event, clinical investigators generally follow GCP already, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is approximately \$127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product.

We do not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

### *A. Objectives of the Final Rule*

The objectives of the final rule are to ensure the quality and integrity of foreign clinical data supporting FDA decisionmaking on product applications and to help ensure the protection of human subjects participating in foreign clinical studies. High-quality data from foreign studies may be critical to our decisionmaking on applications and product labeling. By increasing our knowledge of a drug, including its effect in more diverse study populations, such data will help us better perform these review functions.

By incorporating the monitoring and reporting responsibilities under GCP, the final rule also will reduce the risk to subjects who take part in foreign clinical trials of investigational drug and biological products. Most investigations of new therapeutic products carry potential risks for trial subjects due to the investigational nature of the products. However, if trials are well designed and carefully monitored, these risks can be minimized.

### *B. Background on Current Situation Regarding Foreign Studies*

The current process for marketing a new drug product or amending the conditions of use of an existing product requires us to review and approve the results of clinical investigations included in applications for marketing approval. These applications contain the results of clinical investigations that characterize the therapeutic benefit of the new product and assess its risks. We review the submitted data and decide whether there is sufficient evidence of safety and effectiveness to grant approval.

Clinical data included in an application for marketing approval usually are collected under an IND, for which protocols of the proposed clinical investigations are submitted for review. An IND is needed to lawfully administer an unapproved pharmaceutical or biological product to humans in

the United States. However, not all clinical trials used to support an application for marketing approval take place in the United States. For a variety of reasons (e.g., foreign developer or manufacturer), there has been an increase in the number of foreign clinical investigations of potential new drug products. According to an analysis by the Department of Health and Human Services' Office of the Inspector General (OIG) (Ref. 1), the number of foreign clinical investigators that conducted drug research under INDs increased from 41 in 1980 to 271 in 1990 and 4,458 in 1999. Although trials not conducted in the United States are not required to be conducted under an IND, many sponsors submit an IND before initiating a foreign trial. However, we have always required and reviewed the safety results of non-IND foreign clinical trials of drug products considered for marketing approval in the United States.

According to estimates from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), approximately 650 clinical investigations of investigational products intended for commercial marketing were initiated each year from 1995 through 1999. In addition, commercial sponsors submitted approximately 2,600 new protocols each year for new clinical trials under existing INDs. Therefore, in a typical recent year, we received approximately 3,250 new investigations (initial INDs and new protocols combined) for commercial development of new therapies.

A CDER study of the INDs submitted to support development of new molecular entities (NMEs) approved between 1995 and 1999 found that up to 35 percent of the trials that were conducted under an IND included foreign sites. Thus, in an average year, we estimate that approximately 1,140 foreign clinical trials ( $3,250 \times 0.35$ ) are conducted under IND review and oversight.

However, this estimate does not include foreign clinical trials that were not subject to IND review. The CDER analysis indicates that as many as 15 percent of the trials submitted in NME marketing applications were not conducted under an IND. If this proportion holds with respect to all clinical trials, we estimate that approximately 3,825 clinical trials are conducted annually to develop data for submission to FDA in support of an application for marketing approval (assuming the 3,250 clinical trials conducted annually under an IND constitute only 85 percent of all trials conducted to develop data for such an application). We can then estimate that 575 non-IND foreign trials are conducted annually for eventual submission to FDA as part of an IND or application for marketing approval ( $3,825 - 3,250 = 575$ ).

We also estimated the number of applications supported by data from foreign trials not conducted under an IND. According to CDER data, each application for marketing approval may cite an average of approximately five investigations that provide important information relative to approval decisions. Lacking data on INDs supported by data from non-IND foreign trials, we will assume the same ratio of investigations to applications is true. Based on these estimates, we estimate that the 575 foreign trials conducted annually are used to support 115 INDs or applications for marketing approval.

### *C. The Final Rule*

Under the final rule, all non-IND foreign clinical studies submitted as support for an IND or application for marketing approval must be conducted under GCP as defined in the rule. Under previous § 312.120, we accepted as support for an IND or application for marketing approval foreign clinical studies not conducted under an IND provided they were well designed, well conducted, performed by qualified investigators, and conducted in accordance

with ethical principles. Sponsors of non-IND investigations used in support of INDs or applications for marketing approval were required to follow either the principles of the 1989 Declaration for patient protection or national laws that provide even greater protection. The final rule is expected to provide greater assurance that such clinical investigations will provide results that are of satisfactory quality while ensuring that the investigations are conducted with subjects' informed consent and do not place subjects unduly at risk. We believe that this change is necessary to ensure that foreign clinical investigations that are intended to be used as support for an IND or U.S. application for marketing approval are well designed and well conducted and provide sufficient protection to subjects. Consequently, under the final rule, we will not accept any non-IND foreign clinical results as support for sponsor claims of efficacy unless the trials are conducted in conformance with GCP. The results of all clinical trials must in any case be submitted with new product applications to evaluate the safety of the new therapy.

