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Acceptance of Clinical Data to Support Medical Device Applications and Submissions
Frequently Asked Questions

Guidance for Industry and Food and Drug Administration Staff

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Food and Drug Administration
Center for Devices and Radiological Health
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Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

On February 21, 2018, FDA amended its regulations on the acceptance of data from clinical investigations for medical devices.[1] Under the new rule, FDA is requiring that data submitted from clinical investigations conducted outside of the United States (OUS) 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 humanitarian device exemption (HDE) application, or a product development protocol (PDP) application, be from investigations conducted in accordance with good clinical practice (GCP), which includes review and approval by an independent ethics committee (IEC) and informed consent from subjects.[2] The GCP requirements in the final rule encompass both data quality and integrity and ethical standards for device clinical investigations.

The final rule, effective one year after publication, is codified at 21 CFR parts 807, 812, and 814.[3] It is intended to help ensure the quality and integrity of clinical data and the protection of human subjects. In particular, we have updated the requirements in 21 CFR part 814 for acceptance of data from clinical investigations conducted OUS, and we have amended 21 CFR parts 807 and 812 to identify criteria for acceptance of data from clinical investigations conducted OUS as well as investigations conducted within the United States (US), which are based on the requirements in 21 CFR part 814. Thus, the final rule provides consistency in

[1] "Human Subject Protection; Acceptance of Data from Clinical Investigations for Medical Devices" 83 FR 7366.
[2] 21 CFR 812.28(a)(1).
[3] 83 FR 7366.

FDA requirements for acceptance of data from device clinical investigations, whatever the application or submission type, and whether conducted domestically or overseas.

This guidance document is intended to help sponsors and applicants understand and comply with the new requirements of 21 CFR parts 807, 812 and 814.[4] It provides recommendations for the submission of information, whether in an IDE or marketing application or submission for a device,[5] to demonstrate that when clinical data from investigations conducted within the US or OUS are submitted to support such application or submission, the investigations conformed with FDA's regulations in 21 CFR parts 50 (human subject protection), 56 (institutional review boards), and 812 (investigational device exemptions), orGCP, as applicable.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[6]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

FDA recognizes that more multinational clinical investigations are being conducted and more research and marketing applications and submissions submitted to FDA are being supported by such investigations. The new rule helps to clarify the GCP criteria for FDA acceptance of data from clinical investigations conducted OUS as well as those conducted within the US. In view of increasing reliance on foreign clinical data, in 2012, a new provision was added to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by the Food and Drug Administration Safety and Innovation Act (FDASIA).[7] This provision requires FDA, in deciding whether to approve or clear a device, to accept data from clinical investigations conducted OUS provided that the applicant demonstrates that the data are adequate under FDA's applicable standards to support clearance or approval of the device.[8] While the new rule addresses acceptance of clinical data in terms of data quality and integrity and human subject protection, other factors, such as applicability to the US population and medical practice, also need to be considered.

[4] Regulatory citations throughout this document reflect the regulations in 21 CFR parts 807, 812 and 814 as amended by the new rule.
[5] For the purposes of this guidance, all references to *devices* include devices regulated by CDRH and CBER, unless otherwise specified. Marketing applications and submissions for devices include premarket notification (510(k)) submission, requests for De Novo classification, premarket approval (PMA) application, product development protocol (PDP) application, and humanitarian device exemption (HDE) application.
[6] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
[7] Pub. L. No 112-144, 126 Stat. 1113 (2012).
[8] Section 569B of the FD&C Act (21 U.S.C. 360bbb-8b).

This guidance is only intended to explain and clarify the requirements of the new rule.[9] Much of the information in this guidance comes from the preamble to the final rule and is organized in a question and answer format that tracks the regulatory provisions. In addition to addressing the substantive requirements of the final rule, this guidance addresses submission considerations.

FDA notes that the intent of the new rule is to address the conditions for FDA acceptance of clinical data when submitted to support an IDE or device marketing application or submission. It requires sponsors and applicants to provide statements regarding the conduct of clinical investigations. For investigations conducted in the US, the rule requires applicants and sponsors to state whether the investigation complied with 21 CFR parts 50, 56, and 812.[10] These regulations address data quality and integrity and human subject protection and are considered part of FDA's GCP regulations. Likewise, for investigations conducted OUS, the rule requires a statement regarding conformance with GCP and the submission of supporting information to demonstrate that conformance.[11] The rule does not specify the GCP standard to be followed and allows sponsors and applicants to choose a GCP standard provided it meets the definition in the rule.[12] We believe that conducting clinical investigations according to such a GCP standard will help ensure the integrity and quality of the data and the protection of subjects, similar to FDA's GCP regulations for investigations conducted in the US.

