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Using Foreign Clinical Trial Data not Conducted Under an IND to Support a US Application

PDA Midwest Chapter Meeting

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What this Presentation will Cover

- Reasons Companies would choose to submit clinical data not generated under an IND.
- Specific Regulations and FDA Guidance documents to consider
- Breakdown of each specific requirement for submission of clinical data not generated under an IND.
  - Examples of specific data or supporting evidence to meet each of the requirements.
- How to approach FDA

Use of Clinical Data not Generated Under a US IND

There are many reasons a company may chose this option:

As part of Global Product Expansion Strategy

Commonly seen with Biosimilars and Biologics as EU is ahead of the US in marketing approvals in these two categories

In support of a 505(b)2 application to show safety and efficacy from previously generated data

In conjunction with data generated under an IND to bolster specific label claims or provide sufficient population representation for safety and efficacy.

Lastly, and most importantly, financial considerations. Clinical trials are expensive.

Foreign studies must meet the same requirements of 21 CFR Part 312 or 21 CFR Part 812, respectively, that apply to U.S. studies conducted under an IND or IDE.

The presentation covers drug products or biologics only, and not include medical devices requirements.

FDA Regulations and Guidance Overview

- 21 CFR 312.120-Foreign clinical studies not conducted under an IND and other applicable sections of 21 CFR 312 for IND data generation
- 21 CFR 314.106 (Governs marketing approval of a new drug based solely on foreign clinical data)
- 21 CFR part 50 (protection of human subjects and informed consent)
- 21 CFR part 56 (covering Institutional Review Boards)
- ICH E3 (Structure and Content of Clinical Reports)
- ICH E6 (Guidelines for Good Clinical Practice)
- FDA Guidance Document “Acceptance of Foreign Clinical Studies” March 2001

What is it that we should understand from each of these Regulations and Guidance Documents?

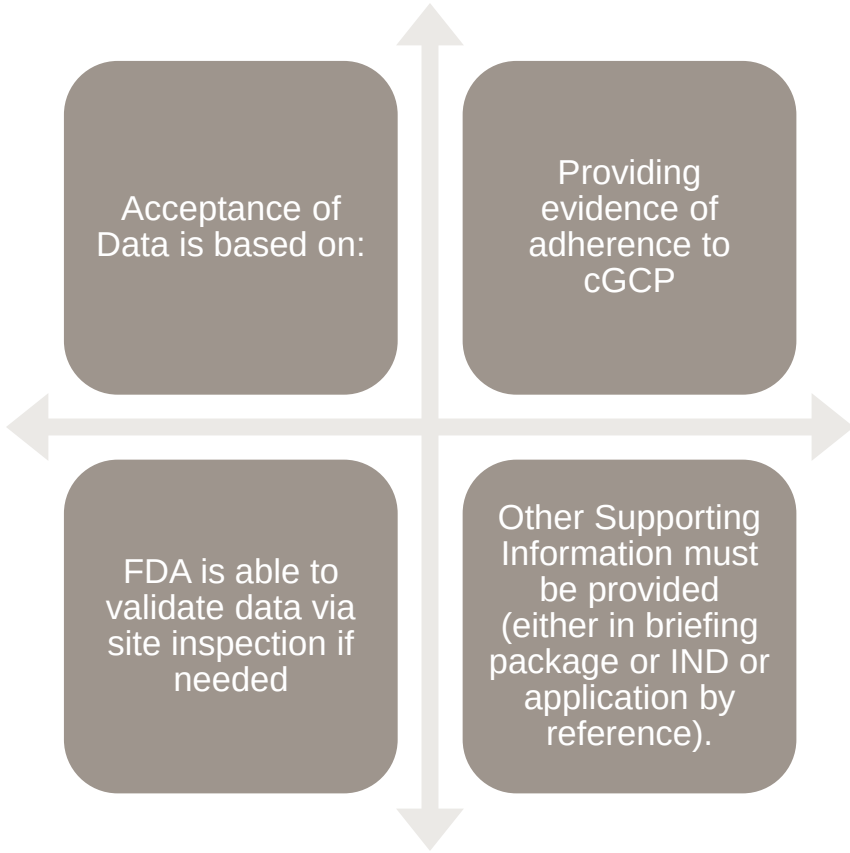
Let's Break it down into specifics

21 CFR 312.120

Replaces the requirement that these studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki (Declaration)

The revised requirement: studies must be conducted in accordance with good clinical practice (GCP)

And includes independent ethics committee (IEC) review and approval



21 CFR 312.120

Other Supporting Information requirements as outlined in 21CFR 312.120 include:

- Investigator's qualifications
- A description of the research facilities
- Study Protocol Information
- A description of the drug substance and drug product,
- Name and address of the IEC and a statement that the IEC meets the definition in § 312.3
- A summary of the IEC's decision
- Informed consent was obtained and any incentives to patients
- Study monitoring

21 CFR 314.106

21 CFR 314.106 Governs marketing approval of a new drug based solely on foreign clinical data.

An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:

(1) The foreign data are applicable to the U.S. population and U.S. medical practice;

(2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA

- or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means.

