Order 1050.1F, ''Environmental Impacts: Policies and Procedures,'' paragraph 5–6.5a. This airspace action is not expected to cause any potentially significant environmental impacts, and no extraordinary circumstances exist that warrant preparation of an environmental assessment.

Lists of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

Adoption of the Amendment

In consideration of the foregoing, the Federal Aviation Administration amends 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D, AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for part 71 continues to read as follows:

Authority: 49 U.S.C. 106(f), 106(g); 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of FAA Order 7400.11B, Airspace Designations and Reporting Points, dated August 3, 2017, and effective September 15, 2017, is amended as follows:

Paragraph 6005 Class E Airspace Areas Extending Upward From 700 Feet or More Above the Surface of the Earth.

* * * * *

ANM CO E5 Rangely, CO [New]

Rangely Airport, CO

(Lat. 40°05′38″ N, long. 108°45′47″ W)

That airspace extending upward from 700 feet above the surface of Rangely Airport within the area bounded by lat. 40°04′58″ N, long. 109°01′51″ W; to lat. 40°12′20″ N, long. 108°35′41″ W; to lat. 40°09′07″ N, long. 108°32′59″ W; to lat. 40°01′42″ N, long. 108°36′14″ W; to lat. 39°59′18″ N, long. 108°45′09″ W; to lat. 40°00′25″ N, long. 109°01′00″ W; thence to the point of beginning.

Issued in Seattle, Washington, on February 7, 2018.

B.G. Chew,

Acting Manager, Operations Support Group, Western Service Center.

[FR Doc. 2018–03401 Filed 2–20–18; 8:45 am]

BILLING CODE 4910–13–P

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 Investigations for Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending its regulations on acceptance of data from clinical investigations for medical devices. We are requiring that data submitted from clinical investigations conducted outside the United States intended to support an investigational device exemption (IDE) application, a premarket notification (510(k)) submission, a request for De Novo classification, a premarket approval (PMA) application, a product development protocol (PDP) application, or a humanitarian device exemption (HDE) application be from investigations conducted in accordance with good clinical practice (GCP), which includes obtaining and documenting the review and approval of the clinical investigation by an independent ethics committee (IEC) and obtaining and documenting freely given informed consent of subjects, which includes individuals whose specimens are used in investigations of medical devices. The final rule updates the criteria for FDA acceptance of data from clinical investigations conducted outside the United States to help ensure the quality and integrity of data obtained from these investigations and the protection of human subjects. As part of this final rule, we are also amending the IDE, 510(k), and HDE regulations to address the requirements for FDA acceptance of data from clinical investigations conducted inside the United States. The final rule provides consistency in FDA requirements for acceptance of data from clinical investigations, whatever the application or submission type.

DATES: This rule is effective February 21, 2019. See section III of this document for additional explanation of the effective date of this final rule.

FOR FURTHER INFORMATION CONTACT: Soma Kalb, Director, Investigational Device Exemptions Staff, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1534, Silver Spring, MD 20993, 301–796–6359; and Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993, 240–402–7911.

SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of the Final Rule

Through this rule, FDA is updating the standards for FDA acceptance of data from clinical investigations conducted outside the United States to help ensure the quality and integrity of data obtained from these investigations and the protection of human subjects. In this rule, FDA is amending the regulations for PMA applications, HDE applications, IDE applications, and premarket notification submissions. As part of this rule, FDA also is amending the IDE regulations and the premarket notification regulations to address the requirements for FDA acceptance of data from clinical investigations conducted inside the United States. The amendments are intended to provide consistency in FDA requirements for acceptance of clinical data, whatever the application or submission type.

Legal Authority

FDA is issuing this rule under the authority of the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) that apply to medical devices (21 U.S.C. 301 *et seq.*), including section 520(g) regarding IDEs (21 U.S.C. 306j(g)), section 515(c)(1)(A) and (d)(2) regarding PMAs (21 U.S.C. 360e(c)(1)(A) and (d)(2)), sections 510(k) and 513(i) regarding premarket notifications and determinations of substantial equivalence (21 U.S.C. 360(k) and 360c(i), respectively), section 520(m) regarding HDEs, section 513(f)(2) regarding De Novo classifications, section 569B regarding acceptance of data from clinical investigations conducted outside the United States (21 U.S.C. 360bbb–8b), and section 701(a) regarding regulations for the efficient enforcement of the FD&C Act (21 U.S.C. 371(a)).

Summary of the Major Provisions of the Final Rule

This rule requires that sponsors and applicants of submissions and applications that include clinical investigations conducted outside the United States and submitted to support an IDE or device marketing application or submission provide statements and information regarding how the

investigations conform with GCP. FDA defines GCP as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes review and approval by an IEC before initiating an investigation, continuing IEC review of ongoing investigations, and obtaining and documenting the freely given informed consent of subjects. FDA also is including requirements for the acceptance of data from clinical investigations conducted in the United States submitted to support an IDE application, an HDE application, or a premarket notification submission. The changes require a statement regarding compliance with FDA regulations for human subject protection, institutional review boards, and IDEs when the investigations are conducted in the United States. With the above described changes, the rule is intended to update the standards for FDA acceptance of data from clinical investigations and to help ensure the quality and integrity of data obtained from these investigations and the protection of human subjects.

Summary of Costs and Benefits

The total estimated annualized costs of complying with these requirements, over 10 years, range from $0.8 million to $22.1 million with a 7 percent discount rate and range from $0.7 million to $22.0 million with a 3 percent discount rate. We lack data to quantify benefits, but expect the final rule will provide greater assurance of clinical data quality and integrity and human subject protection.

Table of Contents

I. Background

In the **Federal Register** of February 25, 2013 (78 FR 12664), FDA issued a proposed rule to revise the regulations in parts 807, 812, and 814 (21 CFR parts 807, 812, and 814) on the conditions under which FDA will accept data from clinical studies as support for an IDE application, a 510(k) submission, a PMA application, a PDP application, or an HDE application. The proposed rule addressed revisions to update the criteria for acceptance of data from clinical studies to help ensure the quality and integrity of data obtained from those studies and the protection of human subjects. In particular, the proposed rule addressed revisions to part 814 to update the criteria for acceptance of data from clinical studies conducted outside the United States. The proposed rule also addressed revisions to parts 807, 812, and 814, subpart H, to identify criteria for acceptance of data from clinical studies conducted both inside and outside the United States. The proposed rule identified similar criteria for acceptance of clinical data for all application and submission types for medical devices.

FDA received comments on the proposed rule from 13 entities: 7 medical device manufacturers, 2 academia, 2 associations, 1 drug manufacturer, and 1 consumer. The comments were supportive of GCP for medical devices as a mechanism to help ensure the quality and integrity of the data obtained from clinical investigations and human subject protection. Comments generally supported FDA's efforts to clarify the criteria for acceptance of clinical data submitted to FDA to support an IDE or a device marketing application or submission. Many comments, however, raised concerns about the proposed rule and some believed the rule was premature.

II. Overview of the Final Rule

FDA considered all comments received on the proposed rule and we have made several important changes, primarily for clarity and accuracy, to reduce burden, and to provide flexibility in meeting regulatory requirements. The main changes from the proposed rule include:

- Deleting proposed § 812.2(e) because comments received indicated confusion regarding the scope of the rule. Proposed § 812.2(e) described the principles of good clinical practice applicable to studies conducted outside the United States that will be submitted to FDA in support of an IDE or device marketing application or submission. Including this information within the applicability section of the IDE regulations led some to believe that FDA intended for part 812 to apply to all clinical investigations conducted outside the United States. We have deleted proposed § 812.2(e) and included the supporting information requirements for clinical investigations conducted outside the United States in new § 812.28(a)(2).
- Clarifying that the rule applies to clinical data from ''investigations'' as defined in § 812.3(h) rather than using other terms, such as ''clinical study'' and ''clinical trial,'' in an interchangeable manner.
- Clarifying that the rule applies to the acceptance of data from clinical investigations conducted outside the United States when submitted to support an IDE or a device marketing application or submission rather than to all clinical data contained in such applications or submissions.
- Adding new § 812.28(a)(2), which identifies different supporting information requirements based on whether the investigation is for a significant risk device or a non-significant risk device, or meets the exemption criteria in § 812.2(c). Also, for investigations meeting the exemption criteria in § 812.2(c), the specified supporting information is required to be maintained and be made available for Agency review upon request by FDA.
- Adding a requirement in new § 812.28(a)(2) that the sponsor's or applicant's rationale for considering an investigation to be of a non-significant risk device or to meet the exemption criteria in § 812.2(c) be made available upon request by FDA. We also clarify in the preamble that we do not expect foreign IECs to provide oversight of the significant risk versus non-significant risk device determination and that sponsors and applicants may proceed based upon their own determination or based on a determination by FDA.
- Changing the requirements related to supporting information on incentives provided to subjects to require that the information be maintained for all clinical investigations but only require submission for significant risk device investigations. For investigations of non-significant risk devices and investigations meeting the exemption criteria in § 812.2(c), the final rule requires that information on incentives be made available upon FDA's request. We made this change because of concerns that incentives can affect data integrity for all investigations. We do not believe this requirement will be

overly burdensome. Informed consent documents usually describe incentives and the IEC reviews this information. Therefore, providing the description of incentives to FDA should not be a burden. FDA will allow some flexibility in how sponsors or applicants comply with this provision. If the informed consent form includes an explanation of any incentives provided to subjects, a sponsor or applicant could submit a model consent form to meet the requirement. Alternatively, a sponsor or applicant could also satisfy the requirement by submitting a description of any incentives provided to subjects to participate in the investigation.

- Adding a waiver provision in new § 812.28(c) to allow sponsors and applicants to request a waiver of any applicable requirements under § 812.28(a)(1) and (b) if adequate justification can be provided. Although we believe the rule is flexible enough to address concerns about compliance with the laws and regulations of other countries and in situations when the sponsor or applicant did not initiate or conduct the clinical investigations, this revision will allow sponsors and applicants to request a waiver if they can provide adequate justification. Although the proposed rule included provisions that would allow a sponsor or applicant to explain why a clinical investigation was not conducted in accordance with GCP when submitted in support of an IDE or a device marketing application or submission, addition of the waiver provision would allow sponsors and applicants to request a waiver prior to submitting an application or submission supported by clinical data from investigations conducted outside the United States. A waiver may be requested prior to initiation of an investigation. The waiver provision requires a sponsor or applicant to justify a waiver request and allows FDA to decide whether to grant or deny a waiver on a case-by-case basis, taking into account all appropriate circumstances, based on whether or not the waiver would be in the interest of public health.
- Adding a provision in new § 812.28(e) to clarify that, for clinical investigations conducted outside the United States that do not meet the conditions under § 812.28(a), FDA may accept the information from such clinical investigations to support an IDE or a device marketing application or submission if FDA believes that the data and results from such clinical investigations are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. Although this was implied in the provisions of the proposed rule allowing a sponsor or applicant to explain why a clinical investigation was not conducted in accordance with GCP, new § 812.28(e) makes this clear.
- Modifying the definition of an IEC in § 812.3(t) by changing the reference to the definition of an institutional review board (IRB). In the proposed rule, we referenced § 56.102(g) (21 CFR 56.102(g)). In the final rule, we reference § 812.3(f), which incorporates § 56.102(g), because § 812.3(f) is specific to devices. While these definitions vary slightly, we interpret the definitions as having the same meaning. We have elected to reference the definition in § 812.3(f) in order to reference definitions in part 812 whenever possible.
- Changing the requirement in proposed § 812.28(a)(2), now § 812.28(a)(3), that a statement is provided assuring the availability of the data from the study to FDA for validation through an onsite inspection to a requirement that FDA is able to validate the data from the investigation through an onsite inspection if the Agency deems it necessary.
- Amending §§ 812.28 and 812.140(d) to clarify that these provisions apply to requests for De Novo classifications, which are a type of device marketing submission. FDA intended for §§ 812.28 and 812.140(d) to encompass all device marketing applications and submissions. As stated in the proposed rule, ''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'' (78 FR 12664 at 12665). This amendment will provide for consistency by ensuring that FDA requirements for acceptance of data from clinical investigations conducted outside the United States are the same for all device marketing applications and submissions, and will help to provide greater assurance of the quality and integrity of the data from such investigations submitted in support of this type of device marketing submission.