FDA does not intend to regulate clinical investigations conducted OUS. We expect that foreign clinical investigations will be conducted in accordance with local laws and regulations. The requirements outlined in the rule allow the flexibility needed to accommodate those 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. 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.[13]

Alternatively, a waiver provision allows sponsors and applicants to request a waiver from one or more applicable requirements in the rule regarding conformance to GCP and submission of supporting information.[14] If a sponsor or applicant cannot meet GCP for an investigation, for example, because a country's GCP requirements are not congruent with the definition in the rule or with a GCP standard, the sponsor or applicant may either provide an explanation of the departure from GCP or request a waiver.[15] FDA will take this information into account when considering the extent to which the Agency can rely on the data on a case-by-case basis. This flexibility is consistent with FDA's efforts to ensure the timely availability of safe and effective products.

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[9] 83 FR 7366

[10] 21 CFR 807.87(j)(1), 812.27(b)(4)(i), and 814.104(b)(4)(i). These requirements parallel those in 21 CFR 814.20(b)(6)(ii)(A) and (B).

[11] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 812.28(a) and (b), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).

[12] 21 CFR 812.28(a)(1).

[13] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).

[14] 21 CFR 812.28(c).

[15] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).

The rule is consistent with FDA's least burdensome approach to medical device regulation, while not lowering the statutory criteria for demonstrating substantial equivalence or reasonable assurance of safety and effectiveness.[16] It is FDA's intention to ensure that quality data, whether from clinical investigations conducted within or outside the US, are used to support IDEs and marketing applications and submissions. As previously indicated, this rule is intended to provide predictability, consistency and transparency of the review process to sponsors and applicants while allowing some flexibility to meet GCP requirements.

III. Discussion

Under FDA's regulations, sponsors and applicants may rely on data obtained from clinical investigations conducted within the US, OUS, or both to support research and/or marketing applications or submissions to the Agency. Some sponsors and applicants may seek to rely solely on OUS clinical data as support for an IDE or device marketing application or submission, and this is permitted under the regulations.[17] As stated by the new rule, FDA will accept data from well-designed, well-conducted clinical investigations conducted OUS as support for an IDE or device marketing application or submission if the investigations were conducted in accordance with GCP, supporting information is provided as applicable, and FDA is able to validate the data from the investigation through an onsite inspection, if necessary.[18]

The GCP requirements at 21 CFR 812.28 help enhance the quality and integrity of the clinical data and protect human subjects. They further help ensure that OUS clinical investigations are conducted in a manner comparable to that required for IDE investigations. The requirement to conduct clinical investigations in accordance with GCP as defined in 21 CFR 812.28(a)(1) is intended to provide consistency with FDA's GCP regulations at 21 CFR parts 50, 56, and 812 as well as certain international ethical and policy standards for clinical trials (e.g., International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Good Clinical Practice: Consolidated Guideline" (ICH E6), which FDA adopted for use as guidance for industry in 1997, and "Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice," ISO 14155:2011, which FDA recognized in 2012 as a consensus standard).

A. Conformity with GCP

GCP is defined in 21 CFR 812.28(a)(1) as "a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that

[16] Congress first added least burdensome provisions to the FD&C Act under the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115). Congress enacted additional least burdensome provisions to the FD&C Act through FDASIA (Public Law 112-144) and the 21ST Century Cures Act (Public Law 114-225). See Sections 513(i)(1(D)(i), 513(a)(3)(D)(ii)-(iv), and 513(c)(5)(A)-(D).

[17] Marketing approval of a new device based solely on foreign clinical data is governed by 21 CFR 812.28 and 814.15 in addition to other provisions in 21 CFR part 814.

[18] 21 CFR 812.28(a).

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.[19] 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 21 CFR 50.23 or 50.24(a), or that the measures described in the protocol or elsewhere will protect the rights, safety, and well-being of subjects.[20]

Sponsors and applicants are required to provide statements regarding the conformity of investigations with GCP when submitted in support of device applications and submissions.[21] 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, ethically derived data. Conformance with GCP is one way to help ensure clinical data are credible, accurate, and ethically procured.

