U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

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Acceptance of Data from Clinical Investigations for Medical Devices

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Office of Device Evaluation

Center for Devices and Radiological Health

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Publication Date: February 21, 2018

Final Rule

Human Subject Protection; Acceptance of Data From Clinical Investigations for Medical Devices

Associated Guidance

FDA Acceptance of Clinical Data to Support Medical Device Applications and Submissions

Frequently Asked Questions

Effective Date: February 21, 2019

Purpose of Device Rule

- Update and clarify the requirements for FDA acceptance of clinical data
  - for all device application and submission types, and
  - for investigations conducted inside and outside the United States

- Expressly incorporate good clinical practice (GCP)
  - Ensure the quality and integrity of the data
  - Ensure the protection of human subjects

- Harmonize with drug regulations

- Ensure FDA's decisions are based on valid, ethically derived data.

Center for Devices and Radiological Health Vision Statement

Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.

Agenda

- Background
- Requirements for Acceptance of Data From Device Clinical Investigations
- FDA Implementation and Recommendations
- Questions

Objectives

Understand the following elements:

- The purpose of the requirements for acceptance of data from device clinical investigations
- Documentation requirements from device clinical investigations to support premarket submissions
- Recommendations and resources for complying with the rule

Definitions

- **Investigation** - research involving one or more subjects to determine the safety or effectiveness of a device [812.3(h)]
  - United States (US) investigation: conducted solely in US
  - Outside US (OUS) investigation: conducted solely outside the US
  - Multinational investigation: conducted at sites both within and outside the US

- **Investigational Device Exemption (IDE) application:** mechanism to request approval for a significant risk clinical investigation of an unapproved device or unapproved use of a device

- **Marketing application or submission:** Premarket Notification (510(k)), Request for De Novo Classification (De Novo), Premarket Approval Application (PMA), Product Development Protocol (PDP), Humanitarian Device Exemption (HDE)

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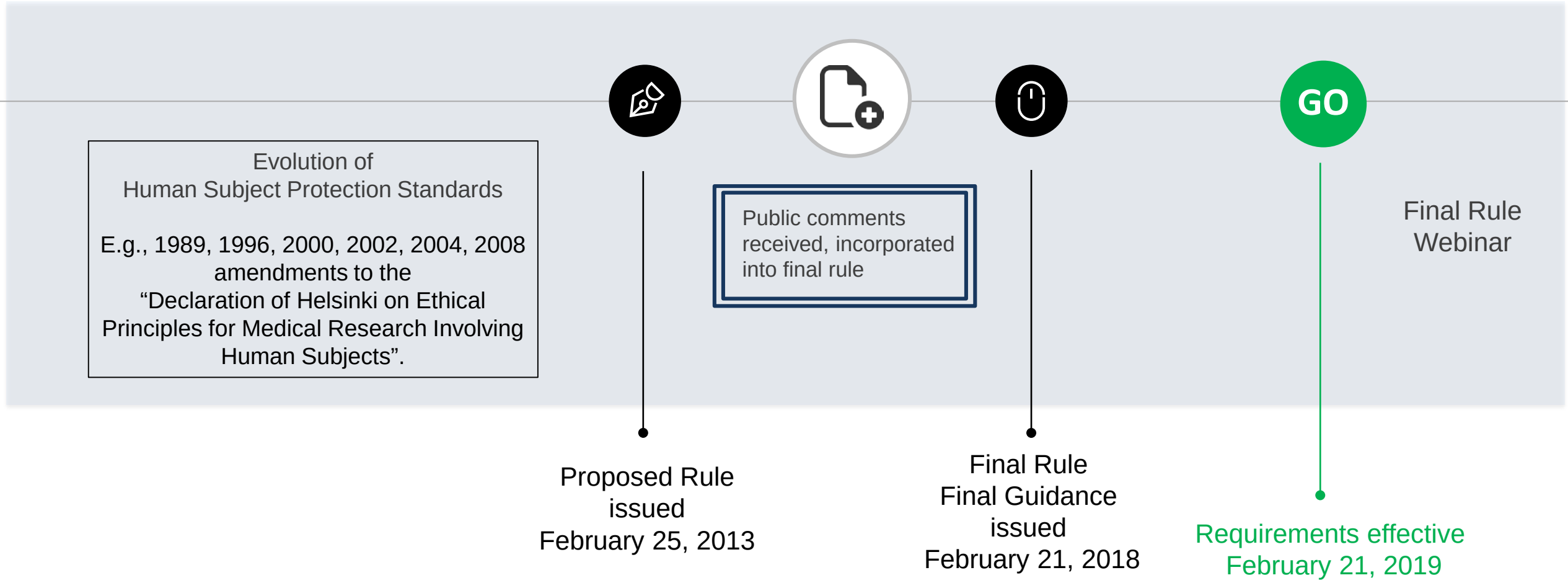
Background