III. Effective Date

In response to comments, and after consideration of the intent and purpose of the new requirements, we have determined that the effective date will be 1 year after the publication of this final rule in the **Federal Register.** This final rule will apply to all clinical investigations that enroll the first subject on or after the effective date of this rule and that support an IDE or a device marketing application or submission to FDA. For the purposes of this rule, a subject is considered enrolled when the subject, or the subject's legally authorized representative, agrees to participate in a clinical investigation as indicated by signing of the informed consent document(s), or participates in an investigation meeting the requirements of § 50.24 (21 CFR 50.24).

If an investigation conducted outside the United States enrolled the first subject prior to the rule's effective date, then the requirements in § 814.15 (21 CFR 814.15) prior to the rule's effective date would apply. Specifically, if data from clinical investigations conducted outside the United States that enrolled the first subject prior to the effective date of this rule are submitted in support of a PMA application, FDA will accept the data 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 shall state in detail any differences between those standards and the ''Declaration of Helsinki'' and explain why they offer greater protection to the human subjects. (See § 814.15(b).)

In section IV.K of this document, we discuss the effective date further in our response to the comments concerning the implementation of the rule.

IV. Comments on the Proposed Rule

A summary of the comments submitted to the docket and our responses follow. To make it easier to identify comments and our responses, the word ''Comment,'' in parentheses, will appear before each comment; and the word ''Response,'' in parentheses, will appear before each response. We have numbered the comments to make it easier to distinguish between comments. The numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with them. We have combined similar comments under one numbered comment.

A. International Harmonization

Section 812.28(a) of the proposed rule would identify criteria for FDA acceptance of data from clinical studies conducted outside the United States and submitted in support of an IDE or a device marketing application or submission. Those criteria would require that such studies be conducted in accordance with GCP. This

requirement would replace the requirement in the PMA regulations that studies be conducted in conformance with the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever accord greater protection to human subjects. The requirement would be new for IDE applications and other device marketing applications and submissions that previously did not address acceptance of data from clinical studies conducted outside the United States.

(Comment 1) Several comments raised concerns that FDA was not seeking a harmonized global approach to the regulation of medical devices. Comments raised concerns with various aspects of the proposed rule, such as a harmonized GCP standard, definitions of various terms, and expectations for requirements.

(Response) FDA disagrees. The rule only addresses the criteria for FDA acceptance of clinical data submitted to FDA that support an IDE or a device marketing application or submission. The rule does not address other aspects of medical device regulations, such as when an application or submission must be supported by clinical data, the type of clinical data needed, etc.

FDA has and will continue to promote global harmonization in many aspects of medical device development and regulation. With respect to medical device good clinical practice, FDA's international activities include harmonizing regulatory requirements with our foreign counterparts, industry, and other international stakeholders. For example, FDA plays a key role in forums such as the International Medical Device Regulators Forum (IMDRF) where global medical device good clinical practice was discussed during the IMDRF meeting in Florianopolis, Brazil, in September 2016. Additionally, FDA continues to be directly involved in good clinical practice standard development, including those of the International Organization for Standardization (ISO) and the International Conference on Harmonisation (ICH).

(Comment 2) Several comments raised concerns that an internationally accepted GCP standard for medical devices does not exist and the rule should not be finalized until harmonized international GCP guidelines for medical devices have been established. They note that the ICH E6 GCP guidelines for pharmaceuticals were developed through a collaborative approach involving international regulators and drug and biological product manufacturers with all stakeholders having an equal voice. They state that such guidelines do not exist for medical devices and that FDA should first seek a collaborative global approach and establishment of a harmonized guidance through the IMDRF organization, or similar group, with industry participation.

(Response) FDA disagrees that there has not been global collaboration in the development of a GCP standard for medical devices. The ''Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice'' standard, ISO 14155:2011, represents an international GCP standard for medical devices that FDA has recognized (March 16, 2012, 77 FR 15765). FDA acknowledges that the standard development processes are different between ICH and ISO, but notes that several countries participated in the development of ISO 14155:2011, including Australia, Belgium, Brazil, Canada, China, France, Ireland, Italy, Japan, Spain, the United Kingdom, and the United States. Several medical device companies also participated in the standard development process. Additionally, ISO 14155:2011 is recognized by most of the members of the IMDRF (Australia, Brazil, Canada, European Union, Japan, and the United States) as well as other countries, including Indonesia, Malaysia, Singapore, Thailand, and Taiwan.

FDA's rule does not identify a specific GCP standard for sponsors and applicants to follow. Instead, the rule includes a definition of GCP in § 812.28(a)(1), which is consistent with the definition in § 312.120 (21 CFR 312.120), that embodies well recognized GCP principles and has been generally accepted. This allows sponsors of clinical investigations conducted outside the United States to determine an appropriate GCP standard to use for clinical investigations that will produce data to support an IDE or a device marketing application or submission to FDA. The rule helps to ensure that the data and results from such investigations are credible and accurate and that the rights, safety, and well-being of human subjects are adequately protected, while also being sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical investigations.

(Comment 3) One comment suggested that once a harmonized GCP guideline is adopted, many of the requirements should be waived for countries that adopt the harmonized GCP guideline.

(Response) FDA disagrees with this suggestion. For FDA acceptance of data from clinical investigations conducted outside the United States to support an IDE or a device marketing application or submission, the rule requires, among other things, that sponsors and applicants provide a statement that the investigation was conducted in accordance with GCP and provide supporting information. If these requirements were waived, a submission or application would not contain information regarding the sponsor's or applicant's conformity with GCP. The fact that the country where the investigation is conducted had adopted a GCP guideline would only identify the GCP guideline that should be followed but would not provide information regarding conformity of the clinical investigation with the GCP guideline.

(Comment 4) Two comments raised a concern that the rule may run into resistance from foreign regulators and clinical communities who may interpret the rule as FDA unilaterally imposing FDA GCP standards on them. Two other comments were concerned that the rule may conflict with the rules and regulations of other countries. A fifth comment stated that FDA does not have the authority to regulate the conduct of studies conducted outside the United States.

(Response) FDA does not intend to regulate clinical investigations conducted outside the United States. The rule only identifies the criteria for FDA acceptance of clinical data submitted to FDA to support an IDE or a device marketing application or submission. We have modified the rule by removing proposed § 812.2(e) to clarify that the rule does not apply part 812 to investigations conducted outside the United States but rather addresses the conditions for FDA acceptance of clinical data when submitted to support an IDE or device marketing application or submission. FDA expects that foreign clinical investigations will be conducted in accordance with local laws and regulations. The application of a GCP standard would be in addition to the local laws and regulations to the extent that the local laws and regulations do not incorporate such a standard.

FDA's rule does not identify a specific GCP standard for sponsors and applicants to follow. Instead, the rule includes a definition of GCP in § 812.28(a)(1), which is consistent with the definition in § 312.120, that embodies well recognized GCP principles and has been generally accepted. Although the rule does not identify a specific GCP standard, we note that ISO 14155:2011, a GCP standard for medical devices that FDA has recognized, includes provisions for meeting local requirements. FDA

believes that sponsors and applicants who follow ISO 14155:2011 in the conduct of clinical investigations will be able to meet the requirement in § 812.28(a)(1) of this rule as well as the local laws and regulations of the countries where the investigations are conducted.

FDA believes the requirements outlined in the rule allow the flexibility needed to accommodate the laws and regulations of other countries. We also believe that conducting a clinical investigation according to a standard that meets the definition of GCP as provided in the rule will help to ensure the integrity and quality of the data and the protection of subjects. If needed, the rule allows sponsors and applicants to explain why GCP was not followed and to describe the steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of human subjects have been adequately protected. Additionally, we have added a waiver provision to allow sponsors and applicants to request a waiver from any applicable requirement in § 812.28(a)(1) and (b) of the rule (see new § 812.28(c)). If a country's clinical investigation requirements are not congruent with the GCP definition in this rule or with a GCP standard and the sponsor or applicant cannot meet GCP for the investigation, they may provide an explanation of the departure from GCP or request a waiver. FDA will take this information into account when considering the extent to which the Agency can rely on the data from these clinical investigations on a case-by-case basis.

B. Application of the Rule

(Comment 5) Several comments raised concerns that the rule may be interpreted as expanding the types of studies required to be included in applications and submissions and requiring GCP for all studies. Some comments requested clarification of the use of the terms ''clinical investigation,'' ''clinical study,'' and ''clinical trial'' in a seemingly interchangeable manner. The comments noted that the terms ''clinical study'' and ''clinical trial'' are not defined but the term ''investigation'' is defined in § 812.3(h).

(Response) While FDA intended that ''clinical study'' and ''clinical trial'' have the same meaning as ''clinical investigation,'' to avoid any confusion, FDA has revised the rule to use the term ''clinical investigation'' with the meaning as defined in § 812.3(h) (''*Investigation* means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.''). We have also revised the rule to clarify that it applies when data from clinical investigations are provided to support an IDE or a device marketing application or submission; for example, when clinical data are submitted in: (1) A 510(k) submission to demonstrate substantial equivalence, (2) a PMA application to demonstrate a reasonable assurance of safety and effectiveness, or (3) an HDE application to demonstrate reasonable assurance of safety and probable benefit. When clinical data from investigations are included in applications and submissions as supplementary information and not as support, demonstration of conformity with GCP is not required.

(Comment 6) One comment noted that the proposed rule identified different requirements for acceptability of results from clinical investigations depending on the location of the study, that is, inside or outside the United States. The comment indicated applying this differential regimen would be difficult when a multicenter clinical investigation has sites both inside and outside the United States. The comment recommended that the requirements should not apply to clinical investigations per se but to clinical data. This would allow data originating from within the United States to be subject to existing GCP regulations (for example, parts 50, 56, and 812 (21 CFR parts 50, 56, and 812)) and data originating from outside the United States to be subject to the new GCP provisions even if the data were part of the same clinical investigation.

(Response) FDA notes that for a multicenter investigation with sites both inside and outside the United States, each site would need to comply with the local requirements. Clinical investigations conducted in the United States to determine the safety or effectiveness of a device are subject to parts 50, 56, and 812. The rule does not govern investigational sites located outside the United States, but rather specifies the criteria for FDA acceptance of data from investigations conducted outside the United States to support an IDE or device marketing application or submission. When a multicenter investigation includes sites both inside and outside the United States, the sponsor or applicant may provide a statement regarding the international nature of the investigation, the compliance of sites with their applicable local requirements, and a statement regarding conformance with GCP along with the required supporting information.

(Comment 7) Two comments noted that § 812.2(e) identifies requirements for non-significant risk device investigations but IECs from other countries may not be familiar with this terminology and classification and may be unable to provide oversight of the sponsor's determination as in the United States. One comment recommended that sponsors use their own determinations.

(Response) FDA agrees with these comments and notes that the significant risk versus non-significant risk determination in the rule relates only to the supporting information required to be submitted and maintained by sponsors and applicants while the requirement to follow GCP applies to all investigations submitted to FDA in support of device applications and submissions. As discussed previously, we have removed proposed § 812.2(e) but we have maintained the provisions for different supporting information requirements in new § 812.28(a)(2).

FDA does not intend that foreign IECs provide oversight of the significant risk versus non-significant risk determination. FDA recognizes that IECs outside the United States may not be familiar with FDA's terminology related to significant risk and non-significant risk device investigations. Under the IDE regulations, sponsors may make an initial determination. Similarly, sponsors and applicants may make an initial determination for investigations conducted outside the United States. If the sponsor or applicant proceeds based on their own determination, they should maintain documentation of the rationale for their determination because FDA may request it, as stipulated at § 812.28(a)(2).