#### *D. Costs of the Final Rule*

We interviewed seven pharmaceutical manufacturers that had submitted results from non-IND foreign clinical studies to us during 1998 through 2001. These firms indicated that they currently conduct all research, including investigations not conducted under an IND, in accordance with ICH standards for GCP. However, the final rule requires that an applicant submit a description of the actions taken to ensure that the research conformed to GCP. Several items included in GCP (as defined in the final rule) are not specifically required to be documented and submitted in an application for marketing approval for results to be accepted by FDA. In particular, documentation that includes attestations by investigators and evidence that study protocols have

been reviewed and approved by an IEC is not always included in INDs and applications for marketing approval. For studies under an IND, there are specific regulatory requirements for obtaining informed consent, ensuring IRB review, and carrying out appropriate monitoring. The absence of these requirements for non-IND studies makes it difficult for us to determine the adequacy of pre-initiation review of study protocols. The final rule will help ensure that these documents are available for our inspection at research sites and that information on IEC review is included in INDs and applications for marketing approval.

The amount and detail of the necessary documentation will vary according to the size and complexity of the proposed clinical trial. The general position among the seven sponsors we interviewed was that providing a description of their compliance with GCP, including related documentation and recordkeeping, would take between 18 and 32 additional hours for each non-IND clinical trial.

We obtained information on typical nonproduction, salaried labor costs for the pharmaceutical industry from the Bureau of Labor Statistics (North American Industrial Classification System (NAICS) 325412). Including wages and benefits, the average cost for these labor resources is slightly more than \$30 per hour. As noted previously in this document, we estimate that approximately 575 non-IND foreign commercial clinical trials are conducted annually. Using the high estimate of the additional hours of documentation needed for each non-IND clinical trial, this would result in a total annual cost of about \$552,000 to the sponsoring firms (32 hours x 575 non-IND foreign trials x \$30 = \$552,000).

### *E. Benefits of the Final Rule*

We believe that improvement in the conduct of clinical trials will improve the quality of clinical data submitted, allowing these data to provide support for applications for marketing approval. We further believe that the final rule will decrease the possibility that subjects in foreign clinical trials will be placed unnecessarily at risk.

We have not quantified the benefit of improvements in the data being included with applications for marketing approval resulting from the use of GCP in lieu of previous requirements. However, if these data were determined to be adequate to support an application, beneficial therapies could become available earlier. Similarly, we expect that the greater integrity of data from non-IND studies will result in an additional benefit, also difficult to quantify, due to better quality data about the safety and effectiveness of products and greater public confidence in the scientific basis for FDA decisions.

### *F. Small Business Impact*

The final rule is not expected to have a significant impact on a substantial number of small entities. Nevertheless, we have prepared a voluntary regulatory flexibility analysis.

#### 1. Nature of the Impact

As discussed previously in this document, we estimate that the final rule will increase total costs to sponsors of foreign clinical studies by approximately \$552,000 per year. The increased costs will be due to greater costs of review and documentation of the approval of study protocols by IECs. The resources needed to comply with this rule are not specialized. Assuming, for purposes of this calculation, that each of the approximately 115 INDs or applications for marketing approval submitted annually (in which are reported

approximately 575 non-IND foreign clinical studies) is submitted by a different sponsor, each sponsor would incur costs of approximately \$4,800 per year to comply with the final rule ( $\$552,000 \div 115 = \$4,800$ ).

## 2. The Affected Industry

The Census of Manufacturers defines the pharmaceutical preparations industry in NAICS 325412. This industry consists of 712 companies and 837 establishments. Average revenues per company are over \$100 million annually.

However, the Small Business Administration has defined any entity with 750 or fewer employees as a small entity. According to the Census of Manufacturers, approximately 95 percent of the industry establishments would meet this criterion. With the industry-wide average of approximately 1.2 establishments per company, it is likely that at least 90 percent of the companies would be considered small entities.

On the other hand, the proportion of sponsors that submit original applications for marketing approval is markedly different from the general industry. We examined the characteristics of sponsors of new drug product applications for marketing approval between October 1996 and October 1999 (Ref. 2). Of the 158 firms that had sponsored applications for marketing approval during that period, 56 (or about 33 percent) were considered domestic small entities (750 or fewer employees). The remaining firms were either foreign sponsors or large innovating enterprises. The 56 small firms submitted a total of 76 NDAs during that period, which is about 1.5 applications each over a 3-year period (or 0.5 annually per small entity).

