



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 807, 812, and 814

[Docket No. FDA-2013-N-0080]

RIN 0910-AG48

Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations on acceptance of data from clinical studies for medical devices. We are proposing to require that clinical studies conducted outside the United States as support for an investigational device exemption (IDE) application, a premarket notification (510(k)) submission, a premarket approval (PMA) application, a product development protocol (PDP) application, or a humanitarian device exemption (HDE) application be conducted in accordance with good clinical practice (GCP), which includes obtaining and documenting the review and approval of the study by an independent ethics committee (IEC) and obtaining and documenting freely given informed consent of study subjects. The proposed rule is intended to update the standards for FDA acceptance of data from clinical studies conducted outside the United States and to help ensure the protection of human subjects and the quality and integrity of data obtained from these studies. As part of this proposed rule, we are also proposing to amend the IDE and 510(k) regulations to address the requirements for FDA acceptance of data from clinical studies conducted inside the United States. The proposed amendments are intended to provide

consistency in FDA requirements for acceptance of clinical data, whatever the application or submission type.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section VIII of this document for the proposed effective date of a final rule based on this proposed rule. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], (see the “Paperwork Reduction Act of 1995” section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA-2013-N-0080 and/or Regulatory Information Number (RIN) number 0910-AG48, by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 (the PRA) must be submitted to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB) (see the “Paperwork Reduction Act of 1995” section of this document):

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following way:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-0080 and RIN 0910-AG48 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Request for Comments” heading 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.regulations.gov> and insert the docket number(s), found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

A. Current Regulations on Clinical Studies for Medical Devices

B. Reasons for Proposing to Revise the Regulations

II. Description of the Proposed Rule

A. Definitions

B. Clinical Studies Conducted Outside the United States

C. Revisions to § 812.2--Applicability

D. Requirements for Report of Prior Investigations in IDE Applications

E. Requirements for 510(k) Submissions

F. Requirements for PMA Applications

G. Correction to the Regulations Regarding Record Retention for Clinical Studies

Conducted Under IDE

III. Legal Authority

IV. Analysis of Economic Impacts

A. Introduction

B. Summary

V. Environmental Impact

VI. Paperwork Reduction Act of 1995

VII. Federalism

VIII. Proposed Effective Date

IX. Request for Comments

X. References

I. Background

A. Current Regulations on Clinical Studies for Medical Devices

1. Clinical Studies Conducted Outside the United States

FDA regulations for PMA of medical devices in part 814 (21 CFR part 814) permit the acceptance of data from clinical studies conducted outside the United States and submitted in support of a PMA application if certain conditions are met. Current § 814.15(a) states that a study conducted outside the United States submitted in support of a PMA and conducted under an IDE shall comply with part 812 (21 CFR part 812). The provision in § 814.15(a) further states that a study conducted outside the United States submitted in support of a PMA and not conducted under an IDE shall comply with the provisions in paragraph (b) or (c) of § 814.15, as applicable.

Under § 814.15(b), FDA will accept studies submitted in support of a PMA which have been conducted outside the United States and begun on or after November 19, 1986, if the data are valid and the investigator has conducted the studies in conformance with the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects. If the standards of the country are used, the applicant must state in detail any differences between those standards and the Declaration of Helsinki and explain why they offer greater protection to the human subjects.

Under § 814.15(c), FDA will accept studies submitted in support of a PMA that have been conducted outside the United States and begun before November 19, 1986, if FDA is satisfied that the data are scientifically valid and that the rights, safety, and welfare of human subjects have not been violated.

Additionally, § 814.15(d) specifies criteria for acceptance of a PMA application for marketing approval based solely on foreign clinical data, and § 814.15(e) encourages applicants to meet with FDA officials prior to submission of a PMA application that will be based solely on foreign clinical data.

Currently, FDA regulations for premarket notification in part 807, subpart E (21 CFR 807, subpart E), commonly referred to as a “510(k) submission,” and investigational device exemptions in part 812 do not address the requirements for FDA acceptance of data from clinical studies conducted outside the United States.

2. Clinical Studies Conducted Inside the United States

FDA’s PMA regulations require applications that include the results of clinical investigations involving human subjects to include a statement with respect to each study that:

- (1) It was conducted in compliance with the institutional review board regulations in part 56 (21 CFR part 56), or was not subject to those regulations under §§ 56.104 or 56.105, and it was conducted in compliance with the informed consent regulations in part 50 (21 CFR part 50); or
- (2) if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance (see § 814.20(b)(6)(ii)(A)).

The regulations also require a statement that each study was conducted in compliance with part 812 concerning sponsors of clinical investigations and clinical investigators, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance (§ 814.20(b)(6)(ii)(B)).

Currently, FDA’s 510(k) and IDE regulations do not address the requirements for FDA acceptance of data from clinical studies conducted inside the United States to support a 510(k) submission or IDE application.

B. Reasons for Proposing to Revise the Regulations

FDA believes that the requirements for FDA's acceptance of data from clinical studies should be consistent regardless of the type of submission or application in which the data are submitted to FDA. For data from clinical studies conducted inside the United States, we propose to require statements in 510(k) submissions and IDE applications that are similar to those currently required for PMA applications, to help ensure the protection of human subjects and the quality and integrity of data obtained from these studies. For data from clinical studies conducted outside the United States, FDA believes that revision of the requirements for FDA acceptance of data from these clinical studies is needed for several reasons, described in this document.