For multinational investigations that include sites in the United States, the determination of the IRBs overseeing the sites in the United States should be used. In addition, sponsors and applicants may request a determination from FDA, just as they may for investigations conducted in the United States.

Note that any determination made by FDA, whether requested or not, will supersede any determination made by the sponsor or applicant (or IRB, if the sponsor or applicant relied on an IRB's determination). If FDA determines that an investigation is of a significant risk device that was submitted as an investigation of a non-significant risk device or exempt investigation, FDA may request the additional supporting information required for significant risk device investigations. Likewise, if FDA determines that an investigation is of a non-significant risk device that was submitted as an exempt investigation, FDA may request the additional

supporting information required for non-significant risk device investigations.

(Comment 8) One comment recommended that the same requirements for IDE exempt studies apply regardless of where the study sites are located. The comment stated that studies exempt under § 812.2(c) are not required to meet any requirements of part 812 except § 812.119 when conducted in the United States, while the proposed rule levies a long list of requirements for these same studies when conducted outside the United States.

(Response) FDA agrees in principle with the comment. We acknowledge that the supporting information to be submitted in an application or submission could be viewed as greater when data from clinical investigations conducted outside the United States are provided to support an IDE or device marketing application or submission than when data from clinical investigations conducted inside the United States that meet the exemption criteria in § 812.2(c) are provided to support an IDE or device marketing application or submission. While we have deleted proposed § 812.2(e), new § 812.28(a)(2) includes a paragraph that addresses the supporting information requirements for device investigations that would meet the exemption criteria in § 812.2(c), as well as paragraphs addressing the supporting information to be provided for significant risk and non-significant risk device investigations. The supporting information requirements for investigations that meet the exemption criteria now only require that this information be made available upon request. That is, the information is not required to be included in an IDE or device marketing application or submission unless FDA requests the information.

In § 812.28(a), we require that clinical investigations conducted outside the United States and submitted to support an IDE or device marketing application or submission be conducted in accordance with GCP as defined in § 812.28(a)(1). GCP includes review and approval (or provision of a favorable opinion) by an IEC and obtaining and documenting the freely given informed consent of the subject (or the subject's legally authorized representative if the subject is unable to provide informed consent). Similarly, FDA notes that investigations conducted in the United States that are exempt under § 812.2(c) are still required to comply with parts 50 and 56, regarding informed consent and IRB review, when the data support applications or submissions to FDA.

C. Non-Compliant Studies

(Comment 9) One comment questioned the need for a statement in IDE applications and 510(k) submissions regarding compliance of clinical studies conducted in the United States with parts 50, 56, and 812. The comment stated that FDA must approve IDE applications, so it is not clear why data from a study that is run according to an approved IDE would not be acceptable for clinical studies conducted inside the United States.

(Response) FDA disagrees with the comment. Not all clinical investigations of medical devices in the United States require an IDE application to be submitted to FDA. Investigations conducted under the abbreviated IDE requirements in § 812.2(b) or under the exemptions in § 812.2(c) do not require submission of an IDE application to FDA. Therefore, a clinical investigation could be conducted in the United States without FDA's review and approval of an IDE application. The statement required in §§ 807.87(j)(1) and 812.27(b)(4)(i) mirrors the statement required in § 814.20(b)(6)(ii) for PMA applications supported by clinical data from investigations conducted in the United States. Requiring this statement also provides consistency with the new requirements that apply when data from clinical investigations conducted outside the United States are provided to support an IDE or device marketing application or submission by providing assurance that the investigations conducted inside the United States were conducted in compliance with FDA's GCP regulations. These statements will aid FDA in assessing the quality and integrity of the clinical data and the protection of human subjects.

(Comment 10) A comment noted that compliance with the IDE, IRB, and informed consent regulations are not always required for all clinical studies but if a study should have complied and did not, this is a compliance matter and FDA's determination on an application or submission should not be held up.

(Response) FDA disagrees that a clinical investigation that was not conducted in compliance with regulatory requirements is solely a compliance matter. As a result of noncompliance there may be serious concerns related to data quality or integrity, the safety of subjects, or with the device itself that would prevent FDA's review of the application from moving forward. FDA does not intend to withhold a determination on an application or submission when it is possible to render a determination irrespective of an outstanding compliance issue. However, data from a clinical investigation that was not conducted in a manner that ensures that the data and results are credible and accurate and that the rights, safety, and well-being of human subjects have been adequately protected can impact FDA's ability to render a determination. The information required by the rule will assist FDA in determining whether the clinical data are unreliable and may not be used to support an application or submission.

(Comment 11) Several comments indicated that FDA should not exclude from consideration data from studies that were not conducted in accordance with GCP. These comments identified a number of reasons why a study may not comply with GCP or the sponsor or applicant may not have information on how the study was conducted. Many comments did not object to providing information describing the extent to which the principles of GCP were followed and suggested alternative language for the rule.

(Response) FDA agrees, in general, that data from clinical investigations that were not conducted in conformity with GCP may still provide useful information and could be relied upon to make regulatory decisions. The intent of the rule is not to disallow the use of data from certain investigations but rather to ensure FDA's decisions are based on scientifically valid and ethically derived data. Conformance with GCP is one way to help ensure clinical data are credible, accurate, and ethically procured.

The rule includes provisions that allow a sponsor or applicant to provide an explanation if the investigation was not conducted in accordance with GCP. These provisions are in §§ 807.87(j), 812.27(b)(4), and 814.20(b)(6)(ii). If an investigation was not conducted in accordance with GCP, these provisions allow a sponsor or applicant to provide a brief statement of the reason for not conducting the investigation in accordance with GCP and to describe the steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of human subjects have been adequately protected.

FDA has also added a waiver provision as an alternative option that allows sponsors and applicants to request a waiver from any applicable requirement under § 812.28(a)(1) and (b). (See § 812.28(c).) The request must provide an explanation of 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.

Through these mechanisms, sponsors and applicants can provide information for FDA's consideration in deciding whether to accept, on a case-by-case basis, data from a clinical investigation that is not conducted in accordance with GCP or for which the sponsor or applicant does not have information on how the investigation was conducted.

(Comment 12) Two comments noted that sponsors and applicants may not be able to conduct all studies according to GCP due to requirements in the country where the study is conducted. The comments noted that in at least one country, ethics committees will not review post-market on-label studies because their scope is limited to investigational studies even though such studies may be submitted in support of applications and submissions to FDA.

(Response) FDA agrees that there may be situations where full conformity with GCP may be difficult or not feasible. FDA believes that conducting a clinical investigation in accordance with GCP will help to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of human subjects are adequately protected. If the sponsor or applicant cannot meet GCP for the investigation, the sponsor or applicant may provide an explanation of the departure from GCP or request a waiver, as noted previously. FDA will take this information into account when considering the extent to which the Agency can rely on the data from these investigations on a case-by-case basis.

D. In Vitro Diagnostic (IVD) Devices

(Comment 13) Several comments recommended that FDA exempt from the informed consent provisions IVD studies conducted with de-identified samples consistent with FDA's ''Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.'' The comments state that application of GCP in this context would provide no additional protection and could deter innovation. One comment suggested that the concepts in the guidance be codified in the final rule.

(Response) The ''Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable'' does not exempt any clinical investigations from the informed consent requirements. In that guidance, FDA stated that we intend to exercise enforcement discretion with regard to the requirement for informed consent under the circumstances described in section 4 of the guidance. FDA issued the guidance to address concerns about obstacles to the development of IVDs and to facilitate development in a manner consistent with the principles of good clinical practice, including human subject protection. In addition to sponsors being able to apply the guidance to certain IVD investigations conducted in the United States, FDA does not intend to object if sponsors and applicants follow this guidance for similar IVD investigations conducted outside the United States provided there is no conflict with local laws and regulations.

The 21st Century Cures Act (Cures Act) (Pub. L. 114–255) was enacted on December 13, 2016. Title III, section 3023 of the Cures Act requires the Secretary of Health and Human Services (HHS), to the extent practicable and consistent with other statutory provisions, to harmonize the differences between the HHS human subject regulations and FDA's human subject regulations. FDA will be working with others at HHS in carrying out this statutory directive, including with respect to de-identified human specimens.

(Comment 14) Three comments indicated that the rule should not apply to technical and analytical (or bench) studies that support IVD devices, especially when de-identified leftover specimens are used. Two comments indicated that these studies are subject to Good Laboratory Practices regulations and are conducted with IRB oversight and informed consent except under the circumstances described in the FDA's ''Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.'' These comments stated that application of GCP would provide no additional protection and would slow or deter innovation.

(Response) FDA disagrees with these comments. FDA considers investigations that use human specimens, including leftover specimens that are de-identified, to be clinical investigations. The definition of subject in § 812.3(p) includes individuals on whose specimens an investigational device is used. Data from investigations using human specimens are subject to the GCP rule when submitted to FDA in support of an IDE or a device marketing application or submission. FDA disagrees that the application of GCP would provide no additional protection. The application of GCP helps to ensure the quality and integrity of data from investigations using human specimens. We agree that these investigations should be conducted with IEC oversight and informed consent. However, as stated previously, in addition to sponsors being able to apply the ''Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable'' to certain IVD investigations conducted in the United States, FDA does not intend to object to sponsors and applicants following the guidance for similar IVD investigations conducted outside the United States, provided that there is no conflict with local laws and regulations.

As noted above, investigations using human specimens are considered clinical investigations. The Good Laboratory Practices regulation (part 58 (21 CFR part 58)) does not apply to clinical investigations, including investigations using human specimens. Further explanation of the applicability of part 58 is provided in FDA's ''Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies—Frequently Asked Questions.''

(Comment 15) One comment noted that there is no harmonized, international IVD GCP guideline.

(Response) FDA recognizes that the ISO 14155:2011 standard states that it does not apply to IVD medical devices. FDA, however, considers conformity with the principles of GCP important for all clinical investigations, including those of IVD devices, to help ensure that the data and results from clinical investigations are credible and accurate and that the rights, safety, and well-being of human subjects are adequately protected. As stated above, FDA does not intend to object to sponsors and applicants following the ''Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable,'' provided that there is no conflict with local laws and regulations.

(Comment 16) One comment noted that the United States classifies IVDs as medical devices but other countries, for example, countries within the European Union, have separate directives governing medical devices and IVDs. Additionally, the Global Harmonization Task Force guidance documents on Clinical Evidence for IVD Medical Devices differentiate IVDs from other medical devices and the proposed regulations do not reflect these differences.

(Response) FDA agrees that there are differences in how other countries regulate medical devices and IVDs. The rule, however, does not address when evidence obtained from using human specimens is needed or what clinical evidence is required for a medical device, including an IVD. Instead, the rule only addresses the conditions for FDA acceptance of data from clinical investigations to support an IDE or a device marketing application or submission to FDA, including data from clinical investigations conducted outside the United States. Conformity with GCP helps to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of human subjects are adequately protected. This is equally important for investigations of IVDs as it is for other medical devices. FDA believes the rule allows for the flexibility needed to accommodate the rules and regulations of other countries.

E. Independent Ethics Committee

Proposed § 812.3(t) would add a definition for IEC. We proposed to define IEC to mean a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.

(Comment 17) Three comments were concerned with the use of the term ''adequately constituted'' in the definition of IEC because the term is not defined. One comment noted that a global, harmonized definition of ''adequately constituted'' does not exist, nor is there agreement on the makeup of an IEC. Another comment recommended that existing definitions of IEC, such as in ICH E6 and ISO 14155:2011, be used.

(Response) FDA disagrees with the comments. The proposed definition of IEC is at a level of specificity and detail appropriate for regulation. We recognize that the organization and membership of IECs may differ among countries because of the local needs of the host country. We believe that such variation should not affect an IEC's ability to perform its functions of protecting the rights, safety, and well-being of human subjects involved in the clinical investigation. Further, we intended for the rule to be sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical research, including the composition of an IEC. Therefore, we have not specifically defined IEC membership requirements in the regulations.