There may be some situations where investigations that do not fully conform with GCP are submitted in support of an IDE or device marketing application or submission. Such investigations may elicit concerns about the credibility and accuracy of the data submitted in support of such application or submission. However, the regulations offer the sponsor or applicant the opportunity to provide 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.[22] Alternatively, the sponsor or applicant may request a waiver if the sponsor or applicant can justify why the requirement is unnecessary, cannot be achieved, or can be satisfied through an alternative course of action.[23] FDA will review the explanation or waiver request on a case-by-case basis, taking into account all appropriate circumstances, when considering the extent to which the Agency can rely on the data. Sponsors and applicants are reminded that they must submit data from all clinical investigations, including investigations that do not comply with the requirements of 21 CFR 812.28 or 21 CFR parts 50, 56, or 812, and other information, as required under the applicable regulations for devices.[24]

(1) Statements regarding the conduct of clinical investigations

For clinical investigations conducted within the US, in accordance with applicable regulations, the IDE or device marketing application or submission must include a statement that each investigation was conducted in compliance with applicable requirements in the

[19] 21 CFR 812.28(a)(1).
[20] *Id*.
[21] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 812.28(a)(1), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).
[22] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).
[23] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 812.28(c), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).
[24] *See, e.g.*, 21 CFR 812.27(a), 814.20(b)(8)(ii), and 814.104(b)(4)(i).

Protection of Human Subjects regulations in 21 CFR part 50, the Institutional Review Boards regulations in 21 CFR part 56, and the Investigational Device Exemptions regulations in 21 CFR part 812.[25] If the investigation was not conducted in compliance with those regulations, a statement must be included describing the reasons for noncompliance.[26]

For clinical investigations conducted OUS and submitted to support an IDE or device marketing application or submission, a statement must be included that each investigation was conducted in accordance with GCP as described in 21 CFR 812.28(a)(1). If the investigation was not conducted in accordance with GCP, then in accordance with applicable regulations, the IDE or device marketing application or submission must include either a waiver request (in accordance with 21 CFR 812.28(c)) or a statement explaining the reason for not conducting the investigations 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.[27]

For a multi-center investigation with sites both inside and outside the US, each site would need to comply with the local requirements. Clinical investigations conducted in the US are subject to parts 50, 56, and 812. Title 21 CFR 812.28 does not govern the conduct of clinical investigations at sites located outside the US, but rather specifies the criteria for FDA acceptance of data resulting from investigations conducted OUS to support an IDE or device marketing application or submission. When a multi-center investigation includes sites both inside and outside the US, in addition to the required statements discussed above, the sponsor or applicant should provide a statement regarding the international nature of the investigation, and the compliance of sites with their applicable local requirements.[28]

(2) Special considerations for *in vitro* diagnostic (IVD) device investigations using leftover, de-identified biospecimens

FDA recognizes that many investigations of IVDs use leftover, de-identified human specimens. FDA issued the guidance entitled, "Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable"[29] 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 the 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. In addition to sponsors being able to apply the guidance to certain IVD investigations conducted in the US, FDA stated that the Agency does not intend to object if sponsors and applicants follow the guidance for similar IVD investigations conducted OUS provided there is no conflict with local laws and regulations.[30]

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[25] 21 CFR 807.87(j)(1), 812.27(b)(4)(i), 814.20(b)(6)(ii)(A) and (B), and 814.104(b)(4)(i).
[26] *Id*.
[27] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).
[28] 83 FR 7366, see comment 6.
[29] Available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071265.pdf
[30] 83 FR 7366, see comment 14.

B. Supporting Information (21 CFR 812.28)

A sponsor or applicant submitting clinical data from an OUS investigation in support of an IDE or a marketing application or submission for a device must include a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP.[31] The description must provide either the information under 21 CFR 812.28(b), as specified in 21 CFR 812.28(a)(2), or a cross-reference to another section of the application or submission where the information is located.[32] If this information was previously submitted, the sponsor or applicant may indicate the location of the required information by providing cross-references to relevant sections of previously submitted materials. As discussed in Section III.A.(1) above, if the OUS clinical investigation did not conform to GCP, then in accordance with applicable regulations, the IDE or device marketing application or submission must include either a waiver request (in accordance with 21 CFR 812.28(c)) or a statement explaining 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.[33]

The location of all information required by 21 CFR 812.28 should be clearly identified in the application or submission. FDA recommends that for any OUS clinical data intended to support an IDE or device marketing application or submission, the sponsor or applicant clearly indicate where in the application or submission (or in previously submitted materials) the required elements under 21 CFR 812.28 can be found. If a statement of the reasons 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 are submitted, or a waiver request is being made or was previously granted, that should likewise be identified.