21 CFR Part 50

Outlines the requirement for, elements of and exceptions allowed for obtaining informed consent from all subjects within a clinical trial.

- Informed consent form used to the study
- Description of how informed consent was obtained

21 CFR Part 56

IRB review and approval is required before a clinical study can be initiated under an IND (21 CFR 56.103(a)).

The general standards outlined for the Institutional Review Boards Cover:

IRB Composition

IRB Operation

responsibility of an IRB

FDA may waive any of the IRB requirements for specific research activities

Waived only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable.

ICH E3 (Structure and Content of Clinical Reports)

- Assist in the compilation of a single core clinical study report which is acceptable to all regulatory authorities of the ICH regions.
- Recognized by FDA

ICH E6 (Guidelines for Good Clinical Practice)

Good Clinical Practice (GCP)

- Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected
- Facilitate mutual acceptance by European Union (EU), Japan and the United States
- Ensure Data is Credible
- GCP guidelines should be followed when generating clinical trial data

FDA Guidance Document "Acceptance of Foreign Clinical Studies" Frequently Asked Questions

This clarifies for sponsors and applicants how they can demonstrate compliance with the requirements of 21 CFR 312.120.3

Provides specific insights into what FDA expectations are for supporting data to meet the requirements for acceptance of foreign clinical data.

Supporting Data

(1) The investigator's qualifications;

- Qualified based on their training and experience
- Relevance to the proposed clinical study.
- Can be provided as a curriculum vitae or summary of training.

Supporting Data

(2) A description of the research facilities;

- Name and address of the research facility is generally not a sufficient
- FDA must be able to determine the adequacy of the facilities to execute the protocol requirements such as but not limited to:
- Appropriately staffed and equipped?
- Able to provide the appropriate emergent or specialized care.
- Listing any Regulated body inspections which have recently occurred helps.

Supporting Data

(3) A detailed summary of the protocol and results of the study

- **Approved executed protocols along with any amendments.**
- **Integrated, full Clinical summary Reports (CSRs)**

  If not done then must include additional information required by 21 CFR

Should FDA request:

- **Case records maintained by the investigator**
- **Additional background data such as hospital or other institutional records;**
- **FDA review of source documents, whether during an on-site inspection or during data review.**

Supporting Data

(4) A description of the drug substance and drug product including:

- components,
- formulation,
- specifications, and, if available,
- bioavailability of the specific drug product used in the clinical study;

Supporting Data

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under 314.126 of this chapter;

- As an example, integrated, full CSRs in accordance with ICH E3 generally provide appropriate detail to show that the study is adequate and well-controlled as described in 21 CFR 314.126. Note: the sponsor or applicant should also explain how the foreign data are applicable to the U.S. population and U.S. medical practice.

Supporting Data

(6) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in 312.3 of this chapter. The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;

- As provided in ICH E6, an adequate IEC:
- includes at least five members
- at least one member whose primary area is in a nonscientific area
- at least one member who is independent of the institution where the research will be conducted. FDA recommends that every
- Evidence of effort be made to ensure the composition is not limited to only one gender
- Reflects the social and cultural diversity of the community(ies) from which research participants are most likely to be drawn.
- Only those members who are independent of the investigator and the sponsor of the trial should vote on trial-related matters.

Supporting Data

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

- Provide the name and address of the IEC that reviewed the study
- Brief summary of the IEC actions to approve or modify the clinical investigation
- Statement that the IEC meets the definition of an IEC in 21 CFR 312.3(b)

Supporting Data

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

- Generally a copy of the informed consent form used to the study along with a description of how informed consent was obtained is sufficient.