1. Updating Standards for FDA Acceptance of Data From Clinical Studies Conducted Outside the United States

The standards for protecting human subjects have evolved considerably since the issuance of the PMA regulations in 1986. Several notable documents have been published (examples listed in this document) identifying ethical and other principles that provide assurance of the quality and integrity of clinical data and adequate protection of human subjects. As a whole, these documents include principles important to the conduct of clinical trials such as adverse event reporting, sponsor monitoring, and training of study personnel.

- Several documents issued by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, including the document entitled "Good Clinical Practice: Consolidated Guideline" (ICH E6);
- "Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice," issued by the International Organization for Standardization, ISO 14155:2011;

- “Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products,” issued by the World Health Organization, 1995;
- “Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries,” published by the National Bioethics Advisory Commission, 2001;
- “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, 2002;
- “Good Clinical Practices: Document of the Americas,” issued by the Pan American Health Organization, 2004; and
- The 1989, 1996, 2000, 2002, 2004, and 2008 amendments to the “Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects,” adopted by the World Medical Association.

Many of these documents articulate ethical and policy standards for clinical trials, often referred to as GCP. Generally speaking, GCP is defined by research and regulatory communities 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.”¹ GCP incorporates important ethical principles, such as review by an IEC; the need for freely given informed consent; conduct of clinical trials only by qualified individuals; and recognition that the rights, safety, and well-being of trial subjects take precedence over the interests of science and society. GCP enumerates specific roles and responsibilities of various parties, including monitoring of the trial and reporting adverse events.

¹ Definition from the ICH document entitled “Good Clinical Practice: Consolidated Guideline” (ICH E6), which FDA adopted for use as guidance for industry in 1997 (62 FR 25692, May 9, 1997).

Many of the principles underlying GCP have already been incorporated in FDA's regulations, including parts 50, 56, 812, and 814. For example, the regulations in subpart B of part 50 contain the requirements for obtaining the informed consent of human subjects in clinical investigations. Subparts C and E of part 812 describe the responsibilities of sponsors and investigators, respectively, regarding IDE studies, including conformance to parts 50 and 56 on the use of informed consent and institutional review boards (IRBs), respectively. FDA considers an IRB, as defined in § 56.102(g) and subject to the requirements of part 56, to be one type of IEC (see § 312.3 (21 CFR 312.3)).

We are proposing to revise § 814.15 and to amend parts 807 and 812 to incorporate GCP into the requirements for FDA acceptance of data from clinical studies conducted outside the United States to support an IDE or a device marketing application or submission (an application under sections 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360e and 360j, respectively) or a premarket notification submission under section 510(k) of the FD&C Act (21 U.S.C. 360(k)). We believe that the proposed standard helps to ensure adequate human subject protection and the quality and integrity of data obtained from such studies, while also being sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical research and obtain informed consent.

2. Ensuring Quality and Integrity of Data

FDA believes that revising parts 807, 812, and 814 to expressly incorporate GCP will help provide greater assurance of the quality and integrity of the data obtained from clinical studies conducted outside the United States and submitted in support of an application or submission to FDA. It has become increasingly recognized that the development, recording, and reporting of data that are scientifically valid are critical responsibilities of investigators and

sponsors and are part of a responsible relationship between these entities and study subjects. The proposed revisions to parts 807, 812, and 814 should help ensure data quality and integrity in several ways. These include: (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 clinical study conducted outside the United States includes, as appropriate, 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 contribute to the integrity of data obtained in clinical studies. The informed consent process enables each subject to receive high-quality information about the implications of participation 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. Standardizing Human Subject Protections

The current regulations under part 814 require that clinical studies outside the United States submitted in support of a PMA be conducted in conformance with the 1983 version of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects. If the standards of the country are used, the applicant is required to state in detail any differences between those standards and the 1983 version of the Declaration of Helsinki and explain why they offer greater protection to the human subjects.

Under the current regulations, in a study involving multinational investigational sites, several different standards may be followed leading to increased complexity in the conduct of the study. The proposal to require that clinical studies conducted outside the United States comply with GCP provides a unifying approach, which may simplify such trials and decrease the regulatory burden on sponsors.

The investigational new drug regulations in part 312 address FDA 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. Effective October 27, 2008, foreign clinical studies not conducted under an IND are required to be conducted in accordance with GCP as defined in § 312.120. The proposed revisions to parts 807, 812, and 814 will provide greater consistency with the regulations for drugs and biological products regarding FDA acceptance of foreign clinical studies.

4. Clarifying Requirements for FDA Acceptance of Data From Clinical Studies Submitted in Support of Premarket Notifications and Investigational Device Exemptions

Clinical studies may be used to support a 510(k) submission or an IDE application; however, parts 807 and 812 currently do not address the requirements for FDA acceptance of data from such studies. The proposed revisions will identify the requirements for FDA acceptance of data from clinical studies under these regulations, whether the studies were conducted inside or outside the United States. This proposal is intended to ensure the quality and integrity of clinical data submitted to FDA in 510(k) submissions and IDE applications and to bring consistency in FDA requirements for acceptance of clinical data, whatever the application or submission type.

II. Description of the Proposed Rule

A. Definitions

We propose to add a definition for an IEC to the IDE regulation under § 812.3. 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.” Under the proposal, an adequately constituted IEC includes a reasonable number of members with the qualifications and experience to perform the IEC’s functions. The proposed definition of an IEC 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. Clinical Studies Conducted Outside the United States

We propose to amend the IDE regulations by adding a new section, proposed § 812.28, to address the requirements for FDA acceptance of data from clinical studies conducted outside the United States. An IDE is typically not issued for a clinical study conducted outside the United States; however, there is a small subset of trials conducted outside the United States where IDEs have been issued, for example, certain studies conducted by the Department of Defense. The use of the term “clinical studies conducted outside the United States” is intended to address studies not conducted under an IDE and does not indicate a change in overall policy for device studies conducted outside the United States.