Clearly identifying where the required information can be found will facilitate FDA's review of the IDE or device marketing application or submission by enabling review staff to easily confirm the sponsor's or applicant's compliance with the requirements of 21 CFR 812.28. A sponsor or applicant might also use an application's or submission's cover letter to indicate whether the application or submission contains data from OUS clinical investigations that are subject to 21 CFR 812.28. The application or submission should contain page references to the respective clinical investigation reports for the identified investigations.

Below, we discuss in more detail each of the elements of 21 CFR 812.28(b) ("Supporting Information") as required under 21 CFR 812.28(a)(2). Although we make reference throughout these answers to relevant portions of ISO 14155:2011 and ICH E6, we remind sponsors and applicants that they may choose to meet the requirements of 21 CFR 812.28 through other appropriate means.

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[31] 21 CFR 812.28(b).
[32] *Id*.
[33] 21 CFR 807.87(j)(2), 812.27(b)(4)(ii), 814.20(b)(6)(ii)(C), and 814.104(b)(4)(i).

FDA encourages sponsors and applicants to discuss any questions or concerns they may have about the format and content of the required information during pre-submission meetings with FDA.

(1) Names of investigators and names and addresses of the research facilities and sites where records relating to the investigation are maintained (Section 812.28(b)(1))

How may the sponsor or applicant meet this requirement?

Answer: In addition to the names of the investigators, 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.[34] 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.[35] If the location(s) of the records change, FDA should be notified. No additional information is needed to meet this requirement.

(2) Investigator qualifications (Section 812.28(b)(2))

How may the sponsor or applicant meet this requirement?

Answer: 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.[36]

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

Additionally, the GCP standard the sponsor or applicant follows may address information to maintain on investigator qualifications. See Section III.B.(3) below for further information.

(3) Description of the research facilities (Section 812.28(b)(3))

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

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[34] 83 FR 7366, see comment 29.
[35] *Id*.
[36] 83 FR 7366, see comment 30.

Answer: No, the name and address of the research facility is generally not a sufficient description to meet the requirement in 21 CFR 812.28(b)(3). Because FDA is generally less likely to be familiar with the research facilities in which OUS investigations are conducted, greater detail is usually needed. It would generally be adequate to identify and describe the academic medical center, hospital, physician's office, clinical research unit or other type of facility at which the investigation was conducted. The description should include enough information to enable FDA to determine the adequacy of the facilities to execute the investigation and meet its requirements (e.g., 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).[37]

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.

(4) Detailed summary of the protocol and results of the investigation, and if requested, case records or additional background data (Section 812.28(b)(4))

Would a clinical investigation report satisfy the requirement to provide a detailed summary of the protocol and results of the investigation?

Answer: Yes, submitting an integrated, detailed clinical investigation report that includes a detailed summary of the protocol and results of the investigation would meet this requirement, although alternative approaches may also be acceptable. For example, if a sponsor or applicant chooses, FDA would accept the clinical investigation report as described in Annex D of ISO 14155:2011 as a detailed summary of the protocol and results of the investigation.[38]

A detailed clinical investigation report is commonly submitted for clinical investigations that contribute to the evaluation of the safety or effectiveness of the device for the proposed indication or that otherwise support information included in proposed labeling for the product. Sponsors and applicants are reminded that, even if they submit such a detailed clinical investigation report, they must also submit any additional information that is required elsewhere in 21 CFR parts 807, 812 or 814.

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

[37] 83 FR 7366, see comment 30.
[38] 83 FR 7366, see comment 31.