The 76 NDAs submitted by small domestic entities represented about 20 percent of all applications. Using this proportion, we estimate that 20 percent of the 575 annual non-IND foreign clinical trials to develop data for submission

in an FDA application for marketing approval (approximately 115 studies) could be sponsored by small entities. If these trials were distributed equally among each sponsoring small entity, each sponsor would be expected to conduct two non-IND clinical trials per year. If so, the compliance costs would equal about \$9,600 annually per small entity ( $\$4,800 \times 2 = \$9,600$ ).

The Census of Manufacturers also reports that a sizable proportion of the industry has an annual value of shipments of approximately \$1 million. For example, a reported 494 of the 837 establishments had total shipments of approximately \$480 million during 1997. The expected cost of \$9,600 per small firm would not represent a significant impact.

### 3. Alternatives to the Final Rule

We considered several alternatives to the final rule. We rejected leaving § 312.120 unchanged because it would not meet the objectives of enhancing standards for study conduct and ensuring data integrity. We rejected other regulatory options to increase our oversight of foreign clinical investigations because they would be either too costly or unenforceable. We considered changing the inspection strategy for foreign clinical trials, but this option would not ensure GCP compliance, a process that makes all parties to a study responsible for patient safety and study quality. We considered but rejected allowing an exemption from the requirements in the final rule for small entities. We must have confidence that all clinical investigations submitted as support for an IND or application for marketing approval meet basic standards of reliability, patient safety, and data quality.

### 4. Outreach

We received 32 comments on the proposed rule. There were no comments on the “Analysis of Impacts” discussion.

## 5. Conclusion

For the reasons stated previously, we conclude that the final rule will not result in a significant impact on a substantial number of small entities.

### *G. References*

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Department of Health and Human Services, Office of the Inspector General, "The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects," OEI-01-00-00190, September 2001.

2. FDA, "Who Submits NDAs and ANDAs," unpublished document, October 1999.

### **List of Subjects in 21 CFR Part 312**

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 312 is amended as follows:

### **PART 312—INVESTIGATIONAL NEW DRUG APPLICATION**

■ 1. The authority citation for 21 CFR part 312 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 371, 381, 382, 383, 393; 42 U.S.C. 262.

- 2. Section 312.3 is amended in paragraph (b) by alphabetically adding a definition for “Independent ethics committee” to read as follows:

**§ 312.3 Definitions and interpretations.**

\* \* \* \* \*

(b) \* \* \*

*Independent ethics committee (IEC)* means 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. An institutional review board (IRB), as defined in § 56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC.

\* \* \* \* \*

- 3. Section 312.120 is revised to read as follows:

**§ 312.120 Foreign clinical studies not conducted under an IND.**

(a) *Acceptance of studies.* (1) FDA will accept as support for an IND or application for marketing approval (an application under section 505 of the act or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262)) a well-designed and well-conducted foreign clinical study not conducted under an IND, if the following conditions are met:

(i) The study was conducted in accordance with good clinical practice (GCP). For the purposes of this section, GCP is defined 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 and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. 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. GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with those described in § 50.23 or § 50.24(a) of this chapter, or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects; and

(ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

(2) Although FDA will not accept as support for an IND or application for marketing approval a study that does not meet the conditions of paragraph (a)(1) of this section, FDA will examine data from such a study.

(3) Marketing approval of a new drug based solely on foreign clinical data is governed by § 314.106 of this chapter.

(b) *Supporting information.* A sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for an IND or application for marketing approval must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601 of this chapter, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1)(i) of this section. The description is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the description must

provide either the following information or a cross-reference to another section of the submission where the information is located:

- (1) The investigator's qualifications;
- (2) A description of the research facilities;
- (3) A detailed summary of the protocol and results of the study and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;
- (4) A description of the drug substance and drug product used in the study, including a description of the components, formulation, specifications, and, if available, bioavailability of the specific drug product used in the clinical study;
- (5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under § 314.126 of this chapter;
- (6) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in § 312.3 of this chapter. The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;
- (7) A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion;
- (8) A description of how informed consent was obtained;
- (9) A description of what incentives, if any, were provided to subjects to participate in the study;
- (10) A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistently with the study protocol; and

(11) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1)(i) of this section) and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c) *Waivers.* (1) A sponsor or applicant may ask FDA to waive any applicable requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IND or in an information amendment to an IND, or in an application or in an amendment or supplement to an application submitted under part 314 or 601 of this chapter. 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.

(2) FDA may grant a waiver if it finds that doing so would be in the interest of the public health.

(d) *Records.* A sponsor or applicant must retain the records required by this section for a foreign clinical study not conducted under an IND as follows:

(1) If the study is submitted in support of an application for marketing approval, for 2 years after an agency decision on that application;

(2) If the study is submitted in support of an IND but not an application for marketing approval, for 2 years after the submission of the IND.

Dated: April 21, 2008.



Jeffrey Shuren,  
Associate Commissioner for Policy and Planning.

2008

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