Although we have not identified specific requirements for the membership of an IEC in the rule, we note that the definition of an IEC references an IRB subject to the requirements of part 56 as one type of IEC. Another example would be the description provided in ICH E6.

F. Acceptance of Data From Clinical Investigations Conducted Outside the United States

Proposed § 812.28(a) would identify requirements for the acceptance of information from clinical investigations conducted outside the United States as support for an IDE or a device marketing application or submission, including a requirement that a statement be provided that the investigation was conducted in accordance with GCP, which we defined in § 812.28(a)(1).

(Comment 18) One comment questioned whether there are data to support concern with data integrity and human subject protection from studies of medical devices conducted outside the United States, similar to the Office of Inspector General (OIG) June 2010 report, ''Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials,'' for drug and biological product marketing applications (see *https://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf*).

(Response) FDA notes that there is no similar OIG report for devices, but FDA does have experience with investigations conducted outside the United States through the foreign sites we have inspected. From this experience, we are aware of instances of misconduct of clinical investigations that could compromise data integrity and human subject protection. For more information, please see our Bioresearch Monitoring (BIMO) Metrics available at *https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm261409.htm.*

(Comment 19) One comment noted that proposed § 812.28(a)(1) defines GCP to include ''obtaining and documenting the freely given informed consent of the subject . . . before initiating a study'' and suggested we change the sentence to ''obtaining and documenting the freely given informed consent of the subject before that subject participates in the study'' because subjects will enroll in a clinical study throughout the enrollment phase of a study, so stating that informed consent will be obtained from a subject before initiating a study is not realistic.

(Response) FDA declines to make this change to the definition of GCP in § 812.28(a)(1) because the definition is consistent with the definition in § 312.120(a)(1)(i). The intention of the sentence is that informed consent is obtained before initiating the subject's participation in the study.

(Comment 20) One comment suggested adding to the end of proposed 812.28(a)(1): ''For the purpose of definition, device GCP does not include a requirement for sponsor collection and analysis of (i) adverse events beyond those specified in the protocol and those that would meet the definition of a UADE, (ii) concomitant medications and concomitant therapies beyond those specified in the protocol, (iii) any other data not specifically required of clinical investigations conducted under an IDE or not specified in the protocol.'' The change is intended to clarify that the requirements for a drug clinical study are not being systematically required for medical device studies conducted outside the United States.

(Response) FDA disagrees with the suggested change. FDA has written the rule to be flexible to accommodate the laws and regulations of the countries where investigations are conducted. FDA expects that clinical investigations will be conducted in compliance with the local laws and regulations of the countries where the investigations take place and such laws and regulations may address collection and analysis of adverse events, concomitant medications and therapies, and other data. FDA considers the suggested language too restrictive because, during the course of an investigation, additional data may be collected that would be important to establishing the safety and effectiveness of a medical device or to subject safety. Moreover, the suggested language relies on FDA's investigational device exemptions regulations by using a term (unanticipated adverse device effect or UADE) used in FDA's regulations and limits ''collection and analysis'' by not requiring ''any other data not specifically required of clinical investigations conducted under an IDE or not specified in the protocol.'' These changes would modify the definition of GCP based on FDA's regulations and it may appear that FDA is imposing its own GCP regulations on other countries. Additionally, the revisions could raise problems for investigations of combination products.

Adverse event reporting is an important aspect of GCP. The requirements related to collection and analysis of adverse events would be those identified in the GCP standard the sponsor uses. For example, ISO 14155:2011 includes discussion of adverse event documentation, reporting, and analysis in several sections,

including sections 6.4, 8.2.4, 8.2.5, and 9.8. A sponsor could request a waiver from any applicable requirement if the sponsor can justify why it is unnecessary, cannot be achieved, or can be satisfied through an alternative course of action.

(Comment 21) One comment noted that the text in proposed § 812.28(a) uses the term ''data are valid'' but stated this term is vague and recommends changing it to ''relevant and credible.''

(Response) FDA agrees that the language in proposed § 812.28(a) regarding ''data are valid'' should be revised but disagrees with the suggested revision. The term ''data are valid'' was used in previous § 814.15(b) to indicate the data must represent valid scientific evidence, which is appropriate for PMA applications. Section 812.28, however, addresses data supporting other applications and submissions, including clinical data supporting an IDE application. Therefore, we have revised § 812.28(a) to read ''FDA will accept information on clinical investigations conducted outside the United States to support an IDE or a device marketing application or submission if the investigations are well-designed and well-conducted . . .'' consistent with § 312.120, which similarly applies to investigational applications in addition to marketing applications for drugs and biological products.

(Comment 22) One comment stated that phrases like ''compliance with good clinical practice'' might lead the reader to interpret FDA as expecting compliance with ICH E6 versus the phrase ''compliance with the principles of good clinical practice,'' which more readily relates to the concepts described in ISO 14155:2011.

(Response) FDA disagrees with this comment. Both ICH E6 and ISO 14155:2011 use the term ''principles of good clinical practice.'' FDA did use the term ''principles of good clinical practice'' in proposed § 812.2(e); however, we have removed this proposed section from the final rule to eliminate potential misinterpretation that part 812 applies to clinical investigations conducted outside the United States. Section 812.28(a)(1) uses the phrase ''conducted in accordance with good clinical practice.'' This section defines GCP and requires a sponsor or applicant to provide a statement regarding the conduct of the investigation submitted. The sponsor or applicant would indicate conformity with a specific GCP standard but the rule does not specify the GCP standard to use. Therefore, FDA believes the language in the rule is appropriate in the context in which it is used.

(Comment 23) One comment asked whether the Agency looked at the differences between ICH E6 and ISO 14155:2011, related to device stakeholders' requirements, to identify if there are any differences and considered the potential burden to adopt both standards.

(Response) FDA has not identified a specific GCP standard that sponsors must follow. Instead, FDA is allowing sponsors of device clinical investigations conducted outside the United States to follow a GCP standard of their choice, provided it meets the definition provided in § 812.28(a)(1). Although FDA believes that ICH E6 and ISO 14155:2011 represent similar approaches to GCP, we note that ICH E6 addresses drug and biological products, while ISO 14155:2011 addresses medical devices. We believe the differences are appropriate to the different products addressed.

G. Onsite Inspection

Proposed § 812.28(a)(2), as a condition for acceptance of data from a clinical investigation submitted under this section, would require a statement assuring the availability of the data from the clinical investigation to FDA for validation through an onsite inspection if the Agency deems it necessary or through other appropriate means.

(Comment 24) One comment stated that FDA has no authority to inspect foreign clinical study institutions and recommended that proposed § 812.28(a)(2) be struck. Another comment indicated that providing a statement as required by proposed § 812.28(a)(2) would be problematic because of foreign privacy laws.

(Response) FDA disagrees with striking proposed § 812.28(a)(2), now § 812.28(a)(3), because, in some cases (for example, to resolve any uncertainties about whether the investigation was conducted in accordance with GCP), to accept the data from a clinical investigation conducted outside the United States, FDA may need to validate the data through an onsite inspection. Historically, when needed to validate data from clinical investigations conducted outside the United States, FDA has been able to inspect the records of these investigations. When conducting foreign inspections, FDA obtains the consent of foreign governments.

FDA understands that a sponsor cannot disclose foreign records that are prohibited from disclosure by foreign law. If the Agency believes that access to records is necessary to verify certain data or to validate the investigation, and such records are not available because of foreign law, the sponsor and FDA will need to agree upon an alternative means for validation if the Agency is to rely on the data. Such alternative means for validation might entail FDA partnering with other regulatory authorities or other mutually agreed upon means for validation.

(Comment 25) One comment recommended keeping the language the same as in § 312.120(a)(1)(ii): That is, ''FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.'' Another comment recommended modifying the language to ''authorized by local law'' and deleting ''or through other appropriate means'' unless FDA can clarify what it means and what types of activities would satisfy this requirement.

(Response) FDA partially agrees and has modified the language in proposed § 812.28(a)(2), now § 812.28(a)(3), to more closely follow the language in § 312.120. We have modified the requirement that a statement be provided assuring the availability of the data from the study to FDA for validation through an onsite inspection to a requirement that FDA is able to validate the data from the investigation through an onsite inspection. We have also determined that the phrase ''if otherwise authorized by law'' is unnecessary because FDA obtains the consent of foreign governments to do inspections. Therefore, the phrase has been deleted.

We are keeping the phrase ''or through other appropriate means.'' Essentially the same phrase is used in current § 814.15(d)(3) regarding validation of foreign clinical data. This language recognizes that foreign data present unique challenges not usually associated with domestic data. One such challenge may be that FDA is unable to conduct an onsite inspection. If the Agency believes that validation is necessary but is unable to conduct an onsite inspection, the sponsor and FDA will need to agree upon an alternative means for validation if the Agency is to rely on the data. Such alternative means for validation might entail FDA partnering with other regulatory authorities or other mutually agreed upon means for validation. If an agreement cannot be reached that satisfies FDA's need for validation, then the data might not be accepted to support the application or submission.

(Comment 26) One comment noted that the preamble of the proposed rule identified documents that articulate GCP principles but that these documents have broad differences in the

scope, level of detail, and formulation of actual requirements and that no individual document was identified as the authoritative set of enforceable requirements. The comment stated that, if GCP compliance will be subject to FDA inspection, the rule must clearly identify not only the applicable requirements in terms of general principles but also provide a sufficient level of detail to allow an objective basis for a uniform assessment of compliance by the sponsor as well as the Agency.

(Response) FDA disagrees with this comment. Similar to § 312.120, the rule does not identify a specific GCP standard that sponsors must follow. Instead, the rule includes a definition of GCP in § 812.28(a)(1), which is consistent with the definition in § 312.120, and embodies well recognized GCP principles. FDA is allowing sponsors of clinical investigations conducted outside the United States to follow a GCP standard of their choice, provided it meets the definition provided in § 812.28(a)(1). One example of a GCP standard that meets the definition provided in § 812.28(a)(1) is ISO 14155:2011, ''Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice.'' FDA has recognized this standard (77 FR 15765). In addition to following a GCP standard, sponsors would need to comply with the local requirements where the investigational sites are located.

H. Supporting Information

Proposed § 812.28(b) would require a sponsor or applicant submitting data from clinical investigations conducted outside the United States in support of an IDE or device marketing application or submission to submit, in addition to information required elsewhere in parts 807, 812, and 814, supporting information that describes the actions taken to ensure that the research conformed to GCP.

1. General Comments

(Comment 27) One comment stated that the list of supporting information in § 812.28(b) should reflect the approval standard for devices, which is a reasonable assurance of safety and effectiveness.

(Response) FDA disagrees with the comment. The supporting information is not used to establish a reasonable assurance of safety and effectiveness. Instead, the supporting information is used to assess whether the investigation conformed to GCP, which helps to ensure that the data and results submitted are credible and accurate and that the rights, safety, and well-being of human subjects are adequately protected. Data from clinical investigations conducted in accordance with GCP may be used to establish a reasonable assurance of safety and effectiveness for purposes of a PMA application, but may also be used to support other device applications and submissions, including an IDE. Section 812.28(a)(2) of the rule identifies different supporting information requirements based on the level of risk of the clinical investigation, with significant risk device investigations requiring more supporting information and device investigations presenting less risk, as well as those that meet the exemption criteria in § 812.2(c), requiring less supporting information.

(Comment 28) One comment noted that the preamble to the proposed rule states that many of the requirements in § 812.28(b) parallel the requirements in § 312.120(b) for drug applications but the list, in many cases, is more restrictive than the requirements for drug studies, and identified the request for certified copies in § 812.28(b)(4) as an example.

(Response) FDA, in general, disagrees with the comment. Although the comment indicates that the list of supporting information in § 812.28(b) is more restrictive in many cases than in § 312.120(b), only one example is provided, the request for ''certified copies'' in § 812.28(b)(4). Based on concerns raised by this and other similar comments, we have removed the term ''certified copies'' from § 812.28(b)(4), as further discussed in response to comment 33 below.

