Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 2004N–0018]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its regulations on its acceptance of foreign clinical studies not conducted under an investigational new drug application (IND) as support for an IND or marketing application for a drug or biological product. We are proposing to replace the requirement that such studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki (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 proposed rule is intended to update the standards for the acceptance of nonIND foreign studies and to help ensure the quality and integrity of data obtained from such studies.

DATES: Submit written or electronic comments by September 8, 2004. Submit written comments on the information collection requirements by July 12, 2004. See section VIII of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments, identified by Docket No. 2004N–0018, by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. 2004N–0018 in the subject line of your e-mail message.
- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 2004N–0018 or Regulatory Information Number (RIN) for this rulemaking. All comments received will be posted without change to *http://www.fda.gov/dockets/ecomments*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see section IV of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/dockets/ecomments* and/or the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

See section VI of this document for the address to which comments on the information collection requirements of this rule may be sent.

FOR FURTHER INFORMATION CONTACT: David A. Lepay, Office for Science and Health Coordination, Good Clinical Practice Programs (HF–34), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3340.

SUPPLEMENTARY INFORMATION:

I. Introduction

A. Current Regulations on Acceptance of Foreign Studies Not Conducted Under an IND

FDA regulations permit the acceptance of foreign clinical studies in support of an IND, a new drug application (NDA), or a biologics license application (BLA) if certain conditions are met. Foreign studies performed under an IND must meet the same requirements of part 312 (21 CFR part 312) that apply to U.S. studies conducted under an IND. Under § 312.120(a), we generally accept for review 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 acceptable to the world community.

With respect to such ethical principles, § 312.120(c)(1) states that for a foreign clinical study not conducted under an IND to be used to support an IND or marketing application, the study must have been conducted in accordance with the ethical principles stated in the Declaration of Helsinki 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) sets forth the text of the 1989 version of the Declaration.

We first incorporated the Declaration (1964 version) into our regulations on nonIND foreign studies in 1975 (40 FR 16053, April 9, 1975) in what was then § 312.20. We amended § 312.20 in 1981 to replace the 1964 Declaration with the 1975 version (46 FR 8942, January 27, 1981). In 1991, we replaced the 1975 Declaration with the 1989 version (56 FR 22112, May 14, 1991) in what had been recodified as § 312.120.

B. Reasons for Proposing To Revise the Regulations

We believe that a revision of the requirements for the acceptance of foreign clinical studies not conducted under an IND is again needed for several reasons.

1. Updating Standards

First, standards for protecting human subjects have evolved considerably over the past decade. For example, since we last amended § 312.120 in 1991, several notable documents identifying ethical and other clinical practice-related principles have been published. These include the following documents:

- The 1996 and 2000 revisions of the Declaration by the World Medical Assembly;
- ''Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries,'' published by the National Bioethics Advisory Commission;
- ''International Ethical Guidelines for Biomedical Research Involving Human Subjects,'' prepared by the Council for International Organizations of Medical

Sciences in collaboration with the World Health Organization; and

• Several documents issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The ICH documents are notable because they define and incorporate the standard of GCP. GCP principles are addressed comprehensively in an ICH document entitled ''Good Clinical Practice: Consolidated Guideline,'' which we adopted for use as guidance for industry in 1997 (62 FR 25692, May 9, 1997) (Good Clinical Practice guidance). The Good Clinical Practice guidance defines GCP as a ''standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.'' As so defined, GCP shares many important ethical principles with the 1989 Declaration, such as review by an IEC, the need for freely-given informed consent, conduct of clinical trials only by qualified individuals, and a recognition that the rights, safety, and well-being of trial subjects take precedence over the interests of science and society. The GCP concept, however, provides more detail and enumeration of specific responsibilities of various parties, including monitoring of the trial and reporting adverse events. In addition to the Good Clinical Practice guidance, GCP principles are incorporated in other FDA guidances adopted from the ICH, including ''Structure and Content of Clinical Study Reports'' (July 1996) (recommending that any study submitted to us in support of an application provide an assurance that the study complied with GCP).[1]

Many of the principles underlying GCP have already been incorporated in FDA's regulations, including parts 50, 56, 312, 314, and 601 (21 CFR parts 50, 56, 314, and 601). For example, the regulations in subpart B of part 50 contain the requirements for obtaining the informed consent of human subjects in clinical investigations. In addition, subpart D of part 312 describes the responsibilities of sponsors and investigators regarding IND studies, including conformance to parts 50 and 56 (on the use of institutional review boards (IRBs)).