Answer: Yes, FDA may need to review source documents such as medical records to verify data, whether during an onsite inspection or upon request.[39] For example, a review division within FDA may request submission of investigator, hospital, or other institutional records. If so, these records must be made available to the Agency for FDA to rely on the data.[40] In addition, FDA believes that informed consent documents should notify subjects that international regulatory authorities may need to have access to the subjects' medical records for verification of clinical investigation procedures and data.[41] For examples of methods for managing data and documents, refer to ISO 14155:2011, Section 6.8 or ICH E6, Section 5.5.

If the necessary records are not available, FDA may not accept the data in support of an IDE or device marketing application or submission.[42] If the records exist but a sponsor or applicant cannot disclose them to FDA because such disclosure is prohibited by applicable foreign law, the sponsor or applicant may seek a waiver of this requirement, as described below in Section III.C. For 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.[43] The sponsor or applicant can then submit such information in a waiver request to FDA.[44] For FDA to rely on such data, the sponsor or applicant and FDA would need to agree on an alternate means for validation.[45] Such alternative means for validation might entail FDA partnering with other regulatory authorities or other mutually agreed upon means for validation.[46]

(5) Information regarding the device (Section 812.28(b)(5))

How may the sponsor or applicant meet this requirement?

Answer: Either a statement must be provided that the device used in the clinical investigation is identical to the one that is the subject of the application or submission, or a detailed description of the device used in the investigation, including each important component (including all materials and specifications), ingredient, property, and principle of operation, must be provided.[47] If the detailed description of the device required under 21 CFR 812.28(b)(5) is already included in other sections of the IDE or device marketing application or submission, this requirement can be met by cross-referencing those other sections of the application or submission. In addition to the detailed description of the device, a comparison explaining the similarities and differences, if any, between the device used in the investigation and the device that is the subject of the application or submission must be provided.[48]

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[39] 21 CFR 812.28(a)(3) and (b)(4).
[40] *Id*.
[41] Note that the submission of case report forms (CRF) as specified by 21 CFR 814.20(b)(6)(ii) are required for PMA applications.
[42] FDA may not accept data from clinical investigations conducted OUS to support an IDE or device marketing application or submission if the conditions specified in 21 CFR 812.28(a) are not met.
[43] 83 FR 7366, see comment 31.
[44] *Id*.
[45] *Id*.
[46] *Id*.
[47] 21 CFR 812.28(b)(5).
[48] *Id*.

(6) Discussion demonstrating that the data and information constitute valid scientific evidence (Section 812.28(b)(6))

What data and information constitute valid scientific evidence under 21 CFR 860.7?

Answer: Adherence to GCP standards alone does not ensure that the data collected constitute valid scientific evidence. As defined in 21 CFR 860.7, valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.[49] Note: the sponsor or applicant should also explain how the OUS data are applicable to the US population and US medical practice.[50]

(7) The name and address of the IEC that reviewed the investigation and a statement that the IEC meets the definition in section 812.3(t) (Section 812.28(b)(7))

What does FDA consider an "adequately constituted" IEC?

Answer: FDA regulations at 21 CFR 812.3(t) define an IEC as "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." FDA believes an "adequately constituted" IEC is one that consists of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed clinical investigation.

FDA recommends that every nondiscriminatory effort be made to ensure that the IEC composition is not limited to only one gender and that it reflects the social and cultural diversity of the community(ies) from which research participants are most likely to be drawn.[51] It is further advised that only those members who are independent of the investigator and the sponsor of the investigation vote on investigation-related matters.[52] FDA recognizes that the organization and membership of IECs may differ among countries because of the local needs of

[49] 21 CFR 860.7(c)(2).

[50] Under 21 CFR 814.15, if a PMA application is based solely on OUS clinical data, the application may be approved if, among other criteria, the OUS clinical data are applicable to the US population and US medical practice.

[51] These recommendations are consistent with FDA requirements for institutional review boards. See 21 CFR 56.107(a) and (b).

[52] ICH E6, Section 3.2 (note the term trial is used interchangeably with the term investigation in ICH E6).

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.

How may the sponsor or applicant meet the requirement to provide a statement that the IEC meets the definition in section 812.3(t)?