The current requirements for FDA acceptance of data from clinical studies conducted outside the United States in support of a PMA application are located at § 814.15, in the PMA regulations. We are proposing to place the revised requirements primarily in the IDE regulations, in part because the requirements for device clinical studies are primarily located in these regulations and in part to create consistency with the drug regulations, which address

requirements for FDA acceptance of foreign clinical data in the investigational new drug regulations in part 312. Additionally, similar to these drug regulations, which address requirements for FDA acceptance of foreign clinical data as support for an IND or marketing application for a drug or biological product, the proposed revised device regulations address requirements for FDA acceptance of foreign clinical data as support for not only a PMA but also an IDE or other device marketing application or submission, including a 510(k) or an HDE application.

1. Requirements for FDA Acceptance of Data From Clinical Studies Conducted Outside the United States

Proposed § 812.28(a) would identify requirements for FDA acceptance of data from clinical studies conducted outside the United States to support an IDE or device marketing application or submission. It would rely upon conformance with GCP, including review and approval by an IEC and obtaining and documenting the freely given informed consent of study subjects. Under proposed § 812.28(a)(1), we would require a statement 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 § 812.28(a)(1) states that 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 a subject (or the subject's legally authorized representative if the subject is unable to provide informed consent) before initiating a study. Proposed § 812.28(a)(1) further states that 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 that either 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 the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects. This provision would be consistent with the Good Clinical Practice guidance², which recommends that a legally authorized representative provide informed consent or that the requirement of informed consent be waived under such circumstances.

Proposed § 812.28(a)(2) states the second condition for FDA's acceptance of data from a clinical study conducted outside the United States as support for an IDE or a device marketing application or submission to FDA. A statement would be required assuring the availability of the data from the study to FDA for validation through an onsite inspection if the Agency deems it necessary (and an inspection is otherwise authorized by law) or through other appropriate means. FDA may need to inspect records relating to data from a foreign study submitted in support of a PMA, for example, to resolve any uncertainties about whether the study was conducted in accordance with GCP.

2. Requirements for Supporting Information

Proposed § 812.28(b) describes the supporting information to be submitted, in addition to information required elsewhere in parts 807, 812, and 814, when data from clinical studies conducted outside the United States are submitted as support for an IDE or device marketing application or submission. Under proposed § 812.28(b)(1) through (b)(12), the description of the

² "Good Clinical Practice: Consolidated Guideline" (ICH E6), which FDA adopted for use as guidance for industry in 1997 (62 FR 25692, May 9, 1997).

actions the sponsor or applicant took to ensure that the research conformed to GCP as described in § 812.28(a)(1) would include the following information:

- Names and addresses of investigators and research facilities (if an address has changed since the research was conducted, the address where records are maintained should be provided);
- The investigator's qualifications;
- A description of the research facility(ies);
- A detailed summary of the protocol and results of the study, and, should FDA request, certified copies of case records maintained by the investigator or additional background data such as hospital or other institutional records;
- Either a statement that the device used in the clinical study conducted outside the United States is identical to the device that is the subject of the submission or application, or a detailed description of the device and each important component (including materials and specifications), ingredient, property, and principle of operation of the device used in the clinical study conducted outside the United States and a comparison to the device that is the subject of the submission or application that indicates how the studied device is similar to and/or different from the device that is the subject of the submission or application;
- If the study is intended to support the safety and effectiveness of a device, a discussion demonstrating that the data and information constitute valid scientific evidence within the meaning of § 860.7 (21 CFR 860.7);
- The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in § 812.3(t). The sponsor or applicant must maintain records

supporting such a statement, including records describing the qualifications of IEC members, and make these records available for Agency review upon request. Although the names of IEC members are required under § 312.120(b)(6) for foreign clinical studies used to support drug and biological product applications, we are proposing to require only the qualifications of the IEC members for device studies due to the reported difficulties of obtaining the names of IEC members in some countries;

- 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 § 812.28(a)(1)) 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 written commitments by investigators to comply with GCP and the study protocol must be maintained by the sponsor or applicant and made available for Agency review upon request.

We believe that the proposed supporting information, combined with an onsite inspection, if necessary, would provide us with the ability to determine whether a particular clinical study conducted outside the United States had been conducted in accordance with GCP.

3. Requirements for Records

Proposed § 812.28(c) describes the retention requirements for records required by this section with regard to a clinical study conducted outside the United States. If the study is submitted in support of an IDE, the records must be retained for 2 years after the termination or completion of the IDE, as described in proposed § 812.28(c)(1). If the study is submitted in support of a premarket notification, premarket approval application, a notice of completion of a product development protocol, or a humanitarian device exemption application, the records must be retained for 2 years after an Agency decision on that submission or application, as described in proposed § 812.28(c)(2).

C. Revisions to § 812.2--Applicability

We propose to amend § 812.2 by removing current paragraphs (b)(2) and (e), which refer to requirements that are no longer necessary because the dates involved have passed.

Specifically, paragraph (b)(2) indicated that investigations of a device, except as described in paragraph (e), that were begun on or before July 16, 1980, and were completed on or before January 19, 1981, would be considered to have approved applications for IDEs, unless FDA notified a sponsor under § 812.20(a) that approval of an application was required.

Paragraph (e) required a sponsor who had an IND application for a device in effect on July 16, 1980, and who wished to continue the investigation after 90 days after that date, to comply with paragraph (b)(1) if not a significant risk device or obtain FDA approval under § 812.30 of an IDE application.