We are now proposing to revise § 312.120 to incorporate GCP into the requirements for acceptance of nonIND foreign studies.

The GCP standard in proposed § 312.120 is consistent with the ICH standard developed through an international collaborative process. We believe that the proposed standard is 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.

2. Ensuring Quality of Data

Another reason for revising § 312.120, related to the adoption of GCP, is to help provide greater assurance of the quality of the data obtained from nonIND foreign studies. It has become increasingly recognized that the development of data that are scientifically sound is a critical responsibility of investigators and sponsors and is part of a responsible relationship between these entities and study subjects. The 1989 Declaration endorses this view but does not address in detail how to ensure study quality. The 1989 Declaration notes that it is unethical to enroll human subjects in poorly designed or conducted clinical trials because subjects may be exposed to risks without the opportunity for potential benefit, but the Declaration does not provide guidance on how to ensure proper conduct of trials. The proposed revisions to § 312.120 seek to help ensure data quality and integrity in several ways including the following: (1) Specifying that GCP includes providing assurance that study data and reported results are credible and accurate and (2) requiring that supporting information on a nonIND foreign clinical study include a description of how the sponsor monitored the trial and ensured that the study was carried out consistent with the study protocol.

The informed consent provisions embodied in GCP also may contribute to the integrity of data obtained in clinical studies. The informed consent process enables each subject to receive high-quality information about the consequences of participating in the clinical trial. The process also provides an opportunity for the subject and investigator to discuss important information about the subject's condition, potential adverse events, and other factors (such as use of concurrent therapy, illegal drug use, or alcohol abuse) that could confound the study results if they remained undisclosed.

3. Eliminating Reference to the Declaration

Finally, we also are issuing this proposed rule to eliminate the reference in § 312.120 to the Declaration. The Declaration is a document that is subject to change independent of FDA authority. As a result, it could be modified to contain provisions that are inconsistent with U.S. laws and regulations. Although revisions to the Declaration could not supersede U.S. laws and regulations, such changes could create the potential for confusion about the requirements for nonIND foreign studies.

C. Consultation with FDA

We are confident that the requirements in proposed § 312.120 will facilitate our acceptance for review of data obtained from foreign studies in support of INDs and U.S. marketing applications. As always, we encourage applicants to meet with responsible officials in FDA's Center for Drug Evaluation and Research (CDER) or FDA's Center for Biologics Evaluation and Research (CBER) as early as possible in the development of a drug or biological product to determine if a particular foreign clinical study appears to meet the standards for acceptance for review.

II. Description of the Proposed Rule

A. Definitions

We propose to add under § 312.3, under definitions and interpretations, a definition for IEC. We propose to define an IEC 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''. An adequately constituted IEC 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). The definition of independent ethics committee also specifies that an IRB, as defined in § 56.102(g) and subject to the requirements of part 56, is one type of IEC.

B. Requirements for Acceptance as Support for an IND or Marketing Application

Current § 312.120(a) states that the provision describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. It

[1] Sponsors seeking additional guidance on GCP generally should consult the Good Clinical Practice guidance. Additional relevant guidance may be found in sections of other FDA guidances adopted from the ICH, including ''E11 Clinical Investigation of Medicinal Products in the Pediatric Population'' (December 2000) and ''E10 Choice of Control Group and Related Issues in Clinical Trials'' (May 2001). These guidances are available electronically at *http://www.fda.gov/cder/guidance/index.htm.*

states that, in general, FDA accepts such studies provided they are well-designed, well-conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Section 312.120(a) further states that studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Finally, § 312.120(a) states that marketing approval of a new drug based solely on foreign clinical data is governed by § 314.106.