Final Rule Timeline



Public Comments on the Proposed Rule

Key Feedback (13 entities)

- Application of the rule
  - Investigations within scope (e.g., Nonsignificant risk investigations, In Vitro Diagnostic (IVD) investigations using de-identified biospecimens)
- Implementation of the rule
  - Effective date
- International standards and other laws
  - Lack of a harmonized international good clinical practice (GCP) standard
  - Privacy laws that may vary by country
- Acceptance of data from noncompliant studies

FDA's Response to Public Comments

- Changes to the Final Rule
  - Adjusted supporting information requirements to vary by study risk
  - Delayed effective date (from 6 months to 1 year)
  - Added additional regulatory flexibility, such as a waiver provision

- Other Information in the Preamble
  - Clarified that FDA's policy, outlined in the FDA Guidance, "Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable," may be used to address informed consent for certain IVD studies using leftover, de-identified human specimens.

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Requirements for Acceptance of Data from Device Clinical Investigations

Scope of Final Rule

- 21 CFR parts 807, 812, and 814 have been amended to identify criteria for acceptance of clinical data for all premarket submissions
  - Investigational Device Exemption (IDE), Premarket Notification (510(k)), Request for De Novo Classification (De Novo), Premarket Approval Application (PMA), Product Development Protocol (PDP), Humanitarian Device Exemption (HDE)

- The rule applies to clinical investigations that begin (enroll their first subject) on or after February 21, 2019

Supporting Data vs. Supplementary Data

Supporting clinical data – Final Rule requirements apply

"…provided to support an IDE or device marketing application or submission; for example, when clinical data are submitted in:

- A 510(k) submission to demonstrate substantial equivalence,
- A PMA application to demonstrate a reasonable assurance of safety and effectiveness, or
- An HDE application to demonstrate reasonable assurance of safety and probable benefit."

Supplementary clinical data – Final Rule requirements do not apply

Reference: 83 FR 7366, see comment 5

Good Clinical Practice (GCP)
An Established Framework

GCP – "… *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*."

Key Principles:

- Independent Ethics Committee (IEC)
  - Initial review and approval, continuing review
- Obtaining and documenting freely given informed consent prior to subject participation

Reference: GCP defined in 21 CFR 812.28(a)(1)
IEC defined in 21 CFR 812.3(t)

FDA GCP Regulations

- Investigations conducted inside the U.S. comply with FDA GCP regulations including:
  - 21 CFR 812 Investigational Device Exemptions
  - 21 CFR 50 Protection for Human Subjects, Informed Consent (IC) Regulation
  - 21 CFR 56 Institutional Review Boards (IRBs)

Address data quality and integrity and protection of human subjects

Final Rule Requirements
US Investigations

For acceptance of data that are from clinical investigations **conducted inside the United States,** the Final Rule requires that sponsors or applicants provide**:**

- A statement that *each* investigation was conducted in compliance with the applicable requirements in parts 21 CFR 50, 56, and 812

- If *not conducted in compliance* with these regulations, a brief statement of the reason for noncompliance

Reference: Sections 807.87(j)(1), 812.27(b)(4)(i) and 814.20(b)(6)(ii)(A) & (B)

Final Rule Requirements
OUS Investigations

1. A statement that *each* investigation was conducted in accordance with GCP.

    - If *not conducted in accordance with GCP* 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.