There are only a few other differences between §§ 812.28(b) and 312.120(b). In § 312.120(b)(1) and (2), the investigator's qualifications and a description of the research facilities are required, respectively. In § 812.28(b)(1), we require the names of investigators and the names and addresses of research facilities and sites where records relating to the investigation are maintained, separate from the requirement for the investigators' qualifications in § 812.28(b)(2) and the description of the research facilities in § 812.28(b)(3). We believe this difference is appropriate because the information on names of investigators and names and addresses of research facilities and sites where records relating to the investigation are maintained is needed for all clinical investigations of medical devices. However, the information on investigators' qualifications and the description of the research facilities is needed for significant risk device investigations but not for exempt and non-significant risk device investigations. These items are discussed further in comments 29 and 30 below.

The required information in § 812.28(b)(5), describing the device used in the investigation, is also different from § 312.120(b)(4), describing the drug substance and drug product. The difference is appropriate because it relates to the differences in information needed to adequately describe devices and drugs.

The difference between §§ 812.28(b)(6) and 312.120(b)(5) is related to different regulatory requirements for FDA decisions on device applications, as described in § 860.7 (21 CFR 860.7), and drug applications, as described in § 314.126. Therefore, FDA believes this difference is appropriate.

The last difference concerns the information required for the IEC that reviewed the investigation. In § 812.28(b)(7), we do not specify that records of the IEC members' names be maintained as required in § 312.120(b)(6). We decided not to require that records of the IEC members' names be maintained because drug sponsors and applicants reported occasional problems fulfilling this requirement due to foreign laws.

Therefore, FDA considers the supporting information identified in § 812.28(b) to be similar to the supporting information required for drug applications in § 312.120(b), with the few differences being appropriate and not more restrictive.

2. Investigators and Research Facilities

Proposed § 812.28(b)(1) would require the names and addresses of the investigators and research facilities; proposed § 812.28(b)(2) would require the qualifications of investigators; and proposed § 812.28(b)(3) would require a description of the research facilities.

(Comment 29) One comment disagreed with providing investigators' addresses and noted that personal details like this are not usually obtained and could be subject to more stringent foreign regulations. A second comment stated that the European Union Privacy Directive would protect from transfer to the United States the names and addresses of foreign investigators and that investigators would have to agree to this information sharing in advance or at the time of submission to FDA. The comment further stated that difficulties currently exist with obtaining investigators' names from certain foreign sites, even when the data collection is part of an IDE.

(Response) FDA believes that some clarification is needed but disagrees that investigators' names should not be required. We did not intend to imply that investigators' personal addresses would be required. We have reworded this element to require ''names of investigators and names and addresses of research facilities and sites where records relating to the investigation are maintained.'' This change clarifies that the investigators' personal addresses are not required, but that the names and addresses of all facilities that took part in the investigation are required, such as the investigational sites, laboratories, and specimen collection sites. Additionally, if study records are maintained at other locations, such as an investigator's office, the names and addresses of those locations must also be provided.

We also note that the European Commission has recognized ISO 14155:2011, which includes providing names and addresses of investigators to regulatory authorities. ISO 14155:2011, Annex A, describes the clinical investigation plan (CIP) and includes, in section A.1.4, the name, addresses, and professional position of principal investigator(s). The CIP is included in the clinical investigation report as described in section D.13 of Annex D. The clinical investigation report includes ''the list of principal investigators and their affiliated investigation sites, including a summary of their qualifications or a copy of their CVs'' (see Annex D.13 c). This report is provided to regulatory authorities per section 7.3f.

(Comment 30) One comment stated that the items in § 812.28(b)(2) and (3) are vague and sponsors or applicants will have difficulty knowing how to comply with the requirements.

(Response) In general, the information provided on investigator qualifications should be adequate to show that the investigator is qualified to serve as an investigator based on his or her training and experience specifically related to the clinical investigation (for example, such information could include a curriculum vitae (CV) or summary of training and experience). The description of the research facilities should include enough information to enable FDA to determine the adequacy of the facilities to execute the investigation and meet its requirements (for example, whether the site is appropriately staffed and equipped to conduct the investigation and is able to provide the appropriate emergent or specialized care, if required). Additionally, the GCP standard the sponsor or applicant follows may address information to maintain on investigator and research facility selection. For example, ISO 14155:2011 addresses verification and documentation of the qualifications of the principal investigator(s) and the adequacy of the research facility and the rationale for selecting the facility in sections 5.8, 9.2, and 9.3.

The investigator's qualifications and the description of the research facilities will also help us to assess the need for an onsite inspection.

3. Detailed Summary of Protocol and Results of Investigation

Proposed § 812.28(b)(4) would require submission of a detailed summary of the protocol and results of the investigation. In addition, the sponsor or applicant would be required to submit certified copies of case records maintained by the investigator or additional background data, such as hospital records or other institutional records, if requested by FDA.

(Comment 31) Several comments stated that stricter privacy laws outside the United States may partially or completely restrict the ability of sponsors and applicants to provide copies of patient records to FDA. The comments noted that investigational sites typically archive the originals of completed case records and these records would generally not be available to sponsors. Two comments noted that the records may be available through an inspection at the investigational site. One comment noted that providing redacted patient information to a regulatory authority may be possible but would require changes to clinical trial agreements and informed consent documents and would impose significant burden and costs. Comments recommended modifying or deleting the requirement for providing records.

(Response) FDA acknowledges that in some instances there may be difficulties providing records should FDA request them but disagrees with deleting the requirement. FDA understands that a sponsor cannot disclose foreign records that are prohibited from disclosure by foreign law. If FDA requests case records or other records but these documents cannot be provided as required by § 812.28(b)(4) because disclosure is prohibited by governing law, the sponsor or applicant should document this disclosure prohibition by the foreign entity. For example, the sponsor or applicant should document the countries that prohibit such disclosure, the nature of the prohibitions, and the extent to which these prohibitions may impede sponsors or applicants in carrying out other obligations regarding record access. The sponsor or applicant can then submit such information in a waiver request to FDA. For FDA to rely on the affected data, the sponsor or applicant and FDA would need to agree on an alternative means for validation. Such alternative means for validation might entail FDA partnering with other regulatory authorities or other mutually agreed upon means for validation.

Additionally, in the informed consent documents, it may be helpful to notify subjects that regulatory authorities will have direct access to the subject's medical records for verification of clinical investigation procedures and data, which is consistent with ISO 14155:2011, section 4.7.4(d)3.

If FDA needs source documents such as hospital records to verify certain data or to validate the investigation and such records are not available because of foreign law, and an alternative means for validation is not available, FDA might not accept the data from the clinical investigation as support for an IDE or device marketing application or submission.

(Comment 32) Two comments requested clarification of the term ''case record.''

(Response) FDA clarifies that the term ''case record'' as used in § 812.28(b)(4) is used to indicate records investigational sites commonly maintain in relation to clinical investigations. The term includes records as described in § 812.140(a)(3).

(Comment 33) Two comments requested that the term ''certified copies'' be defined.

(Response) FDA has reevaluated the provision related to ''certified copies.'' We acknowledge that the term has different meanings in other countries and have determined that this term is not needed. We have amended the rule accordingly.

(Comment 34) One comment recommended modifying § 812.28(b)(4) to require that the clinical investigation report, as described in ISO 14155:2011 Annex D, be included in the supporting information because it provides the relevant information from the protocol as well as the results of the clinical investigation.

(Response) FDA disagrees with modifying the requirement to specify providing the clinical investigation report as described in ISO 14155:2011. We believe that the supporting information required by the rule is sufficient for its purpose. Additionally, the rule does not require following ISO 14155:2011; however, if a sponsor or applicant chooses, FDA would accept the full clinical investigation report as

described in Annex D of ISO 14155:2011 as a detailed summary of the protocol and results of the investigation.

(Comment 35) One comment asked about FDA's procedure and methods for review, retention, and destruction of the detailed summaries and records identified in § 812.28(b)(4) and the reasons why records would be needed and the intent of review.

(Response) FDA may request records to help understand the conduct of the investigation, to verify certain data, and to validate the investigation and the results obtained. When records from investigations conducted outside the United States are submitted, FDA will review and handle those records in the same manner as records from investigations conducted in the United States.

4. Valid Scientific Evidence

Proposed § 812.28(b)(6) would require a discussion demonstrating that the data and information, when intended to support the safety and effectiveness of a device, constitute valid scientific evidence.

(Comment 36) One comment stated that § 812.28(b)(6) is redundant and should be struck. A study complying with the principles of GCP is a well-controlled study conducted by qualified experts.

(Response) FDA disagrees that § 812.28(b)(6) is redundant. Section 812.28(b)(6) requires that the sponsor or applicant provide a discussion demonstrating that the data and information constitute valid scientific evidence within the meaning of § 860.7. FDA relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective (see § 860.7). Although there may be some overlap, the principles addressing valid scientific evidence more readily relate to the types of evidence that may support the safety and effectiveness of a device, while the principles of GCP relate more to the conduct of the investigation.

5. IEC Information

Proposed § 812.28(b)(7) would require 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 would be required to maintain records supporting such statement, including records describing the qualifications of IEC members, and would be required to make these records available for Agency review upon request.

(Comment 37) Two comments opposed the requirement that a statement be provided that the IEC meets the definition in § 812.3(t). One comment indicated that sponsors may not know whether an IEC meets a given definition. Another comment recommended requiring a statement obtained from the IEC that it meets the definition in § 812.3(t) and is organized and operates according to applicable laws and regulations.

(Response) FDA agrees that a statement from the IEC would also be acceptable. To satisfy this requirement, FDA will accept a statement from the IEC indicating it meets the definition of an IEC in the rule. We also added a waiver provision (see new § 812.28(c)) to the rule that sponsors and applicants may consider using when they are unable to meet the requirements in § 812.28(a)(1) and (b) of the rule. For example, a waiver may be requested when the sponsor cannot submit a statement that the IEC meets the definition in § 812.3(t). A waiver request could identify, as an alternative to the statement that the IEC meets the definition in § 812.3(t), a statement that the IEC is organized and operates according to the applicable laws and regulations of the country where it operates and provide a description of the laws and regulations under which the IEC is organized and operates. FDA will decide whether to grant or deny a waiver on a case-by-case basis, taking into account all appropriate circumstances.

(Comment 38) Three comments stated that the proposed rule requires sponsors to qualify IECs but there is no parallel requirement for a sponsor to qualify an IRB for a study in the United States. One comment noted that no rationale was provided for requiring greater regulation outside the United States than is required in the United States. Another comment indicated the requirement is likely because FDA recognized it does not have the authority to verify and document the adequacy of a foreign IEC but failed to recognize that sponsors do not have such authority and would face legal challenges to meet this requirement.

(Response) FDA acknowledges that the sponsor of an investigation under an IDE is not required to qualify and submit information on the adequacy of the reviewing IRBs. FDA routinely obtains information about IRBs in the United States through onsite inspections of the IRBs. To obtain information on the adequacy of the reviewing IEC for foreign investigations, given that inspections of foreign IECs are usually not feasible, FDA believes it is appropriate to ask the sponsor to document the adequacy of the reviewing IEC because the sponsor already interacts with the IEC, either directly or through the investigators, to obtain IEC review.

FDA believes that the oversight of a clinical investigation by an adequately constituted IEC is an essential component of human subject protection. Information about the adequacy of an IEC is important in assessing the competence of the committee to protect the rights, safety, and well-being of human subjects. To satisfy this requirement, FDA will accept a statement from the IEC indicating it meets the definition of an IEC in the rule. We also added a waiver provision to the rule that sponsors and applicants may consider using when they are unable to meet the requirements in § 812.28(a)(1) and (b) of the rule. For example, a waiver may be requested when the sponsor cannot submit a statement that the IEC meets the definition in § 812.3(t).

(Comment 39) Several comments indicated sponsors may have difficulty obtaining and documenting the qualifications of IEC members and making the records available to the Agency upon request. One comment noted that the term ''qualification'' is open to interpretation. Another comment indicated it may not be feasible to obtain the names of IEC members. A third comment noted that the European Union Privacy Directive may protect from transfer to the United States the information sought for the IEC.