Current § 312.120(c)(1) states that foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the Declaration (which is set forth in current § 312.120(c)(4)) 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)(2) states that for each foreign clinical study submitted under § 312.120, the sponsor must explain how the research conformed to the ethical principles in the Declaration or the foreign country's standards, whichever were used. Under § 312.120(c)(3), when the research has been approved by an independent review committee, the sponsor must submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. A ''review committee'' means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). Section 312.120(c)(3) further states that the investigator may not vote on any aspect of the review of his or her protocol by a review committee.

We are proposing to revise the conditions under which we will accept, as support for an IND or marketing application for a drug or biologic, a foreign clinical study not conducted under an IND, principally by specifically requiring conformance with GCP, including review and approval by an IEC, and by deleting the reference to the Declaration. Under proposed § 312.120(a)(1), we would accept as support for an IND, NDA, or BLA a well-designed and well-conducted foreign clinical study not conducted under an IND if two conditions are met. The first condition, stated in proposed § 312.120(a)(1)(i), is that the study was conducted in accordance with GCP. For purposes of this section, GCP would be 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. Proposed § 312.120(a)(1)(i) states that GCP includes review and approval (or provision of a favorable opinion) by an IEC[2] before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of a subject (or the subject's legally authorized representative if the subject is unable to provide informed consent) before initiating a study. Proposed § 312.120(a)(1)(i) further states 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) of this chapter (concerning exemptions from informed consent requirements in life-threatening situations), 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. This provision would be consistent with the Good Clinical Practice guidance, which recommends that a legally authorized representative provide informed consent or that the requirement of informed consent be waived under such circumstances.

Proposed § 312.120(a)(1)(ii) states the second condition for our acceptance of a nonIND foreign study as support for an IND, NDA, or BLA. We must be able to validate the data from the study through an onsite inspection if the agency deems it necessary. The ability to inspect records relating to a foreign study is essential to our ability to resolve any uncertainties about whether the study was conducted in accordance with GCP.

Proposed § 312.120(a)(2) states 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)(1), we will examine data from such a study. We remind sponsors and applicants that they must submit all studies and other information required under applicable FDA regulations for drugs and biologics, including §§ 314.50, 314.80, 314.81, 600.80 (21 CFR 600.80), and 601.2. For example, as part of our review of an NDA, we consider all relevant data bearing on the safe use of the proposed drug product, including data obtained in any foreign clinical studies not conducted under an IND—even data from studies that are not carried out in accordance with GCP.

Proposed § 312.120(a)(3) reiterates the statement in current § 312.120(a) that marketing approval of a new drug based solely on foreign clinical data is governed by § 314.106.

C. Requirements for Supporting Information

Under current § 312.120(b)(1) through (b)(5), a sponsor who wishes to rely on a foreign clinical study to support an IND or to support an application for marketing approval must submit to FDA the following information:

- A description of the investigator's qualifications;
- A description of the research facilities;
- A detailed summary of the protocol and results of the study, and, if FDA requests, case records maintained by the investigator or additional background data such as hospital or other institutional records;
- A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications, and bioavailability of the specific drug product used in the clinical study, if available; and
- 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.

Proposed § 312.120(b) would retain the requirements listed in the previous paragraphs and would add certain requirements concerning IECs and other aspects of GCP. Under proposed § 312.120(b), a sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for IND, NDA, or BLA must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601, respectively, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in § 312.120(a)(1)(i). Under proposed § 312.120(b)(1) through (b)(11), the description would include the following information:

- The investigator's qualifications;
- A description of the research facilities;
- A detailed summary of the protocol and results of the study, and, at FDA's request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

[2] See, e.g., section 1.27 of the Good Clinical Practice guidance, stating that an IEC either approves or provides a favorable opinion on matters such as trial protocols, the suitability of investigators, and the methods and materials used in obtaining and documenting informed consent.