2. Supporting information to demonstrate conformance with GCP

Reference: Sections 807.87(j)(2), 812.27(b)(4)(ii), 814.20(b)(6)(ii)(C) and 812.28(a)

OUS Investigations

Closer look at required Supporting Information

- Names and addresses of investigators and research facilities
- Investigator qualifications
- Summary of protocol and study results
- Description of the device
- Discussion demonstrating that the data and information constitute valid scientific evidence
- Adequately constituted IEC

Reference: §812.28(b)

OUS Investigations

Closer look at required Supporting Information

- Summary of IEC's decision to approve or modify and approve the clinical investigation
- Description of how informed consent was obtained
- Description of incentives provided to subjects
- Description of how the study was monitored
- Investigator training and commitments

Requirements are not intended to be duplicative with information already included in the submission and may be cross-referenced

Reference: §812.28(b)

OUS Investigations
Supporting Information to Submit to FDA

- Based on sponsor's or applicant's risk determination
  - Sponsor/applicant maintains documentation of the rationale for their determination

- Submission requirements vary by risk
  - **Significant Risk investigations:** Submission of all required elements
  - **Non-significant Risk investigations:** Submission of some elements while others are to be available for agency review upon request
  - **Exempt investigations:** Some elements are to be available for agency review upon request

Reference: Significant Risk Device defined in 812.3(m)
Exempt study criteria given in 812.2(c)

Regulatory Flexibility

1. Sponsors and applicants may choose a GCP standard that meets the regulatory definition

2. Allowance for explaining why GCP was not followed and other measures used to ensure data integrity and subject protections

3. Waiver(s) may be requested in accordance with §812.28(c)

Reference: 21 CFR 814.20(b)(6)(ii)(C), 807.87(j)(2) & 812.27(b)(4)(ii)

Summary of Provisions

For investigations that enroll the first subject on or after February 21, 2019

	US	OUS	Multinational
IDE 510(k) De Novo PMA HDE PDP	Statement of compliance* with: 21 CFR 50 21 CFR 56 21 CFR 812	1. Statement of conformance with GCP** 2. Supporting information to demonstrate conformance**	• US sites - Statement of compliance with FDA regulations* • OUS sites - Statement of conformance with GCP and supporting information**

* Or a rationale for noncompliance

** Or a rationale for noncompliance or a waiver request

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Implementation and Recommendations

Acceptance Review

The following guidances and associated acceptance checklists have been updated to incorporate provisions of the Final Rule:

- Refuse to Accept Policy for 510(k)s
- Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)

Acceptance Review
An Example

Scope

U.S. Investigations

OUS Investigations

			Yes	No	N/A	*Page #
c.		Statements of Compliance for Clinical Investigations *Select "N/A" if the submission does not contain any clinical data from investigations (as defined in 21 CFR 812.3(h)) to demonstrate substantial equivalence.* *For multicenter clinical investigations involving both United States (US) and outside United States (OUS) sites, part (i) should be addressed for the US sites and part (ii) should be addressed for the OUS sites. 21 CFR 812.28 applies to all OUS clinical investigations that enroll the first subject on or after February 21, 2019.* *Please refer to the guidance document entitled "Acceptance of Clinical Data to Support Medical Device Applications and Submissions - Frequently Asked Questions," for more information*	☐		☐	
	i.	For each clinical investigation conducted in the US, the submission includes a statement of compliance with 21 CFR parts 50, 56, and 812. **OR** The submission includes a brief statement of the reason for noncompliance with 21 CFR parts 50,56 and 812. *Select "N/A" if the clinical investigations were conducted solely OUS.*	☐	☐	☐	
	ii.	For each clinical investigation conducted OUS, the submission includes a statement that the clinical investigations were conducted in accordance with good clinical practice (GCP) as described in 21 CFR 812.28(a)(1). **OR** The submission includes a waiver request in accordance with 21 CFR 812.28(c). **OR** The submission includes 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. *Select "N/A" if the clinical investigations were conducted solely inside the US.*	☐	☐	☐	