(Response) FDA believes that oversight of a clinical investigation by an adequately constituted IEC is an essential component of human subject protection. Information about the adequacy of an IEC is important in assessing the competence of the committee to protect the rights, safety, and well-being of human subjects. Recognizing that privacy laws in some countries may not allow the release of personal information, FDA is requiring that sponsors or applicants maintain records describing the qualifications of IEC members and not their names. Qualifications would include, for example, information on occupation, training, and experience.

Additionally, we have added a waiver provision to the rule that sponsors and applicants may consider using when they are unable to meet the requirements in § 812.28(a)(1) and (b) of the rule. If sponsors or applicants cannot obtain IEC member qualifications as required by § 812.28(b)(7), FDA recommends that

the sponsor or applicant clearly document attempts made to obtain the qualifications of IEC members along with an explanation as to why the qualifications cannot be obtained. Such information can be submitted to FDA in a waiver request.

(Comment 40) One comment questioned how FDA would review information on the qualifications of IEC members stating that, without a harmonized, globally accepted definition of ''qualification,'' there will be variability in interpretation of acceptable qualification based on reviewer interpretation or bias and may place FDA in the position of accepting or rejecting qualifications of IEC members from foreign nations.

(Response) FDA disagrees with the comment. We recognize that the membership of IECs may differ among countries because of local needs of the host country. Such variation is acceptable as long as the IEC can ensure the protection of the rights, safety, and well-being of human subjects involved in the clinical investigation. As we do for IRBs located in the United States, in its review FDA will be looking to see that, collectively, the IEC members have the qualifications needed to review and evaluate the science, medical aspects, and ethics of the proposed clinical investigation.

6. Summary of IEC's Decision

Proposed § 812.28(b)(8) would require submission of a summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion.

(Comment 41) One comment recommended changing proposed § 812.28(b)(8) to require the correspondence relating to the IEC's decision to approve the investigation because the approval letter would be clearer and less ambiguous than a summary, which could be interpreted differently by different people.

(Response) FDA disagrees with the comment; however, FDA believes that providing the approval letter(s) from the IEC(s) would be one way to provide a summary of the IEC's decision to approve or provide a favorable opinion. We note that these letters are usually issued in the local language of the country in which the investigation is conducted and official translations may need to be provided.

7. Description of Informed Consent Process

Proposed § 812.28(b)(9) would require submission of a description of how informed consent was obtained.

(Comment 42) One comment recommended that § 812.28(b)(9) require that the blank informed consent document approved by the IEC or IRB be submitted instead of a ''description of how'' consent was obtained.

(Response) FDA disagrees that the blank informed consent document approved by each IEC or IRB should be submitted instead of a description of how consent was obtained. Providing information about how informed consent is obtained is important in ensuring transparency and accountability for the ethical conduct of the investigation. The description should address such concerns as who obtained informed consent (ensuring that the person obtaining informed consent was knowledgeable about the investigation and capable of answering all questions), when was consent obtained (ensuring that consent was obtained prior to a subject's participation in the investigation, for example, prior to any research procedures), and the conditions under which consent was obtained (ensuring that consent was obtained under conditions that minimized coercion or undue influence).

(Comment 43) One comment recommended revising § 812.28(b)(9) to state ''a description of how informed consent was obtained, and that this method was approved by the IEC.''

(Response) FDA disagrees with the comment. FDA defines GCP to include the review and approval (or provision of a favorable opinion) by an IEC that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. Ensuring the protection of human subjects would include review and approval of how informed consent is obtained. An applicant's statement that an investigation was conducted in accordance with GCP would indicate that an IEC had approved (or provided a favorable opinion) of how informed consent was obtained. Therefore, FDA believes the proposed revision is unnecessary.

8. Description of Incentives to Subjects

Proposed § 812.28(b)(10) would require submission of a description of what incentives, if any, were provided to subjects to participate in the study.

(Comment 44) One comment recommended deleting § 812.28(b)(10) because this is a new requirement, not required for investigations in the United States, and may lead to unnecessary burden of review for FDA. The comment stated that the information is reviewed by the IRB or IEC as part of consent and is held by the sponsor as part of their records and subject to audit by the Agency.

(Response) FDA disagrees with the comment and does not believe this requirement will be overly burdensome. Informed consent documents usually describe incentives and the IEC reviews this information. Therefore, providing the description of incentives to FDA should not be a burden. FDA will allow some flexibility in how sponsors or applicants comply with § 812.28(b)(10). If the informed consent form includes a description of any incentives provided to subjects, a sponsor or applicant could submit a model consent form to meet the requirement. Alternatively, a sponsor or applicant could also satisfy the requirement by submitting a description of any incentives provided to subjects to participate in the investigation, or if such a description was included elsewhere, such as in the detailed summary of the protocol required under § 812.28(b)(4), the sponsor or applicant could reference where the description may be found to meet the requirement under § 812.28(b)(10).

FDA is requiring this information because incentives can affect data integrity. In the proposed rule, FDA only required the submission of information about incentives for significant risk device investigations. In the final rule, FDA is requiring that information about incentives be made available upon request for non-significant risk and exempt device investigations. FDA has made this change because incentives could affect the integrity of all investigations.

(Comment 45) One comment recommended revising § 812.28(b)(10) to state, ''a description of what incentives, if any, were provided to subjects to participate in the study, and that these incentives, if any, were approved by the IEC.''

(Response) FDA disagrees with the comment. FDA defines GCP to include the review and approval (or provision of a favorable opinion) by an IEC that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. Ensuring the protection of human subjects would include review and approval of the incentives to be provided to subjects. An applicant's statement that an investigation was conducted in accordance with GCP would indicate that an IEC had approved (or provided a favorable opinion) of the incentives provided to subjects. Therefore, FDA believes the proposed revision is unnecessary.

9. Description of Study Monitoring

Proposed § 812.28(b)(11) would require submission of a description of how the sponsor monitored the study and ensured that the study was carried out consistently with the study protocol.

(Comment 46) One comment recommended including a statement supporting a sponsor's performance of a risk assessment to determine the approach to monitoring for sites outside the United States, as they would for sites in the United States, because standardization may cause more burdens (for example, resources, time, and cost) related to the requirement to increase monitoring.

(Response) FDA has not identified a specific GCP standard that sponsors and applicants must follow. Instead, the rule defines GCP and allows sponsors and applicants to determine an appropriate GCP standard for their investigations that produce data to support device research and marketing applications and submissions to FDA. Sponsors and applicants may use a risk-based approach to monitoring, as described in FDA's guidance document entitled ''Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring,'' provided it is consistent with the laws and regulations of the countries where the investigation takes place.

10. Description of Investigator Training and Signed Written Commitments

Proposed § 812.28(b)(12) would require submission of a description of how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained.

(Comment 47) One comment recommended that § 812.28(b)(12) only require that the investigator agree to comply with the protocol and with institutional and legal requirements. The principles of GCP do not require the sponsor to train investigators in GCP compliance.

(Response) FDA disagrees. Simply obtaining the investigator's agreement to comply with the protocol and institutional and legal requirements may not be adequate. Protocols may be complex and additional steps may be needed to prepare investigators and to standardize performance of the investigation. A description of the steps taken to ensure consistent conduct of the investigation and recording of data among investigators is needed. Such a description may identify investigator meetings or other steps that the sponsor took to ensure compliance with GCP and the protocol.

I. Record Retention

Proposed § 812.28(c), now § 812.28(d) in the final rule, would require a sponsor or applicant to maintain records for a clinical investigation conducted outside the United States. If the investigation supported an IDE, the records would be retained for 2 years after the termination or completion of the IDE. If the investigation supported a device marketing application or submission, the records would be retained for 2 years after an Agency decision on that submission or application.

The proposed rule would amend § 812.140(d) to include humanitarian device exemption applications and premarket notification submissions as types of applications and submissions that would require the maintenance of IDE records.

(Comment 48) One comment indicated that FDA should clarify in § 812.28(c)(2) (now § 812.28(d)(2)) that the requirement only applies to studies sponsored by the sponsor or applicant of the submission or application in which the data were submitted.

(Response) FDA disagrees with the comment. The requirement to maintain appropriate records is to ensure that FDA will be able to validate an investigation through an onsite inspection, if necessary. Therefore, the record retention requirement must apply to all investigations from which clinical data are submitted to FDA in support of an application or submission, whether or not the investigation was sponsored by the sponsor or applicant. If a sponsor or applicant submits data from a clinical investigation they did not sponsor, they should obtain the commitment of the sponsor and investigators to retain the records. If FDA needs access to the records and the records are not available, FDA may not accept the data in support of an IDE or device marketing application or submission.

(Comment 49) One comment recommended that proposed § 812.140(d) be changed to read similarly to proposed § 812.28(c), namely, ''The date on which the investigation is terminated or completed or for 2 years after an agency decision on that submission or application.''

(Response) FDA disagrees with the proposed change. As noted in the preamble to the proposed rule, we are revising § 812.140(d) to indicate that retention requirements for IDE records apply to those records used to support HDE applications and 510(k) submissions, as well as the application types already listed. In the final rule, we also clarify that the retention requirements apply to records used to support requests for De Novo classifications. We do not intend to further change the record retention requirements for IDEs.

J. Denial or Withdrawal of PMA

Proposed §§ 814.45(a)(5) and 814.46(a)(4) would allow FDA to deny or withdraw, respectively, approval of a PMA if any clinical investigation 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.

(Comment 50) Several comments stated that the proposed rule should allow denial or withdrawal of a PMA based only on those investigations relied on for a determination of safety and effectiveness. One comment noted that, for PMAs, reporting of all prior studies is required despite not relying on all studies for a determination of safety and effectiveness. Two comments indicated that denial and withdrawal of approval should not be extended to other applications and submissions such as IDEs and 510(k)s.

(Response) FDA agrees that the rule should allow denial or withdrawal of a PMA for noncompliance with GCP referenced in § 814.15(a) and described in § 812.28(a) with respect to those clinical investigations conducted outside the United States that were relied upon for a determination of the safety and effectiveness of the device. FDA notes that the PMA regulations (see § 814.20(b)(8)) require the applicant to provide, among other things, an identification, discussion, and analysis of any other data, information, or report relevant to an evaluation of the safety and effectiveness of the device, known to or that should reasonably be known to the applicant from any source, foreign or domestic, including information derived from investigations other than those proposed in the application and from commercial marketing experience. While this information is required to be submitted, the applicant or sponsor may not have been involved in the conduct of the investigation and may not know the conditions under which the investigation was conducted (for example, a previous developer or competitor may have been involved in the conduct of the investigation).

As explained elsewhere in this document, § 812.28(a) requires demonstration of conformity with GCP

when data from clinical investigations conducted outside the United States are provided to support an IDE or a device marketing application or submission; for example, when clinical data are submitted in a PMA application to demonstrate a reasonable assurance of safety and effectiveness. When clinical data from investigations are included in applications and submissions as supplementary information and not as support, demonstration of conformity with GCP is not required.

FDA also notes that the rule only addresses denial and withdrawal of approval related to PMAs and does not address denial or withdrawal of authorization for other types of applications and submissions. However, if FDA determines that any clinical investigation conducted outside the United States and submitted in support of an IDE or a device marketing application or submission was represented to have been conducted in conformity with GCP but was not, FDA may take appropriate action under the FD&C Act and FDA regulations.

(Comment 51) Two comments noted data collected outside the United States but not in compliance with the principles of GCP may nevertheless be relevant data for determining the safety and effectiveness of a device. One comment noted that, elsewhere in the proposed rule, the use of non-GCP compliant studies is allowed where appropriate justification is provided.