To accommodate the proposed removal of paragraph (b)(2), paragraphs (b) and (b)(1) would be combined and proposed paragraph (b) states that unless FDA has notified a sponsor under § 812.20(a) that approval of an application is required, an investigation of a device other

than a significant risk device is considered to have an approved application for IDE, if the device is not a banned device and the sponsor complies with paragraphs (b)(1) through (b)(7). Note that paragraphs (b)(1) through (b)(7) are the proposed redesignated paragraphs (b)(1)(i) through (b)(1)(vii).

The current IDE regulations identify varying requirements for clinical investigations of devices based on whether the study is of a significant risk or nonsignificant risk device or would meet the exemption requirements in § 812.2(c). We propose that requirements for clinical studies conducted outside the United States, which are to be submitted to FDA in support of an IDE or a device marketing application or submission, also be subject to varying requirements, depending on whether the study is of a significant risk device or nonsignificant risk device or would meet the exemption requirements in § 812.2(c).

Proposed paragraph (e) identifies these varying requirements. Proposed § 812.2(e)(1) requires studies of a significant risk device, as defined in § 812.3(m), to comply with the requirements of the principles of good clinical practice, as defined in § 812.28(a), maintenance of supporting information as described in § 812.28(b), and records retention as described in § 812.28(c). Proposed § 812.2(e)(2) requires studies of a device, other than a significant risk device, or clinical device investigations that would otherwise meet the exemption requirements in § 812.2(c), to comply with these same requirements concerning good clinical practice and records retention, but with lesser requirements concerning maintenance of the supporting information (i.e., only those requirements at § 812.28(b)(1), (4), (5), (7), (8), (9), and (11)), in recognition of their differing regulatory status compared to significant risk device investigations.

D. Requirements for Report of Prior Investigations in IDE Applications

Current § 812.27(a) requires the report of prior investigations to include reports of all prior clinical, animal, and laboratory testing of the device but does not include specific requirements for reports of clinical testing. Proposed § 812.27(b)(4) would describe the specific requirements for reports of clinical testing conducted both inside and outside the United States.

Proposed (b)(4)(i) requires that, if information on clinical studies conducted in the United States is provided, the report of prior investigations shall include a statement that all such studies have been conducted in compliance with applicable requirements in the protection of human subjects regulations in part 50, the institutional review boards regulations in part 56, and the investigational device exemptions regulations in part 812, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. It also provides that failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical study.

Proposed § 812.27(b)(4)(ii) states, if information on clinical studies conducted outside the United States is provided to support an IDE, the requirements under § 812.2(e) and § 812.28 of this chapter apply, where the requirements for such studies are detailed. If any such study was not conducted in accordance with GCP as described in § 812.28(a), the report of prior investigations shall include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected. This description is necessary for studies conducted outside the United States because of the greater difficulty in conducting bioresearch monitoring inspections of foreign sites. It

further states that failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical study.

We remind sponsors and applicants that they must submit all studies and other information required under applicable FDA regulations for medical devices. For example, as part of our review of an IDE, we consider all relevant data bearing on the safe use of the proposed medical device, including data obtained in any clinical studies conducted outside the United States--even data from studies that are not carried out in accordance with GCP.

E. Requirements for 510(k) Submissions

The requirements for premarket notifications are described in part 807, subpart E. The information required in a premarket notification submission is detailed at § 807.87, but this section does not discuss the requirements relating to clinical data submitted, where applicable, to support a premarket notification submission. Most premarket notifications do not include clinical data and would not be affected by this proposed rule; however, we believe the requirements for FDA acceptance of clinical data should be the same for premarket notifications that do contain clinical data as for other device applications in order to achieve consistency in FDA's clinical data requirements. For 510(k) submissions relying upon literature only, the proposed requirements at new § 807.87(j) would not generally apply.

For the subset of premarket notifications that do contain clinical data, we propose to add a new paragraph (j) to describe requirements relating to clinical data submitted to support a premarket notification and to redesignate existing paragraph (j) as paragraph (k), existing paragraph (k) as paragraph (l), and existing paragraph (l) as paragraph (m).

For a premarket notification submission containing clinical data, proposed paragraph (j)(1) requires, if the data are from clinical studies conducted in the United States, a statement

that each study was conducted in compliance with applicable requirements in parts 50, 56, and 812 of this chapter, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

Proposed paragraph (j)(2) states that, if the data are from clinical studies conducted outside the United States, the requirements under § 812.2(e) and § 812.28 of this chapter apply. If any such study was not conducted in accordance with GCP as described in § 812.28(a), the submission must include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected. This description is necessary for studies conducted outside the United States because of the greater difficulty in conducting bioresearch monitoring inspections of foreign sites. This proposal will help ensure consistency in FDA clinical data requirements, whatever the type of product application or submission at issue.

F. Requirements for PMA Applications

The requirements for premarket approval are described in part 814. The requirements for FDA acceptance of clinical data submitted in support of a PMA from studies conducted outside the United States are currently addressed in § 814.15. As previously indicated, we propose to address these requirements primarily in the IDE regulations. Therefore, removal of current paragraphs (a), (b), and (c) in § 814.15 is proposed. Proposed paragraph (a) will identify the general requirement that a study conducted outside the United States and submitted in support of a PMA shall comply with the relevant provisions of part 812 as set forth in § 812.2(e) and § 812.28. To accommodate this change, current paragraphs (d) and (e) will be redesignated as paragraphs (b) and (c) respectively.