• 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;

• 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;

• The names and qualifications of the members of the IEC that reviewed the study;

• A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion;

• A description of how informed consent was obtained;

• A description of what incentives, if any, were provided to subjects to participate in the study;

• A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistent with the study protocol; and

• A description of how investigators were trained to comply with GCP (as described in § 312.120(a)(1)(i)) and to conduct the study in accordance with the study protocol, and copies of written commitments, if any, by investigators to comply with GCP and the protocol.

We would encourage, but not require, sponsors to obtain written commitments by investigators to comply with GCP and the study protocol. If such commitments were obtained, the proposed rule would require that copies of the commitments be included in the supporting information for a nonIND foreign study.

We believe that this proposed documentation, combined with an onsite inspection, if necessary, would provide us with the ability to determine whether a particular foreign clinical study had been conducted in accordance with GCP.

D. Requirements for Waiver Requests

Under proposed § 312.120(c)(1), a sponsor or applicant may submit a request to FDA to waive any applicable requirements under proposed § 312.120(a)(1) and (b). A waiver request would 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. Proposed § 312.120(c)(1) further states that under proposed § 312.120(c)(1)(i) through (c)(1)(iii), the waiver request must contain at least one of the following:

• An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;

• A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

• Other information justifying a waiver.

Under proposed § 312.120(c)(2), FDA may grant a waiver if it finds that doing so would be in the interest of the public health. For example, we may determine that a waiver is in the interest of the public health if alternative procedures used by the sponsor or applicant satisfy the purpose of these regulations.

III. Legal Authority

We are proposing to issue this rule under the authority of the provisions of the Federal Food, Drug, and Cosmetic Act (the act) that apply to drugs (21 U.S.C. 201 *et seq.*) and section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). These laws authorize us 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 (21 U.S.C. 355) 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. Section 505(d) of the act provides that we may approve an NDA only after finding substantial evidence as follows:

> ''[c]onsisting 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 ''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) of the act, 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 701(a) of the act (21 U.S.C. 371(a)) vests in the Secretary of the Department of Health and Human Services (the Secretary) (who has delegated it to FDA) the authority to issue regulations for the efficient enforcement of the act.

Section 351(a)(2)(B)(i)(I) of the PHS Act authorizes us (by delegation from the Secretary) 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 us (by delegation from the Secretary) 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 trials not conducted under the IND regulations as reliable evidence supporting an IND, NDA, or BLA.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the proposed 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 proposed rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the proposed rule is not an economically significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

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

agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 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 an 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 $110,000,000. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Objectives of the Proposed Rule

The objectives of the proposed 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 the agency's 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 proposed rule also would 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 NDAs and BLAs. These applications contain the results of clinical investigations that characterize the therapeutic benefit of the new product and assess its risks. FDA reviews the submitted data and decides whether there is sufficient evidence of safety and effectiveness to grant approval.

Clinical data included in a marketing application usually are collected under an IND, to 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 NDA or BLA 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. FDA has always required and reviewed the safety results of nonIND foreign clinical trials of drug products considered for marketing approval in the United States.

According to CDER and CBER estimates, approximately 650 clinical investigations of investigational products intended for commercial marketing were initiated each year over the last 5 years. 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 x 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 a marketing application (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 nonIND foreign trials are conducted annually for eventual submission to FDA as part of a research or marketing application (3,825 - 3,250 = 575).

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

C. The Proposed Rule

We are proposing that all nonIND foreign clinical research submitted as support for an IND or marketing application be conducted under GCP as defined in the proposed rule. Currently, we accept as support for an IND or marketing application 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. Sponsors of nonIND investigations used in support of INDs or marketing applications must either follow the principles of the 1989 Declaration for patient protection or national laws that provide even greater protection. The proposed regulations on acceptance of nonIND foreign studies are 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. marketing application are well-designed and well-conducted and provide sufficient protection to subjects. Consequently, under the proposed rule, we would not accept any nonIND foreign clinical results as support for sponsor claims of efficacy unless the trials were 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 Proposed Rule

We interviewed seven pharmaceutical manufacturers that had submitted results from nonIND 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 proposed regulation would require 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 proposed regulation) are not specifically required to be documented and submitted in a marketing application 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 marketing applications. 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 nonIND studies makes it difficult for us to determine the adequacy of preinitiation review of study protocols. The proposed rule would help ensure that these documents are available for our inspection at research sites and that information on IEC review is included in INDs and marketing applications.