[https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf]

Acceptance Review Scope

		Yes	No	N/A	*Page #
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- Defines applicability
- Includes reference to effective date
- Describes which of the subsequent questions apply (U.S., OUS, or multinational investigations)
- Provides link to the FAQ Guidance

[https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf]

Acceptance Review
U.S. Investigations

			Yes	No	N/A	*Page #
	i.	For each clinical investigation conducted in the US, the submission includes a statement of compliance with 21 CFR parts 50, 56, and 812. **OR** The submission includes a brief statement of the reason for noncompliance with 21 CFR parts 50,56 and 812. *Select "N/A" if the clinical investigations were conducted solely OUS.*	☐	☐	☐	

[https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf]

Acceptance Review
OUS Investigations

			Yes	No	N/A	*Page #
	ii.	For each clinical investigation conducted OUS, the submission includes a statement that the clinical investigations were conducted in accordance with good clinical practice (GCP) as described in 21 CFR 812.28(a)(1). **OR** The submission includes a waiver request in accordance with 21 CFR 812.28(c). **OR** The submission includes 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. *Select "N/A" if the clinical investigations were conducted solely inside the US.*	☐	☐	☐	

[https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf]

Waiver Requests

There may be situations where investigations conducted OUS are not able to fully conform to GCP and/or are not able to demonstrate conformity to GCP, as described by 21 CFR 812.28(a).

A sponsor or applicant may ask the FDA to waive any applicable requirements by submitting a waiver request prior to or within an IDE or marketing submission or application

Reference: Section 812.28(c)

Waiver Requests
What to Submit

A Waiver Request is required to include 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

Reference: 21 CFR 812.28(c)(1)

Waiver Requests
When and How to Submit

As part of a premarket submission:

- In an IDE, or an Amendment or Supplement to an IDE;
- In a device marketing application or submission, or in an Amendment or Supplement to a device marketing application or submission;

As a standalone Waiver Request:

- Submit to Document Control Center
- Clearly identify that the submission is a Waiver Request in accordance with 21 CFR 812.28(c)

Waiver Requests
How we communicate decisions

Within a marketing application or submission, or an IDE (report of prior investigations)	• No formal communication with respect to whether a waiver request was granted or denied, unless the decision impacts FDA's acceptance of the data and results in deficiencies to be addressed, in which case information will be provided in deficiency letters. • Final decision on a submission or application does not imply whether or not a waiver request was granted or denied.
Other Waiver Requests: • In a "pre-submission"; or • In a IDE submission (when pertaining to the subject IDE)	• Decision to grant or deny the waiver request is communicated in a letter.

Determination on acceptability of waiver will be determined on a case-by-case basis.