Answer: The sponsor or applicant is required by 21 CFR 812.28(b)(7) to provide the name and address of the IEC that reviewed the investigation and a statement that the IEC meets the definition in 21 CFR 812.3(t). As stated in the preamble, in addition to the sponsor or applicant, it would be acceptable for the IEC to submit a statement that the IEC that reviewed the investigation meets the definition of an IEC in the rule.[53]

Sponsors and applicants may also consider a waiver request, as described in Section III.C, if they are unable to provide a statement that the IEC meets the definition in section 812.3(t). A waiver request could identify, as an alternative to the statement that the IEC meets the definition in section 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.[54] FDA will decide whether to grant or deny a waiver on a case-by-case basis, taking into account all appropriate circumstances.

How may the sponsor or applicant meet the requirement to maintain information to support the statement required by section 812.28(b)(7) that the IEC meets the definition in section 812.3(t)?

Answer: As provided in 21 CFR 812.28(b)(7), the sponsor or applicant must maintain records supporting the statement that the IEC meets the definition of an IEC in section 812.3(t), including records describing the qualifications (e.g., occupation, training, and experience) of all IEC members, and must make these records available for Agency review upon request. If that is not possible because of governing law relating to privacy concerns, FDA recommends that sponsors and applicants clearly document the attempts made to obtain IEC member qualifications along with an explanation as to why the IEC member qualifications cannot be obtained or disclosed.[55] Such information can then be submitted to FDA in a waiver request, as described below in Section III.C. FDA will decide whether to grant or deny a waiver on a case-by-case basis, taking into account all appropriate circumstances. Note: For device clinical investigations conducted OUS, FDA does not require that the names of the IEC members be submitted.

(8) Summary of the IEC's decision to approve, or provide a favorable opinion of, the investigation (Section 812.28(b)(8))

How much detail should the sponsor or applicant provide regarding the IEC's decisions?

[53] 83 FR 7366, see comment 37.
[54] *Id.*
[55] 83 FR 7366, see comment 39.

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

After submitting this required documentation in the IDE or device marketing application or submission, is the sponsor or applicant required to submit IEC actions on continuing review to FDA?

Answer: No, although continuing review by the IEC is required under 21 CFR 812.28(a)(1), documentation of such review need not be submitted under 21 CFR 812.28(b)(8). However, such continuing review information should be maintained and be made available to FDA upon request.

(9) Description of how informed consent was obtained (Section 812.28(b)(9))

What level of detail is needed in this description?

Answer: A description of how informed consent was obtained should address 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).[56] Examples of acceptable means of meeting the requirement in 21 CFR 812.28(b)(9) to describe how informed consent was obtained include submitting documentation of the informed consent process detailed in the following: ICH E6, Section 4.8, or ISO 14155:2011, Sections 4.7 and 9.5.

(10) Description of incentives provided to subjects to participate (Section 812.28(b)(10))

How may the sponsor or applicant meet this requirement?

Answer: FDA believes that there should be some flexibility in how sponsors or applicants comply with 21 CFR 812.28(b)(10). The sponsor or applicant may follow ISO 14155:2011 or ICH E6, by providing a sample or model informed consent form that describes any incentives provided to subjects to participate in the investigation, to satisfy 21 CFR 812.28(b)(10).[57]

[56] 83 FR 7366, see comment 42.
[57] 83 FR 7366, see comment 44.

Alternatively, a sponsor or applicant may satisfy this requirement by submitting a brief narrative description of any incentives provided to subjects who participate in the investigation.

FDA believes incentives could affect the integrity of all investigations. However, FDA is only requiring that the description of any incentives be submitted for significant risk device investigations.[58] For non-significant risk and exempt device investigations, information on incentives must be made available upon FDA request.[59]

(11) Description of how the sponsor monitored the investigation and ensured that the investigation was carried out consistently with the protocol (Section 812.28(b)(11))

How may the sponsor or applicant meet this requirement?

Answer: The sponsor or applicant should describe the methods used to oversee the conduct of the clinical investigation and the reporting of data from the investigation. Sponsors and applicants have flexibility in their selection of monitoring approaches and 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.[60] Other considerations for monitoring investigations are described in ISO 14155:2011, Section 8.2.4 and ICH E6, Section 5.18.

(12) Description of how investigators were trained to comply with GCP and to conduct the investigation in accordance with the protocol (Section 812.28(b)(12))

How may the sponsor or applicant meet this requirement?