The amount and detail of the necessary documentation would 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 nonIND 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 previously noted in this document, we estimate that approximately 575 nonIND foreign commercial clinical trials are conducted annually. Using the high estimate of the additional hours of documentation needed for each nonIND clinical trial, this would result in a total annual cost of about $552,000 to the sponsoring firms (32 hours x 575 nonIND foreign trials x $30 = $552,000).

E. Benefits of the Proposed 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 marketing applications. We further believe that the proposed rule would decrease the likelihood 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 marketing applications resulting from the use of GCP in lieu of current 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 nonIND studies would result in an additional benefit, also difficult to quantify, due to greater public confidence in the scientific basis for FDA decisions.

F. Small Business Impact

The proposed 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 previously discussed in this document, we estimate that the proposed rule would increase total costs to sponsors of foreign clinical studies by approximately $552,000 per year. The increased costs would be due to greater costs of review and documentation of the approval of study protocols by IECs. The resources needed to comply with this proposal are not specialized. Assuming, for purposes of this calculation, that each of the approximately 115 marketing or research applications submitted annually (in which are reported approximately 575 nonIND foreign clinical studies) is submitted by a different sponsor, each sponsor would incur costs of approximately $4,800 per year to comply with this proposal ($552,000 ÷ 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 marketing applications is markedly different from the general industry. FDA examined the characteristics of sponsors of new drug product marketing applications between October 1996 and October 1999 (Ref. 2). Of the 158 firms that had sponsored marketing applications 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 nonIND foreign clinical trials to develop data for submission in an FDA marketing application (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 nonIND clinical trials per year. If so, the compliance costs would equal about $9,600 annually per small entity ($4,800 x 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 Proposed Rule

FDA considered several alternatives to the proposed 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 proposed rule for small entities. We must have confidence that all clinical investigations submitted as support for a research or marketing application meet basic standards of reliability, patient safety, and data quality.

4. Outreach

We are publishing this proposed rule in anticipation of receiving comments from affected small entities. The proposed rule is available to all interested parties through FDA's Internet Web site at *http://www.fda.gov*.

5. Conclusion

For the reasons previously stated, we conclude that the proposed rule would 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 (see **ADDRESSES**) 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.

V. Environmental Impact

FDA has 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.

VI. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to review by 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 below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Foreign Clinical Studies Not Conducted Under an IND

Description: Current § 312.120 states 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. 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 proposed rule would replace the requirement that nonIND 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 proposing this change for the following reasons: (1) We want to provide greater assurance of the quality of data obtained from nonIND 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 in current § 312.120 to the Declaration because that document is subject to change, independent of FDA authority, in a manner that is inconsistent with U.S. laws and regulations.

Under proposed § 312.120(a), we would accept for review as support for an IND, NDA, or BLA a well-designed and well-conducted foreign clinical study not conducted under an IND if the study were conducted in accordance with GCP and we were able to validate the data from the study through an onsite inspection if necessary. GCP would include 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.

Current § 312.120(b) requires a sponsor of a nonIND foreign study who wants to rely on that study as support for an IND or marketing application to provide certain data to FDA. Proposed § 312.120(b) would require this same information as well as the following information: (1) A description of the IEC and 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 consistent 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 copies of any written commitments by investigators to comply with GCP and the protocol.