Recommendations for Submissions

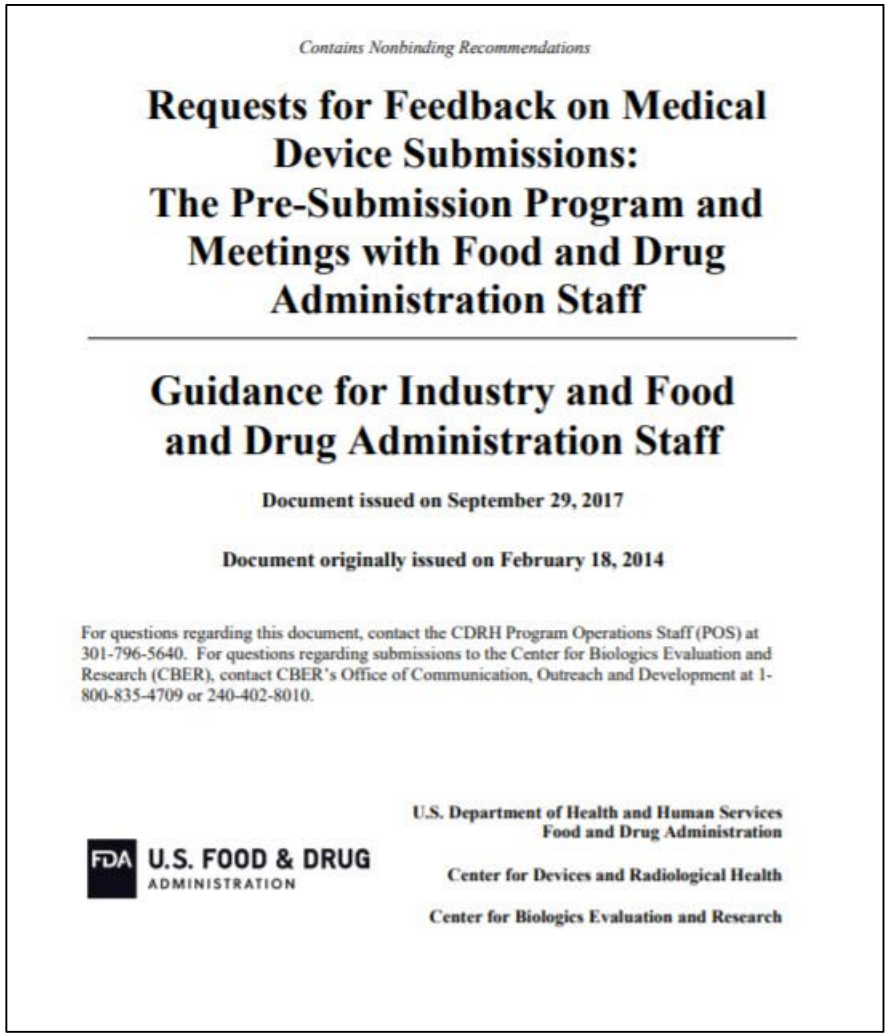
Clearly identify in the premarket submission or application:

- Whether it contains data from OUS clinical investigations that are subject to 21 CFR 812.28 (cover letter)

- Location of all required elements under 21 CFR 812.28:
  - Within the subject submission or application
  - Cross-reference to previously submitted materials
  - Page references to respective clinical investigation reports, etc.

- Whether the submission includes statements of the reasons for not conducting the investigation in accordance with GCP, or a waiver is being requested or was previously granted

Q-Submission Program



Contains Nonbinding Recommendations

Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

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Guidance for Industry and Food and Drug Administration Staff

Document issued on September 29, 2017

Document originally issued on February 18, 2014

For questions regarding this document, contact the CDRH Program Operations Staff (POS) at 301-796-5640. For questions regarding submissions to the Center for Biologics Evaluation and Research (CBER), contact CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-8010.

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U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

- Study Risk Determination for OUS investigations
- Pre-Submission: General Questions about compliance

Conclusions

- The final rule provides clarity and consistency for acceptance of clinical data for all premarket application and submission types for both U.S. and OUS investigations.
  - Applies to investigations beginning on or after February 21, 2019

- The rule requires that data submitted from clinical investigations be from investigations conducted in accordance with GCP.

- It is the FDA's intent to ensure that quality data are used to support IDEs and marketing applications and submissions, and that the rights, safety, and well-being of human subjects have been adequately protected.

Resources

- ***Guidance***
  - Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions
  - Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable

- ***GCP Standards***
  - **ISO 14155:** Clinical investigation of medical devices for human subjects – Good clinical practice
  - **ICH E6:** Good Clinical Practice: Consolidated Guidance

- ***FDA Help***
  - ***CDRHClinicalEvidence@fda.hhs.gov***

Questions?

Division of Industry and Consumer Education:
DICE@fda.hhs.gov

Slide Presentation, Transcript and Webinar Recording will be available at:

http://www.fda.gov/training/cdrhlearn

Under the heading: How to Study and Market Your Device;
Subheading: Clinical Studies/Investigational Device Exemption (IDE)

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