(Response) As discussed in section IV.C, FDA agrees that clinical data from investigations conducted outside the United States that were not conducted in conformity with GCP may be relevant. FDA believes, however, that clinical data that are submitted to support a PMA should be credible, accurate, and ethically derived and that conducting a clinical investigation in accordance with GCP will help to ensure the integrity and quality of the data and the protection of subjects. If a country's laws require less than GCP and the applicant does not or cannot meet GCP for the investigation, the applicant may provide an explanation of the departure from GCP or request a waiver. FDA will take this information into account when considering the extent to which it will rely on the data from these investigations in support of a premarket submission or application on a case-by-case basis, depending on whether the clinical data are credible, accurate, and ethically derived. In such situations, when an applicant requests a waiver and FDA grants the waiver and accepts for support of a PMA clinical data from an investigation that was not conducted in conformity with GCP, FDA generally will not deny or withdraw approval of the PMA under § 814.45(a)(5) or § 814.46(a)(4).

(Comment 52) One comment stated that the sections on denial and withdrawal of a PMA use the term ''unreliable'' without clarifying this term and could make a determination of ''unreliable'' potentially arbitrary, variable, and inconsistent.

(Response) FDA disagrees with this comment. FDA has used the term ''unreliable'' in regulations such as in §§ 812.119 and 312.70 regarding investigator disqualification. FDA uses the term according to its common meaning and may consider data unreliable, for example, if the data are fraudulent or if there was a lack of rigor in the conduct of the investigation, such as not following the protocol.

K. Implementation

(Comment 53) Several comments raised concerns with the implementation of the rule and recommended that the rule not be applied retrospectively to investigations begun prior to the effective date. Two comments recommended that the effective date be established as 18 months after publication. The comments noted that adequate time will be needed to allow for preparation for implementation, such as to revise internal operating procedures, for training, for study planning, and for negotiating and contracting with the necessary parties for future studies conducted outside the United States that are intended to support an application or submission to FDA. One comment recommended that FDA allow requests for waivers of certain requirements for investigations conducted prior to the effective date that are technically out of compliance but did not compromise public health or patient safety.

(Response) FDA agrees that the rule should not be applied to clinical investigations begun prior to the effective date. FDA is implementing the rule for clinical investigations that enroll the first subject on or after the effective date of the rule. FDA also agrees that sponsors may need additional time to prepare to meet the new requirements. Therefore, the effective date is established as 1 year after the publication of the rule in the **Federal Register** to provide additional time for sponsors and applicants to make any changes necessary, for example, to their internal operating procedures, study planning, etc., to incorporate the principles of GCP and compliance with the requirements of the rule for investigations that will support an IDE or device marketing application or submission. We believe that this will provide adequate time for sponsors and applicants to implement changes in their processes to accommodate the new requirements.

In addition, FDA has added a waiver provision to § 812.28. Under this provision, a sponsor or applicant may submit waiver requests and FDA will decide whether to grant or deny waivers on a case-by-case basis, taking into account all appropriate circumstances.

For the purposes of this rule, we will consider a subject enrolled when the subject agrees to participate in a clinical investigation as indicated by the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) signing the informed consent document(s) or participating in a clinical investigation meeting the requirements of § 50.24.

If an investigation conducted outside the United States enrolled the first subject prior to the rule's effective date, then the requirements in § 814.15 prior to the rule's effective date would apply. Specifically, if data from clinical investigations conducted outside the United States that enrolled the first subject prior to the effective date of this rule are submitted in support a PMA application, FDA will accept the data 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 shall state in detail any differences between those standards and the ''Declaration of Helsinki'' and explain why they offer greater protection to the human subjects. (See § 814.15(b).)

L. Guidance Needed

(Comment 54) Two comments recommended that FDA develop guidance and training on GCP and compliance with the requirements. One comment recommended that FDA develop a guidance document similar to the one available for investigational new drug applications (INDs), ''Guidance for Industry and FDA Staff: Acceptance of Foreign Clinical Studies Not Conducted Under an IND, Frequently Asked Questions,'' to provide clarification and definitions to the regulations. Another comment suggested that FDA develop guidance documents and training programs, or sanction third-party training of physicians, sponsors, and IRBs on GCP as it relates to medical devices. The training programs should

provide opportunities to eliminate misinterpretations while raising the standard for GCPs.

(Response) FDA agrees with some of these comments and believes our responses to comments on the proposed rule provide clarification on many issues. FDA intends to issue guidance that explains the requirements of the rule in plain language and how sponsors and applicants can comply with the requirements.

On its website, FDA has provided materials related to GCP training opportunities, including information about the annual GCP training course that FDA has conducted.[1] All of these training materials focus on the regulations governing FDA-regulated clinical investigations. In addition, FDA has been participating, through the Clinical Trials Transformation Initiative, in the development of recommendations identifying principles for GCP training for investigators.[2]

V. Legal Authority

We are issuing 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 FDA [3] 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 ensure 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 clinical investigation.

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 safety or effectiveness of a device depends, in part, on whether the investigation 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 investigations, the data must be submitted in a PMA application under section 515(c)(1)(A) of the FD&C Act.

Under section 510(k) of the FD&C Act, device manufacturers are required to submit a premarket notification to FDA before introducing or delivering for introduction into interstate commerce for commercial distribution a device, unless the device is exempt from premarket notification. FDA reviews a premarket notification submission to determine whether the device is substantially equivalent to a legally marketed (predicate) device. Under section 513(i) of the FD&C Act, 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 investigation 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 investigation 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, as amended by the Cures Act in 2016, FDA may grant an HDE if FDA finds that the device: (1) Is designed to treat or diagnose a disease or condition that affects not more than 8,000 individuals in the United States; (2) 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 (3) 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 investigations submitted in an HDE application support that the probable benefits of the device outweigh its risks depends, in part, on whether the investigation 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 513(f)(2) of the FD&C Act authorizes the submission of a request for De Novo classification for a device for which there is no legally marketed device upon which to base a substantial equivalence determination, and authorizes FDA to classify the device subject to the request under the criteria set forth in section 513(a)(1) of the FD&C Act. Whether data from clinical investigations submitted in a request for De Novo classification support the recommended classification depends, in part, on whether the investigation was conducted in accordance with ethical and other principles that provide assurance of the quality and integrity of

[1] Further information is available at: *https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112925.htm.*

[2] *https://www.ctti-clinicaltrials.org/what-we-do/study-start/gcp-training.*

[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' 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.''

clinical data and adequate protection of human subjects.

Section 569B of the FD&C Act, which was added by the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144) in 2012, requires FDA to accept data from clinical investigations conducted outside the United States, if the applicant demonstrates that such data are adequate under FDA's applicable standards to support clearance or approval of the device.

Section 701(a) of the FD&C Act 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 investigations, whether conducted inside or outside the United States, as reliable evidence supporting an IDE, PMA, 510(k), PDP, request for De Novo classification, or HDE application or submission.

VI. Analysis of 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.

VII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us 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). Executive Order 13771 requires that the costs associated with significant new regulations ''shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.'' We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866. This final rule is not considered an Executive Order 13771 regulatory action.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small entities are not likely to incur more than one percent of their revenue in costs to comply with the final rule, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing ''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 $148 million, using the most current (2016) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 1, Docket No. FDA–2013–N–0080) and at *https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

The final rule will require that data submitted by sponsors and applicants from clinical investigations conducted outside the United States to support an IDE application, a 510(k) submission, a request for De Novo classification, a PMA application, a PDP application, or an HDE application be from investigations conducted in accordance with GCP. We define GCP as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes the review and approval by an IEC before initiating an investigation, continuing IEC review of ongoing investigations, and obtaining and documenting the freely given informed consent of subjects. The changes require a statement regarding compliance with our regulations for human subject protection, IRBs, and IDEs when the investigations are conducted in the United States. With the above described changes, the rule is intended to update our standards of acceptance of data from clinical investigations and to help ensure the quality and integrity of data obtained from these investigations and the protection of human subjects.

We have not quantified the benefits of the final rule that would come from the greater assurance of clinical data quality and integrity and human subject protection, particularly as it pertains to clinical investigations conducted outside the United States. One-time costs would arise to learn the requirements of the rule, and annually recurring costs would arise from increased labor associated with obtaining, documenting, and maintaining records to meet the rule's requirements for those that did not already meet the requirements. Total estimated annualized costs of complying with these requirements, over 10 years, range from $0.8 million to $22.1 million with a 7 percent discount rate and range from $0.7 million to $22.0 million with a 3 percent discount rate.

Table 1 summarizes our estimate of the annualized costs and the annualized benefits of the final rule.

TABLE 1—SUMMARY OF BENEFITS, COSTS AND DISTRIBUTIONAL EFFECTS OF THE RULE

[$ millions]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Benefits:							
Annualized				2016	7	10	
Monetized $millions/year				2016	3	10	
Annualized				2016	7	10	

TABLE 1—SUMMARY OF BENEFITS, COSTS AND DISTRIBUTIONAL EFFECTS OF THE RULE—Continued

[$ millions]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Quantified				2016	3	10	
Qualitative	Increased collection of information that provides greater assurance of clinical data quality and integrity and human subject protection.						
Costs:							
Annualized	$7.4	$0.8	$22.1	2016	7	10	
Monetized $millions/year	7.3	0.7	22.0	2016	3	10	
Annualized				2016	7	10	
Quantified				2016	3	10	
Qualitative							
Transfers:							
Federal				2016	7	10	
Annualized				2016	3	10	
Monetized $millions/year	From:			To:			
Other				2016	7	10	
Annualized				2016	3	10	
Monetized $millions/year	From:			To:			

Effects:
State, Local or Tribal Government: None.
Small Business: None.
Wages: None.
Growth: None.

Table 2 presents a summary of the Executive Order 13771 impacts of the final rule over an infinite time horizon.

TABLE 2—E.O. 13771 SUMMARY TABLE

[In $ millions 2016 dollars, over an infinite time horizon]

	Primary (7%)	Lower bound (7%)	Upper bound (7%)	Primary (3%)	Lower bound (3%)	Upper bound (3%)
Present Value of Costs	101.7	7.9	311.6	232.0	13.0	721.7
Present Value of Cost Savings	0.0	0.0	0.0	0.0	0.0	0.0
Present Value of Net Costs	101.7	7.9	311.6	232.0	13.0	721.7
Annualized Costs	7.1	0.6	21.8	7.0	0.4	21.7
Annualized Cost Savings	0.0	0.0	0.0	0.0	0.0	0.0
Annualized Net Costs	7.1	0.6	21.8	7.0	0.4	21.7

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting and recordkeeping burden. 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.

Title: Human Subject Protection; Data Requirements for Medical Device Related Clinical Investigations (OMB control number 0910–0741)

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 medical device sponsor or applicant.

Section 807.87—Information Required in a Premarket Notification Submission (OMB Control Number 0910–0120)

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

required to submit the information as described in § 807.87(j)(2).

Section 812.27—Report of Prior Investigations (OMB Control Number 0910–0078)

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

Section 812.28—Acceptance of Data From Clinical Investigations Conducted Outside the United States (OMB Control Number 0910–0078)

Section 812.28 is being added 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 a statement as described in § 812.28(a)(1); 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 (12) or a cross-reference to another section of the application or submission where the information is located; submit requests for waivers as described in § 812.28(c); and retain the records as described in § 812.28(d).

Section 812.140—Records Retention (OMB Control Number 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 Number 0910–0231)

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

Section 814.104—Original Applications (OMB Control Number 0910–0332)

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

TABLE 3—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR section/activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
807.87(j)—Human subject protection statement and information in a premarket notification submission supported by clinical data.	1,500	1	1,500	.25 (15 minutes)	375
812.27(b)(4)(i)—Report of prior investigations; U.S	400	1	400	1	400
812.27(b)(4)(ii)—Report of prior investigations; outside the U.S.	100	1	100	.25 (15 minutes)	25
812.28(a)(1)—Data from clinical investigations [2]	1,500	1	1,500	.25 (15 minutes)	375
812.28(b)—Description regarding GCP [2]	1,500	1	1,500	10	15,000
812.28(c)—Waivers [2]	10	1	10	1	10
814.20—Application information	10	1	10	.50 (30 minutes)	5
814.104—Original applications statements and information.	10	1	10	8	80
Total					16,270

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] No precise data is available for requests for De Novo classifications.