Answer: Submitting a statement regarding investigator training (i.e., whether investigator meetings or other steps were taken to prepare investigators and standardize performance) is one acceptable means of complying with 21 CFR 812.28(b)(12), provided that the statement includes a description of how investigators were trained to comply with GCP and to conduct the investigation in accordance with the protocol, and the statement indicates whether written commitments by investigators to comply with GCP and the protocol were obtained. In addition, on its website, FDA has provided materials related to GCP training opportunities, including information about the annual GCP training course that FDA has conducted.[61] FDA has also been participating, through the Clinical Trials Transformation Initiative (CTTI), in

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[58] 21 CFR 812.28(a)(2).
[59] *Id*.
[60] 83 FR 7366, see comment 46. The guidance document is available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269919.pdf.
[61] Further information is available at: https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112925.htm.

the development of recommendations identifying principles for GCP training for investigators.[62]

Is a sponsor required by 21 CFR 812.28(b)(12) to obtain signed commitments from investigators to comply with GCP and the protocol?

Answer: No, although FDA encourages sponsors to obtain written commitments from investigators, such commitments may not be required or may even be prohibited in some countries. Under 21 CFR 812.28(b)(12), sponsors or applicants must submit a statement indicating whether written commitments by investigators to comply with GCP and the protocol were obtained and, if so, to maintain such commitments on file to be provided upon the Agency's request. For those sponsors following ISO 14155:2011 or ICH E6, these documents would be either submitted with the clinical investigation report or kept on file with the sponsor or applicant.

(13) Significant/non-significant risk determination for OUS clinical investigations (Section 812.28(a)(2))

Who is responsible for making the significant risk/non-significant risk determination for a clinical investigation conducted OUS?

Answer: FDA does not intend that foreign IECs provide oversight of this determination.[63] FDA recognizes that foreign IECs may not be familiar with FDA's terminology related to significant risk and non-significant risk device investigations. Under the IDE regulations, the sponsor may make an initial determination. Similarly, for an OUS investigation, the sponsor or applicant may make an initial determination and proceed based on their own determination.[64] 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 under 21 CFR 812.28(a)(2).[65] Upon submission of the data to FDA from an investigation that the sponsor or applicant determined to be of a non-significant risk device, if FDA determines that the investigation was of a significant risk device instead of a non-significant risk device, FDA may request the additional supporting information required for significant risk device investigations (see Q/A below).[66] For multinational investigations that include sites in the US, the determination of the institutional review boards overseeing the sites in the US should be used.[67] In addition, sponsors and applicants may request a determination from FDA through the Q-submission program,[68] just as they may for investigations conducted in the US.

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[62] https://www.ctti-clinicaltrials.org/what-we-do/study-start/gcp-training.
[63] 83 FR 7366, see comment 7.
[64] *Id*.
[65] *Id*.
[66] *Id*.
[67] *Id.*
[68] Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff, available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.

What information must be submitted to FDA under 21 CFR 812.28 for significant risk, non-significant risk and exempt device investigations?

Answer: The significant risk versus non-significant risk determination and exemption status relates to the supporting information required to be submitted by sponsors and applicants under 21 CFR 812.28.

The rule requires that sponsors and applicants of submissions and applications that include clinical investigations conducted OUS and submitted to support of an IDE or device marketing application or submission provide information regarding how the investigations conform to GCP.[69] Title 21 CFR 812.28(a)(2) identifies the different supporting information that is needed for such investigations based on the level of risk of the investigation, with significant risk device investigations requiring the most supporting information in the application or submission and device investigations that meet the exemption criteria in 21 CFR 812.2(c) generally requiring the least supporting information in the application or submission.

- Significant risk device investigations (21 CFR 812.28(a)(2)(i)) – supporting information as described in section 812.28(b) must be submitted in an IDE or device marketing application or submission.
- Non-significant risk device investigations (21 CFR 812.28(a)(2)(ii)) – supporting information as described in sections 812.28(b)(1), (b)(4), (b)(5), (b)(7), (b)(8), (b)(9), and (b)(11) must be submitted in an IDE or device marketing application or submission. Supporting information as described in section 812.28(b)(10) and the rationale for determining the investigation is of a non-significant risk device are not required to be submitted under section 812.28 in an IDE or device marketing application or submission unless requested by FDA.
- Exempt investigations (21 CFR 812.28(a)(2)(iii)) – supporting information as described in sections 812.28(b)(1), (b)(4), (b)(5), (b)(7), (b)(8), (b)(9), (b)(10), and (b)(11), and the rationale for determining the investigation meets the exemption criteria in section 812.2(c), are not required to be submitted under section 812.28 in an IDE or device marketing application or submission unless requested by FDA.