Proposed § 312.120(c) would specify how sponsors or applicants could 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 proposed § 312.120(c)(1), the waiver request would contain at least one of the following requirements: (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 proposed § 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 proposed rule.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

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

[1] 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 nonIND foreign clinical studies in support of an IND or marketing application for a drug or biological product. We conducted consultations with seven large and small companies that had submitted nonIND foreign clinical studies to us within the past 3 years. All respondents indicated that they currently conduct nonIND foreign clinical studies in conformance with GCP and generally document all the items listed in proposed § 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 currently are required (under § 312.120(b)(1) through (b)(5) and (c)(3)) to document the items in proposed § 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 represents the greater protection of the individual (current § 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 nonIND foreign clinical trial. To provide a liberal estimate of costs to industry, we will assume that no companies currently document compliance with any component of GCP and that the documentation required under proposed § 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 compliance with the PRA (44 U.S.C. 3507(d)), we have submitted the information collection requirements of this rule to OMB for review. Interested persons are requested to fax comments regarding information collection to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

VII. Federalism

We have analyzed this proposed 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 proposed 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.

VIII. Proposed Effective Date

We propose to apply any final rule that may issue based on this proposal to foreign clinical studies for which the first subject is enrolled 180 days after the final rule is published in the **Federal Register**.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on this proposal. Two paper copies of any comments are to be submitted, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

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, FDA proposes that 21 CFR part 312 be amended to read 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, 371; 42 U.S.C. 262.

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

§ 312.3 Definitions and interpretations.

* * * * *

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, 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, a new drug application (NDA), or a biologics license application (BLA) 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 that the conditions present are consistent with those described in §§ 50.23 or 50.24(a) of this chapter, 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; 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, NDA, or BLA 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, NDA, or BLA must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601 of this chapter, respectively, 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 must include the following:

(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 names and qualifications for the members of the IEC that reviewed the study;

(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 consistent 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 copies of written commitments, if any, by investigators to comply with GCP and the protocol.

(c) *Waivers.* (1) A sponsor or applicant may request 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.

Dated: February 16, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–13063 Filed 6–9–04; 8:45 am]

BILLING CODE 4160–01–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[TX–70–2–7347b; FRL–7672–6]

Approval and Promulgation of Implementation Plans for Texas; Approval of Section 179B Demonstration of Attainment, Volatile Organic Compound and Nitrogen Oxide Motor Vehicle Emissions Budgets for Conformity for the El Paso Ozone Nonattainment Area

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The EPA is proposing to approve, through direct final action, a revision to the Texas State Implementation Plan, submitted to show attainment of the one-hour ozone National Ambient Air Quality Standard in the El Paso ozone nonattainment area, but for emissions emanating from outside of the United States. The EPA is also proposing to approve the El Paso area's volatile organic compounds and nitrogen oxides emissions budgets. The State submitted the revisions to satisfy sections 179B and other part D requirements of the Federal Clean Air Act.

DATES: EPA is accepting adverse comment until July 12, 2004. If EPA receives adverse comment, EPA will publish a timely withdrawal in the **Federal Register** informing the public that the direct final rule will not take effect.

ADDRESSES: Submit your comments, identified by File ID No. TX–70–2–7347, by one of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the online instructions for submitting comments.
- U.S. EPA Region 6 ''Contact Us'' Web site: *http://epa.gov/region6/r6coment.htm*. Please click on ''6PD'' (Multimedia) and select ''Air'' before submitting comments.
- E-mail: Mr. Thomas Diggs at *diggs.thomas@epa.gov*. Please also cc the person listed in the **FOR FURTHER INFORMATION CONTACT** section below.
- Fax: Mr. Thomas Diggs, Chief, Air Planning Section (6PD–L), at (214) 665–7263.
- Mail: Mr. Thomas Diggs, Chief, Air Planning Section (6PD–L), Environmental Protection Agency, 1445 Ross Avenue, Suite 1200, Dallas, Texas 75202–2733.
- Hand or Courier Delivery: Mr. Thomas Diggs, Chief, Air Planning Section (6PD–L), Environmental Protection Agency, 1445 Ross Avenue, Suite 1200, Dallas, Texas 75202–2733. Such deliveries are accepted only between the hours of 8 a.m. and 4 p.m. weekdays except for legal holidays. Special arrangements should be made for deliveries of boxed information.

Instructions: Please include the text ''Public comment on File ID No. TX–70–2–7347'' in the subject line of the first page of your comments. EPA's policy is that all comments received will be included in the public file without change, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do