TABLE 4—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR section/activity	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
812.28(d)—Records from clinical investigations conducted outside the United States [2]	1,500	1	1,500	1	1,500
812.140—Retention period	10	1	10	1	10
Total					1,510

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] No precise data is available for requests for De Novo classifications.

The total estimated burden imposed by these information collection requirements is 17,780 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 (OMB control number 0910–0741), 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 part 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, subparts A through E, OMB control number 0910–0231; and Medical Devices: Humanitarian Use Devices—21 CFR part 814, subpart H, OMB control number 0910–0332.

The information collection provisions in this final rule have been submitted to OMB for review as required by section 3507(d) of the PRA.

Before the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has 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, the Agency has concluded that the 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.

X. Reference

The following reference is on display in the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at *https://www.regulations.gov.*

1. Regulatory Impact Analysis of the Final Rule to Human Subject Protection; Acceptance of Data from Clinical Investigations 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, 21 CFR parts 807, 812, and 814 are amended as follows:

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

■ 1. The authority citation for part 807 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 360, 360c, 360e, 360i, 360j, 360bbb–8b, 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 supported by clinical data:

(1) If the data are from clinical investigations conducted in the United States, a statement that each investigation 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, or was not subject to the regulations under § 56.104 or § 56.105, and the investigational device exemptions regulations in part 812 of this chapter, or if the investigation was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(2) If the data are from clinical investigations conducted outside the United States, the requirements under § 812.28 of this chapter apply. If any such investigation was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a) of this chapter, include either a waiver request in accordance with § 812.28(c) of the chapter or a brief statement of the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected.

* * * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

■ 3. The authority citation for part 812 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 360bbb–8b, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b–263n.

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

§ 812.3 Definitions.

* * * * *

(t) *Independent ethics committee (IEC)* means an independent review panel that is responsible for ensuring the protection of the rights, safety, and well-being of subjects involved in a clinical investigation and is adequately constituted to ensure that protection. An institutional review board (IRB), as defined in paragraph (f) of this section and subject to the requirements of part 56 of this chapter, is one type of IEC.

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

§ 812.27 Report of prior investigations.

* * * * *

(b) * * *

(4)(i) If data from clinical investigations conducted in the United States are provided, a statement that each investigation 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, or was not subject to the regulations under § 56.104 or § 56.105, and the investigational device exemptions regulations in this part, or if any such investigation was not conducted in compliance with those 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 investigation.

(ii) If data from clinical investigations conducted outside the United States are provided to support the IDE, the requirements under § 812.28 apply. If any such investigation was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a), the report of prior investigations shall include either a waiver request in accordance with § 812.28(c) or a brief statement of the

reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

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

§ 812.28 Acceptance of data from clinical investigations conducted outside the United States.

(a) *Acceptance of data from clinical investigations 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, a premarket notification submission under section 510(k) of the Federal Food, Drug, and Cosmetic Act, or a request for De Novo classification under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act).* FDA will accept information on a clinical investigation conducted outside the United States to support an IDE or a device marketing application or submission if the investigation is well-designed and well-conducted and the following conditions are met:

(1) A statement is provided that the investigation 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 investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating an investigation, continuing review of an ongoing investigation 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 an investigation. GCP does not require informed consent in life-threatening situations when the IEC reviewing the investigation finds, before initiation of the investigation, 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 protocol or elsewhere will protect the rights, safety, and well-being of subjects.

(2) In addition to the information required elsewhere in parts 807, 812, and 814 of this chapter, as applicable, the information in paragraph (b) of this section is submitted, as follows:

(i) For an investigation of a significant risk device, as defined in § 812.3(m), the supporting information as described in paragraph (b) of this section is submitted.

(ii) For an investigation of a device, other than a significant risk device, the supporting information as described in paragraphs (b)(1), (4), (5), (7) through (9), and (11) of this section is submitted, and the supporting information as described in paragraph (b)(10) of this section and the rationale for determining the investigation is of a device other than a significant risk device are made available for agency review upon request by FDA.

(iii) For a device investigation that meets the exemption criteria in § 812.2(c), the supporting information as described in paragraphs (b)(1), (4), (5), (7) through (11) of this section and the rationale for determining the investigation meets the exemption criteria in § 812.2(c) are made available for agency review upon request by FDA.

(3) FDA is able to validate the data from the investigation through an onsite inspection, or through other appropriate means, if the agency deems it necessary.

(b) *Supporting information.* A sponsor or applicant who submits data from a clinical investigation conducted outside the United States to support 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, as specified in paragraph (a)(2) of this section, or a cross-reference to another section of the application or submission where the information is located:

(1) The names of the investigators and the names and addresses of the research facilities and sites where records relating to the investigation are maintained;

(2) The investigator's qualifications;

(3) A description of the research facility(ies);

(4) A detailed summary of the protocol and results of the investigation and, should FDA request, 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 investigation 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 investigation conducted outside the United States and a comparison to the device that is the subject of the submission or application that indicates how the device used in the investigation is similar to and/or different from the device that is the subject of the submission or application;

(6) If the investigation 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 investigation 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 investigation, 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 investigation;

(11) A description of how the sponsor(s) monitored the investigation and ensured that the investigation was carried out consistently with the 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 investigation in accordance with the protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c) *Waivers.* (1) A sponsor or applicant may ask FDA to waive any applicable

requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IDE or in an amendment or supplement to an IDE, in a device marketing application or submission (an application under section 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act, a premarket notification submission under section 510(k) of the Federal Food, Drug, and Cosmetic Act, or a request for De Novo classification under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act) or in an amendment or supplement to a device marketing application or submission, or in a pre-submission. A waiver request is required to contain at least one of the following:

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

(ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(iii) Other information justifying a waiver.

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

(d) *Records.* A sponsor or applicant must retain the records required by this section for a clinical investigation conducted outside the United States as follows:

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

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

(e) *Clinical investigations conducted outside of the United States that do not meet conditions.* For clinical investigations conducted outside the United States that do not meet the conditions under paragraph (a) of this section, FDA may accept the information from such clinical investigations to support an IDE or a device marketing application or submission if FDA believes that the data and results from such clinical investigation are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected.

■ 7. 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, a premarket notification submission, or a request for De Novo classification.

* * * * *

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

■ 8. The authority citation for part 814 is revised to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 360, 360c–360j, 360bbb–8b, 371, 372, 373, 374, 375, 379, 379e, 381.

■ 9. Section 814.15 is amended by revising paragraph (a); by removing paragraphs (b) and (c); by redesignating paragraphs (d) and (e) as paragraphs (b) and (c), respectively; and by removing the parenthetical sentence at the end of the section to read as follows:

§ 814.15 Research conducted outside the United States.

(a) *Data to support PMA.* If data from clinical investigations conducted outside the United States are submitted to support a PMA, the applicant shall comply with the provisions in § 812.28 of this chapter, as applicable.

* * * * *

■ 10. Section 814.20 is amended by revising paragraphs (b)(6)(ii)(A) and (B) and adding paragraph (b)(6)(ii)(C) to read as follows:

§ 814.20 Application.

* * * * *

(b) * * *

(6) * * *

(ii) * * *

(A) For clinical investigations conducted in the United States, a statement with respect to each investigation that it either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter; or if the investigation was not conducted in compliance with those 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 investigation.

(B) For clinical investigations conducted in the United States, a statement that each investigation was conducted in compliance with part 812 of this chapter concerning sponsors of clinical investigations and clinical investigators, or if the investigation was not conducted in compliance with those 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 investigation.

(C) For clinical investigations conducted outside the United States that are intended to support the PMA, the requirements under § 812.28 of this chapter apply. If any such investigation was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a), include either a waiver request in accordance with § 812.28(c) or a brief statement of the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

* * * * *

■ 11. 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.

* * * * *

■ 12. 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.

* * * * *

■ 13. 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 data from clinical investigations, the applicant shall include the statements described in § 814.20(b)(6)(ii)(A) and (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

* * * * *

Dated: February 13, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–03244 Filed 2–20–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

24 CFR Part 2002

[Docket No. FR–6048–F–01]

Streamlining the Office of Inspector General's Freedom of Information Act Regulations and Implementing the FOIA Improvement Act of 2016

AGENCY: Office of Inspector General, HUD.

ACTION: Final rule.

SUMMARY: This final rule amends the Freedom of Information Act (FOIA) regulations for the U.S. Department of Housing and Urban Development (HUD) Office of Inspector General (OIG) to align with HUD's FOIA regulations, to implement the FOIA Improvement Act of 2016, and to explain current OIG policies and practices with respect to FOIA.

DATES: Effective: March 23, 2018.

FOR FURTHER INFORMATION CONTACT: Maura Malone; Deputy Counsel to the Inspector General; Department of Housing and Urban Development; 451 Seventh Street SW, Room 8260, Washington, DC 20410; 202–708–1613 (this is not a toll-free number). Persons with hearing or speech impairments may access this number through TTY by calling the Federal Relay Service at 800–877–8339 (this is a toll-free number).

SUPPLEMENTARY INFORMATION:

I. Background

In July 1967, HUD issued regulations at 24 CFR part 15 containing the policies and procedures governing public access to HUD records under the Freedom of Information Act (FOIA) (5 U.S.C. 552) (Pub. L. 89–487, approved July 4, 1966). The Inspector General Act of 1978 (5 U.S.C. App. 3) was enacted to ''create independent and objective units'' to perform investigative and monitoring functions within Executive agencies of the Federal Government, including HUD. HUD's regulations regarding public access to HUD records under the FOIA are at 24 CFR part 15. To further its independence, OIG officials, as opposed to HUD officials, make determinations concerning the release of OIG records. In 1984, the HUD OIG published 24 CFR part 2002, which explains the procedures for requesting information from the OIG under the FOIA. Part 2002 cross referenced several of HUD's regulations at 24 CFR part 15. The OIG last amended its FOIA regulations in July 2002 (67 FR 47216). Subsequently, HUD made several changes to its FOIA regulation, which has affected some of the regulations referenced in part 2002 (80 FR 49140).

On June 30, 2016, the President signed into law the FOIA Improvement Act of 2016 (2016 Act) (Pub. L. 114–185). The 2016 Act addresses a range of procedural issues, including requirements that agencies establish a minimum of 90 days for requesters to file an administrative appeal and that agencies provide dispute resolution services at various times throughout the FOIA process. The 2016 Act also codifies a ''foreseeable harm'' standard, amends a FOIA disclosure exemption, creates a new Chief FOIA Officer Council within the Executive Branch, and adds two new elements to agency Annual FOIA Reports. The amendments apply to any request made after the date of enactment. The 2016 Act also requires agencies to review and issue updated regulations on procedures for the disclosure of records under FOIA, in accordance with the amendments made by the 2016 Act. On January 12, 2017, HUD issued a direct final rule amending its FOIA regulation to reflect the 2016 Act amendments (82 FR 3619).

II. Changes Made in This Final Rule

In this final rule, the HUD OIG seeks to amend its FOIA regulations to address the 2016 Act changes, conform its regulations with HUD's, and simplify its regulations to make the process clearer to the requesting public. The following is an overview of nontechnical changes made in this final rule:

Section 2002.3 OIG's Overall Policy Concerning Disclosable Records

The OIG adds the title and contact information for the FOIA Public Liaison that is available to answer questions for FOIA requesters, as required by the 2016 Act.

Section 2002.5 How To Make a Request for OIG Records; Records Produced

This section is updated to provide for requests to be made in writing, which aligns with HUD's FOIA regulations, and provides that such requests may be made using the OIG public website. The regulations also reflect the requirement that the requestor, when requesting records on themselves, may be required to identify themselves when making a request or such a request may be found insufficient and closed. Lastly, the OIG also clarifies that for purposes of reasonably describing a record, a more specific FOIA request will likely result in the OIG locating the records requested. The OIG notes that a request for ''any and all'' records over an