C. Waivers (21 CFR 812.28(c))

FDA expects that many sponsors and applicants are already conducting their OUS clinical investigations in accordance with GCP, and therefore, will be able to comply with 21 CFR 812.28. In addition, the final rule allows for a level of flexibility such that when GCP is not met, statements can be included in premarket submissions and applications, for FDA's consideration, explaining why the investigation was not conducted in accordance with GCP and describing the 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. Therefore, FDA does not expect that there will be many waiver requests.

[69] 21 CFR 812.28(a).

Sponsors or applicants may nonetheless ask FDA to waive any applicable requirements under 21 CFR 812.28(a)(1) and (b) by submitting a waiver request under 21 CFR 812.28(c). FDA will decide whether to grant or deny waivers on a case-by-case basis, taking into account all appropriate circumstances.

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

- If FDA requests case records maintained by the investigator or additional background data, such as hospital or other institutional records, but these documents cannot be provided as required by 21 CFR 812.28(b)(4) because disclosure is prohibited by governing law. In this case, the sponsor or applicant should document this disclosure prohibition by the foreign entity (e.g., the countries that prohibit such disclosure, the nature of the prohibitions, and the extent to which these prohibitions may impede sponsors or applicants in carrying out other obligations requiring record access).[70] 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 validation procedure.[71]
- If the sponsor or applicant was not the sponsor of the investigation being submitted and does not have information on conformity with GCP, a waiver may be requested.

(1) Required content and submission of a waiver request (Section 812.28(c)(1))

What must be included in a waiver request?

Answer: Pursuant to 21 CFR 812.28(c)(1), a waiver request is required to contain at least one of the following:

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

When and how should a waiver request be submitted?

Answer: Waiver requests may be submitted as a part of a pre-submission, an original IDE or a device marketing application or submission, a supplemental application or submission, or an amendment to an IDE or device marketing application or submission.[72] A waiver may be requested prior to initiation of an investigation. The affected application or submission should include a cover letter that clearly states that a waiver under 21 CFR 812.28(c) is being

[70] 83 FR 7366, see comment 31.
[71] *Id.*
[72] 21 CFR 812.28(c).

requested. The cover letter should identify the affected investigations and the relevant sections of the application or submission. If a waiver has already been requested and granted by FDA, the previously submitted materials that include the waiver request should be referenced in the cover letter.

In addition, FDA recognizes that there may be certain circumstances where, before submitting a waiver request, sponsors or applicants may wish to discuss with FDA concerns regarding their ability to meet all of the regulatory requirements under 21 CFR 812.28. Depending on the circumstances, these issues may be submitted in a pre-submission and if appropriate, discussed with FDA during a pre-submission meeting.[73]

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

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

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

Answer: The sponsor or applicant should contact the FDA review division to which the waiver request was submitted to inquire about the status of the waiver request. The sponsor or applicant should not assume that no response means that the request for waiver has been granted.

(2) Public health implications of waiver requests (Section 812.28(c)(2))

Under what circumstances would a waiver be granted?

Answer: FDA may grant a waiver if it finds that doing so would be in the interest of the public health.[74] The regulation allows the Agency to decide on a case-by-case basis whether to grant or deny a waiver, taking into account all appropriate circumstances.

D. Records (21 CFR 812.28(d))

How long must a sponsor or applicant retain records required under 21 CFR 812.28?

Answer: If the OUS clinical investigation is submitted in support of a device marketing application or submission, a sponsor or applicant must retain the required records for at least 2 years after an Agency decision on that application or submission or, if the investigation is submitted in support of an IDE, for 2 years after termination or completion of the IDE.[75]

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[73] Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.

[74] 21 CFR 812.28(c)(2).

[75] 21 CFR 812.28(d).

E. Implementation

When will this rule be in effect?

Answer: The effective date is established as one 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.

Will this rule be applied to clinical investigations begun prior to the effective date?

Answer: FDA is implementing the rule for clinical investigations that enroll the first subject on or after the effective date of the rule. 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 of the informed consent document(s), or participates in a clinical investigation meeting the requirements of section 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 section 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.[76]"

[76] 21 CFR 814.15(b)