To address the requirements for PMA applications that include data from clinical studies conducted outside the United States, we propose to amend § 814.20(b), the content requirements for a PMA application, specifically the requirements for technical sections containing results of clinical investigations in paragraph (6)(ii). We propose to add a new subparagraph (C) stating that, for clinical studies conducted outside the United States intended to support the PMA, the requirements under § 812.2(e) and § 812.28 of this chapter apply. Required information may be incorporated by cross-reference to another section of the application that contains such information. If any such study was not conducted in accordance with GCP as described in § 812.28(a), the application must include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected. This description is necessary for studies conducted outside the United States because of the greater difficulty in conducting bioresearch monitoring inspections of foreign sites. We remind sponsors and applicants that failure or inability to comply with these requirements does not justify failure to provide information concerning investigations bearing on the safety or effectiveness of a device undergoing PMA review (see § 814.20(b)(8)(ii) and sections 515(c)(1)(A) and 515(c)(2)(A)(v) of the FD&C Act).

We also propose to amend the provisions in § 814.45 concerning denial of approval of a PMA application. We propose to revise paragraph (a)(5) to include as a reason for denial that any clinical investigation involving human subjects described in the PMA application, which was subject to GCP referenced in § 814.15(a) and described in § 812.28(a), was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable.

Further, we propose to amend § 814.46 regarding withdrawal of approval of a PMA application, specifically to revise paragraph (a)(4) to allow FDA to withdraw approval if FDA determines that any clinical investigation involving human subjects described in the PMA application, subject to GCP referenced in § 814.15(a) and described in § 812.28(a), was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable.

Finally, we propose to amend § 814.104 regarding the required contents of HDE applications. Although these applications remain subject to modified requirements for application contents compared to premarket approval applications, we propose that they would not be exempt from the new proposed requirement in § 814.20(b)(6)(ii)(C) regarding submission of data from clinical studies conducted outside the United States. The proposed language also clarifies that, in those situations where data from clinical studies conducted inside the United States are submitted in support of a HDE application, the requirements in § 814.20(b)(6)(ii)(A)-(B) apply.

Premarket approval is considered to include a PDP declared to be completed by FDA (see § 814.19 and section 515(f) of the FD&C Act). Although PDPs are rarely submitted, if a PDP is supported by data from clinical studies conducted outside the United States, the requirements in § 814.15 would apply.

G. Correction to the Regulations Regarding Record Retention for Clinical Studies Conducted

Under IDE

When the regulations for premarket approval were amended to address HDE applications, the IDE regulations were not amended because at the time clinical studies supporting an HDE application were not anticipated (largely because of the small numbers of patients affected and

the infeasibility of conducting large, randomized clinical trials). Experience has demonstrated that many HDE applications do include data from clinical studies (usually from small, non-randomized studies) in order to meet the required standard for approval. Therefore, we are proposing to revise § 812.140(d) regarding retention of records for clinical research conducted under an IDE to include records supporting an HDE application.

We are similarly proposing to revise § 812.140(d) regarding retention of records for clinical research conducted under an IDE to include records supporting a premarket notification submission, where applicable. Most premarket notification submissions do not include clinical data. For the subset that do contain clinical data, we are proposing that record retention requirements be the same as for other product applications and submissions that contain clinical data, to ensure consistency in FDA clinical data requirements and the integrity and reliability of clinical data submitted. This proposed revision to § 812.140(d) is also consistent with proposed § 812.28(c), described in this document, regarding retention of records for clinical research conducted outside the United States. Each of these proposed revisions would achieve consistency in FDA requirements for clinical data record retention regardless of the application or submission type.

III. Legal Authority

We are proposing to issue this rule under the authority of the provisions of the FD&C Act that apply to medical devices (21 U.S.C. 301 et seq.).

To permit devices to be shipped for investigational use, section 520(g) of the FD&C Act authorizes the exemption of investigational devices from otherwise applicable provisions of the FD&C Act relating to misbranding, registration, premarket notification, performance standards, premarket approval, banned devices, records and reporting requirements, good manufacturing

practice requirements, and requirements relating to the use of color additives in devices. Under section 520(g) of the FD&C Act, the procedures and conditions that FDA³ is authorized to prescribe for granting an IDE include the requirement that an application be submitted to FDA, in such form and manner as the Agency shall specify, and other requirements necessary for the protection of the public health and safety. Section 520(g) also requires that the information submitted in support of an IDE application be “adequate to justify the proposed clinical testing.” In investigations involving human subjects, the person applying for the exemption (the sponsor) must comply with a number of requirements to assure that the rights and safety of subjects are adequately protected. To provide for flexibility in regulatory requirements, section 520(g) of the FD&C Act permits variations in the procedures and conditions governing IDEs, depending on the nature, scope, duration, and purpose of the study.

Section 515(c)(1)(A) of the FD&C Act requires that PMA applications contain, among other information, full reports of all information, published or known to or which should reasonably be known to the PMA applicant, concerning investigations bearing on the safety or effectiveness of the device for which premarket approval is sought. Section 515(d)(2) of the FD&C Act states that FDA shall deny approval of a PMA application if the Agency finds that “there is a lack of a showing of reasonable assurance that such device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof” or “there is a lack of a showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof,” among other reasons. Whether data from an investigation involving human subjects support the

³ In light of section 1003(d) of the FD&C Act (21 U.S.C. 393(d)) and the Secretary of Health and Human Services’ (the Secretary’s) delegation 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.”

safety or effectiveness of a device depends, in part, on whether the study was conducted in accordance with ethical and other principles that provide assurance of the quality and integrity of clinical data and adequate protection of human subjects. Even if the data derive from improperly conducted clinical studies, the data must be submitted in a PMA application under section 515(c)(1)(A) of the FD&C Act.