Supporting Data

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

- If this information is included in your informed consent form this is typically sufficient.
- Otherwise a sponsor or applicant may satisfy this requirement by submitting a brief narrative description of any incentives provided to subjects who participate in the study

Supporting Data

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

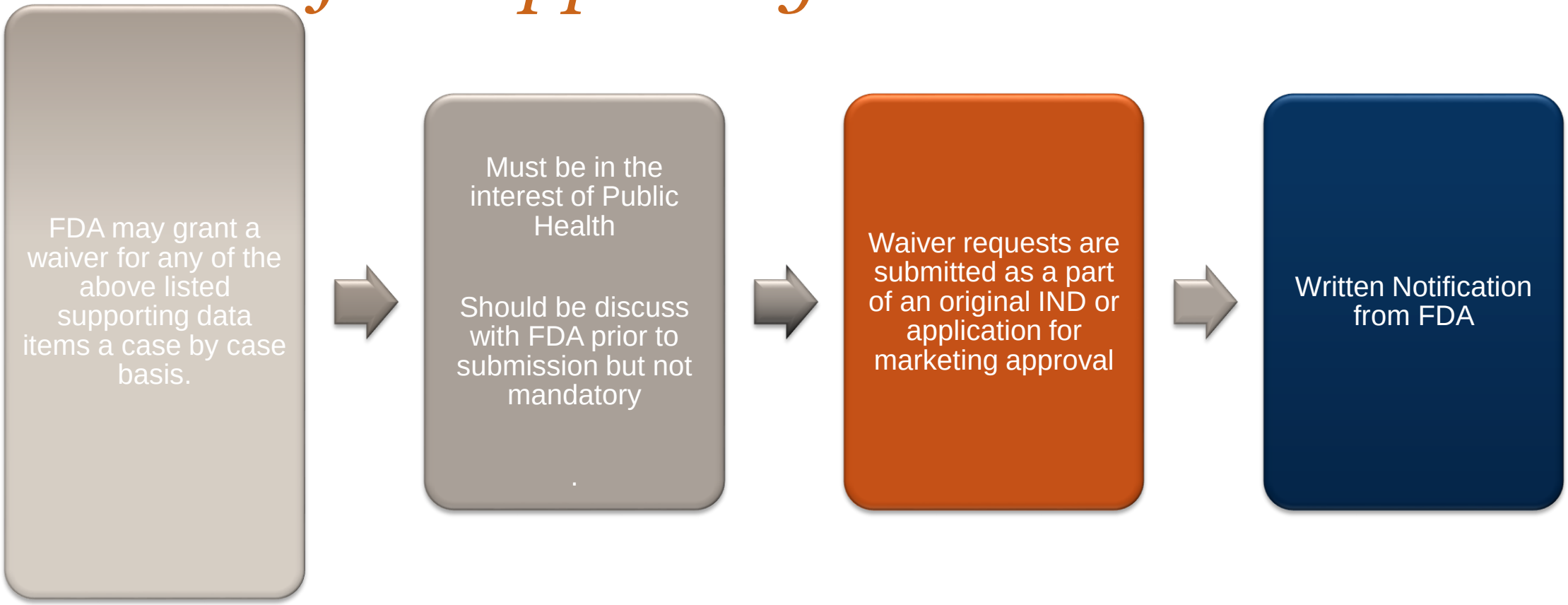
- Clinical Study Monitoring Procedures
- Cross reference to audit-related information for the studies, as applicable (e.g., audit certificates).
- Documentation that the ICH E3 was followed

Supporting Data

(11) 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.

- Signed written commitments by investigators
- Summary of investigator meetings or other steps taken to prepare investigators and standardize performance
- How investigators were trained to comply with GCP and study protocol.
- A signed commitment from investigator(s) stating compliance with GCP and the protocol is not required, however FDA does like to see this when it is possible.

Waivers for Supporting Data



How Do I Approach FDA to Negotiate Use of Foreign Data

Pre-IND Meeting

NDA Type B

BLA BPD Type II/III.

Sponsors or applicants submitting non-IND foreign clinical study, must clearly identify in the cover letter

- (a) that the material is being submitted in accordance with 21 CFR 312.120, and
- (b) where in the submission the information required by 21 CFR 312.120(b) can be located.

So What Does it All Mean?

- A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND.
- When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived.1
- The study complies with the requirements in 21 CFR 312.120
- Specific examples of data requirements to meet 21 CFR 312.120 are provided within this presentation.
- Approach the Agency as early in the process to discuss specific data available, and the acceptability of any waivers where applicable.

FDA has outlined an approach, which when utilized appropriately can save the sponsor significant time and money in the product development phase.

Questions?
Thank you

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