Under section 513(i) of the FD&C Act (21 U.S.C. 360c(i)), determinations of substantial equivalence include some inquiry into the comparable safety and effectiveness of the device, where appropriate. For devices that have the same intended use as the predicate device but different technological characteristics, information submitted to demonstrate substantial equivalence must include “appropriate clinical or scientific data[,] if deemed necessary” by FDA, showing that “the device is as safe and effective as a legally marketed device” and “does not raise different questions of safety and effectiveness than the predicate device.” As described in this document, whether data from a clinical study support the safety or effectiveness of a device--or, in the context of some premarket notifications, the comparable safety and effectiveness of a device as part of a substantial equivalence demonstration--depends in part on whether the study was conducted in accordance with ethical and other principles that provide assurance of the quality and integrity of clinical data and adequate protection of human subjects.

Under section 520(m) of the FD&C Act, FDA may grant an HDE if FDA finds that: The device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States; the device would not be available to a person with such disease or condition unless FDA grants the exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition; and the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable

benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Again, whether data from clinical studies submitted in an HDE application support that the probable benefits of the device outweigh its risks depends, in part, on whether the study was conducted in accordance with ethical and other principles that provide assurance of the quality and integrity of clinical data and adequate protection of human subjects.

Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes the Agency to issue regulations for the efficient enforcement of the FD&C Act.

These statutory provisions authorize us to issue regulations describing when we may consider data from clinical trials, whether conducted inside or outside the United States, as reliable evidence supporting an IDE, PMA, 510(k), PDP, or HDE application or submission.

IV. Analysis of Economic Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct 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). The Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the requirements are

likely to impose a burden on a substantial number of affected small entities, the Agency projects that the proposed rule, if finalized, will have a significant economic impact on a substantial number of small entities, and has conducted an Initial Regulatory Flexibility Analysis as required under the Regulatory Flexibility Act.

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 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 \$139 million, using the most current (2011) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Summary

The proposed rule will require that clinical studies conducted outside the United States and used to support IDE applications, 510(k) submissions, PMA applications, HDE applications, or PDP applications comply with GCP. GCP standards include review and approval by an independent ethics committee and obtaining and documenting human subjects' informed consent. In addition, the proposed rule seeks to amend the 510(k), HDE, and IDE requirements for FDA acceptance of data from clinical studies conducted inside the United States to parallel existing FDA requirements for PMA applications. FDA has not quantified the benefits of the proposed rule that would come from increased collection of information that would provide FDA with greater assurance of clinical data quality and human subject protection, particularly as it pertains to clinical studies conducted outside the United States. Costs would arise from

increased labor costs associated with obtaining, documenting, and maintaining records to meet the proposed requirements. The estimated costs of complying with these requirements range from \$0.30 million to \$24.03 million.

The full analysis of economic impacts is available at

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

(See also Ref. 1).

V. Environmental Impact

The Agency 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 provisions that are subject to review by the OMB under the PRA (44 U.S.C. 3501-3520). A description of these provisions is given in the Description section of this document 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 proposed 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: Human Subject Protection; Data Requirements for Medical Device Related Clinical Studies

Description: In this document is a discussion of the regulatory provisions we believe are subject to the PRA and the probable information collection burden associated with these provisions.

Description of Respondents: The reporting and recordkeeping requirements referenced in this document are imposed on a device sponsor or applicant.

Section 807.87 Information required in a premarket notification submission (OMB Control No. 0910-0120)

Section 807.87 is being amended to address requirements for 510(k) submissions supported by clinical data. For clinical studies conducted in the United States, submitters will be required to submit a statement as described in § 807.87(j)(1). For clinical studies conducted outside the United States, submitters will be required to submit a statement as described in § 807.87(j)(2).

Section 812.2 Clinical studies conducted outside the United States (OMB Control No. 0910-0078)

For any clinical studies conducted outside the United States to be submitted in support of: (1) An IDE, (2) a PMA, (3) a PDP, (4) an HDE or (5) a 510(k), the sponsor or applicant will be required to maintain supporting information and retain records as described in § 812.2(e).

Section 812.27 Report of prior investigations (OMB Control No. 0910-0078)

Section 812.27 is being amended to address requirements for IDE applications supported by clinical data. For clinical studies conducted in the United States, sponsors will be required to submit a statement as described in § 812.27(b)(4)(i). For clinical studies conducted outside the United States, sponsors will be required to submit a statement as described in § 812.27(b)(4)(ii).

Section 812.28 Clinical studies conducted outside the United States (OMB Control No. 0910-

NEW)

Section 812.28 is being proposed to address the requirements for acceptance of foreign clinical data to support an IDE or a device marketing application or submission. The sponsor or applicant will be required to submit statements as described in § 812.28(a)(1) and (a)(2); provide a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP that includes the information in § 812.28(b)(1) through (b)(12) or a cross-reference to another section of the submission where the information is located; and retain the records as described in § 812.28(c).

Section 812.140 Records Retention (OMB Control No. 0910-0078)

Section 812.140 is being amended to address record retention requirements for investigators and sponsors. An investigator or sponsor will be required to maintain records as described in § 812.140(d).

Section 814.20 Application (OMB Control No. 0910-0231)

Section 814.20 is being amended to address requirements for a PMA supported by data from clinical studies conducted outside the United States. The applicant will be required to submit a statement and information as required by § 814.20(b)(6)(ii)(C).

Section 814.104 Original Applications (OMB Control No. 0910-0332)

Section 814.104 is being amended to address submission of data from clinical studies in an HDE. To the extent the applicant includes clinical information, the applicant will be required to include the information and statements described in § 814.104(b)(4)(i).

Table 1.--Estimated Annual Reporting Burden¹

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
807.87	1,500	1	1,500	0.25 (15 minutes)	375
812.27(b)(4)(i)	400	1	400	1	400
812.27(b)(4)(ii)	100	1	100	0.25 (15 minutes)	25
812.28(a)(1)	1,500	1	1,500	0.25 (15 minutes)	375
812.28(a)(2)	1,500	1	1,500	0.25 (15 minutes)	375
812.28(b)	1,500	1	1,500	10	15,000
814.20	10	1	10	0.50 (30 minutes)	5
814.104	10	1	10	8	80
Total					16,635

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

Table 2.--(Ongoing) Estimated Annual Recordkeeping Burden¹

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
812.2(e)	500	1	500	1	500
812.28(c)	1,500	1	1,500	1	1,500
812.140	10	1	10	1	10
Total					2,010

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

The total estimated burden imposed by these information collection requirements is 18,645 annual hours. The estimated burden is based on the most recent empirical data in the relevant collections with the numbers updated to reflect the current burden of these requirements.

It should be noted that while the information collection requirements referenced in this document are revisions to current approved information collections, these collection

requirements are being submitted to OMB as a new information collection, with the expectation the currently approved requirements will be amended. As such the following collections of information will be amended and submitted to OMB for approval as revisions to currently approved information collections once the rule is finalized and the collections are due for renewal. The collections to be amended include: Investigational Device Exemptions Reports and Records--21 CFR 812, OMB control number 0910-0078; Premarket Notification--21 CFR Part 807, Subpart E, OMB control number 0910-0120; Premarket Approval of Medical Devices--21 CFR Part 814, OMB control number 0910-0231; and Medical Devices: Humanitarian Use Device-21 CFR Part 814, Subpart H, OMB control number 0910-0332.

To ensure that comments on these new information collection requirements are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-6974, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the title "Human Subject Protection; Data Requirements for Medical Device Related Clinical Studies."

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the Federal Register.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would 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, the Agency tentatively concludes 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 that any final rule based on this proposal become effective 180 days after the final rule is published in the Federal Register.

IX. Request for Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES) . It is only necessary to send one set of comments. Identify comments 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, and will be posted to the docket at <http://www.regulations.gov>.

X. Reference

The following reference has 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, and are available electronically at <http://www.regulations.gov>.

1. Preliminary Regulatory Impact Analysis of the Proposed Rule to Human Subject Protection; Acceptance of Data From Clinical Studies for Medical Devices, Docket No. FDA-2013-N-0080.

List of Subjects

21 CFR Part 807

Confidential business information, Imports, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

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 parts 807, 812, and 814 be amended as follows:

**PART 807--ESTABLISHMENT REGISTRATION AND DEVICE LISTING FOR
MANUFACTURERS AND INITIAL IMPORTERS OF DEVICES**

1. The authority citation for 21 CFR part 807 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 360, 360c, 360e, 360i, 360j, 371, 374, 381, 393; 42 U.S.C. 264, 271.

2. Section 807.87 is amended by redesignating paragraphs (j), (k), and (l) as paragraphs (k), (l), and (m), respectively, and by adding new paragraph (j) to read as follows:

§ 807.87 Information required in a premarket notification submission.

* * * * *

(j) For a submission containing clinical data:

(1) If the data are from clinical studies conducted in the United States, a statement that each study was conducted in compliance with applicable requirements in the protection of

human subjects regulations in part 50 of this chapter, the institutional review boards regulations in part 56 of this chapter, and the investigational device exemptions regulations in part 812 of this chapter, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(2) If the data are from clinical studies conducted outside the United States, the requirements under §§ 812.2(e) and 812.28 of this chapter apply. If any such study was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a), include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected.

* * * * *

PART 812--INVESTIGATIONAL DEVICE EXEMPTIONS

3. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b–263n.

4. Section 812.2 is amended by removing paragraphs (b) introductory text, (b)(1) introductory text, (b)(2), and (e); redesignating paragraphs (b)(1)(i) through (b)(1)(vii) as paragraphs (b)(1) through (b)(7), respectively; and adding new paragraphs (b) introductory text and (e) to read as follows:

§ 812.2 Applicability.

* * * * *

(b) Abbreviated requirements. Unless FDA has notified a sponsor under § 812.20(a) that approval of an application is required, an investigation of a device other than a significant risk

device is considered to have an approved application for IDE if the device is not a banned device and the sponsor:

* * * * *

(e) Clinical studies conducted outside the United States. Clinical studies conducted outside the United States to be submitted in support of an IDE or a device marketing application or submission (an application under section 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act or a premarket notification submission under section 510(k) of the Federal Food, Drug, and Cosmetic Act), are subject to the following requirements:

(1) For a significant risk device, as defined in § 812.3(m), the principles of good clinical practice, as defined in § 812.28(a), maintenance of supporting information as described in § 812.28(b), and records retention as described in § 812.28(c).

(2) For a device, other than a significant risk device, or a device investigation that would otherwise meet the exemption requirements in § 812.2(c), the principles of good clinical practice, as defined in § 812.28(a), maintenance of the supporting information as described in § 812.28(b)(1), (b)(4), (b)(5), (b)(7), (b)(8), (b)(9), and (b)(11), and records retention as described in § 812.28(c).

5. Section 812.3 is amended by adding paragraph (t) to read as follows:

§ 812.3 Definitions.

* * * * *

(t) 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.

6. Section 812.27 is amended by adding paragraph (b)(4) to read as follows:

§ 812.27 Report of prior investigations.

* * * * *

(b) * * *

(4)(i) If information on clinical studies conducted in the United States is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the protection of human subjects regulations in part 50 of this chapter, the institutional review boards regulations in part 56 of this chapter, and the investigational device exemptions regulations in part 812, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical study.

(ii) If information on clinical studies conducted outside the United States is provided to support the IDE, the requirements under §§ 812.2(e) and 812.28 apply. If any such study was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a), the report of prior investigations shall include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical study.

7. Section 812.28 is added to subpart B to read as follows:

§ 812.28 Clinical studies conducted outside the United States.

(a) Acceptance of data from clinical studies conducted outside the United States to support an IDE or a device marketing application or submission (an application under section 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act or a premarket notification submission under section 510(k) of the Federal Food, Drug, and Cosmetic Act). FDA will accept information on clinical studies conducted outside the United States to support an IDE or a device marketing application or submission if the data are valid, the information specified in paragraph (b) of this section and required elsewhere in parts 807, 812, and 814 of this chapter, as applicable, is submitted, and the following conditions are met:

(1) A statement is provided that all such studies have been 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.

(2) A statement is provided assuring the availability of the data from the study to FDA for validation through an onsite inspection if the Agency deems it necessary, and if otherwise authorized by law, or through other appropriate means.

(b) Supporting information. A sponsor or applicant who submits data from a clinical study conducted outside the United States in support of an IDE or a device marketing application or submission, in addition to information required elsewhere in parts 807, 812, and 814 of this chapter, as applicable, shall provide a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1) of this section. The description is not required to duplicate information already submitted in the application or submission. Instead, the description must provide either the following information or a cross-reference to another section of the application or submission where the information is located:

- (1) Names and addresses of investigators and research facilities;
- (2) The investigator's qualifications;
- (3) A description of the research facility(ies);
- (4) A detailed summary of the protocol and results of the study and, should FDA request, certified copies of case records maintained by the investigator or additional background data such as hospital or other institutional records;
- (5) Either a statement that the device used in the study conducted outside the United States is identical to the device that is the subject of the submission or application, or a detailed description of the device and each important component (including all materials and specifications), ingredient, property, and principle of operation of the device used in the study conducted outside the United States and a comparison to the device that is the subject of the

submission or application that indicates how the studied device is similar to and/or different from the device that is the subject of the submission or application;

(6) If the study is intended to support the safety and effectiveness of a device, a discussion demonstrating that the data and information constitute valid scientific evidence within the meaning of § 860.7 of this chapter;

(7) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in § 812.3(t). The sponsor or applicant must maintain records supporting such statement, including records describing the qualifications of IEC members, and make these records available for Agency review upon request;

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

(9) A description of how informed consent was obtained;

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

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

(12) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1) 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) Records. A sponsor or applicant must retain the records required by this section for a clinical study conducted outside the United States as follows:

(1) If the study is submitted in support of an IDE, for 2 years after the termination or completion of the IDE;

(2) If the study is submitted in support of a premarket notification submission, premarket approval application, a notice of completion of a product development protocol, or a humanitarian device exemption application, for 2 years after an Agency decision on that submission or application.

8. Section 812.140 is amended by revising paragraph (d) to read as follows:

§ 812.140 Records.

* * * * *

(d) Retention period. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, or a premarket notification submission.

* * * * *

PART 814--PREMARKET APPROVAL OF MEDICAL DEVICES

9. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 360, 360c-360j, 371, 372, 373, 374, 375, 379, 379e, 381.

10. Section 814.15 is amended by removing paragraphs (b) and (c); by redesignating paragraph (d) as paragraph (b) and paragraph (e) as paragraph (c); and by revising paragraph (a) to read as follows:

§ 814.15 Research conducted outside the United States.

(a) A clinical study conducted outside the United States and submitted in support of a PMA shall comply with the relevant provisions of part 812 of this chapter as set forth in §§ 812.2(e) and 812.28 of this chapter.

* * * * *

11. Section 814.20 is amended by adding paragraph (b)(6)(ii)(C) to read as follows:

§ 814.20 Application.

* * * * *

(b) * * *

(6) * * *

(ii) * * *

(C) For clinical studies conducted outside the United States that are intended to support the PMA, the requirements under §§ 812.2(e) and 812.28 of this chapter apply. Required information may be incorporated by cross-reference to another section of the application that contains such information. If any such study was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a) of this chapter, include a brief statement of the reason for not conducting the study in accordance with GCP and a description of steps taken to assure that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects were protected. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical study.

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12. Section 814.45 is amended by revising paragraph (a)(5) to read as follows:

§ 814.45 Denial of approval of a PMA.

(a) * * *

(5) Any clinical investigation involving human subjects described in the PMA, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter or GCP referenced in § 814.15(a) and described in § 812.28(a) of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable.

* * * * *

13. Section 814.46 is amended by revising paragraph (a)(4) to read as follows:

§ 814.46 Withdrawal of approval of a PMA.

(a) * * *

(4) Any clinical investigation involving human subjects described in the PMA, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter or GCP referenced in § 814.15(a) and described in § 812.28(a) of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable.

* * * * *

14. Section 814.104 is amended by revising paragraph (b)(4)(i) to read as follows:

§ 814.104 Original applications.

* * * * *

(b) * * *

(4) * * *

(i) In lieu of the summaries, conclusions, and results from clinical investigations required under § 814.20(b)(3)(v)(B), (b)(3)(vi), and the introductory text of (b)(6)(ii), the applicant shall include the summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefits of the device and to the extent the applicant includes such clinical information, the applicant shall include the statements described in § 814.20(b)(6)(ii)(A) and (b)(6)(ii)(B) with respect to clinical investigations conducted in the United States and the information described in § 814.20(b)(6)(ii)(C) with respect to clinical investigations conducted outside the United States; and

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Dated: February 20, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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