Inspecting BE Studies with Clinical Endpoints

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Learning Objectives

- Understand what are clinical endpoint bioequivalence (CEP-BE) studies
- Understand different product types for CEP-BE studies and clinical endpoint assessments
- Understand inspectional findings of CEP-BE studies and how OSIS evaluations of the findings affect data acceptance for the studies

Outline

- What are clinical endpoint bioequivalence studies
- Different product types for CEP-BE studies and clinical endpoint assessments
- Inspectional findings of CEP-BE studies and how OSIS evaluations of the findings affect data acceptance for the studies
- Challenge questions

Definition: Clinical Endpoint Bioequivalence (CEP-BE) Study

- A clinical endpoint bioequivalence study is a comparative clinical study of two products intended to deliver the same active moiety at an equivalent rate and extent to the site(s) of activity.
- This approach may be applied to dosage forms intended to deliver the active moiety locally, forms that are not intended to be absorbed, or drug products for which traditional pharmacokinetic studies are not feasible.

Clinical Endpoint Bioequivalence (CEP-BE) Studies

- Clinical endpoint bioequivalence (CEP-BE) studies are utilized when a pharmacokinetic study alone cannot reliably establish bioequivalence.
- Locally acting products have minimal systemic absorption.
- OSIS uses the same compliance program for clinical parts of biosimilar studies, when we audit records of immunogenicity, PK, or PD components under PHSA 351(k)(2)(A)(i)(I)(cc).

CEP-BE Studies and Clinical Endpoint Assessments Conducted for Different Product Types

Product Type	Clinical endpoint assessments based on desired outcome, clinician's evaluation and subject-reported diaries
Topical steroids	Skin-blanching by "Chromameter"
Topical antibiotics	Inflammatory lesions or bacteria counts
Topical NSAID *nonsteroidal anti-inflammatory drug	Summary pain scores
Nasal spray	Total nasal symptom scores
Inhaler	Forced expiratory volume (FEV)
Dermal patch	Adhesion, irritation, and sensitization
Vaginal cream	Cytology and total symptom scores
Suppository	Symptom summary scores

Inspectional Findings and OSIS Evaluations for CEP-BE Studies

Inspectional findings of CEP-BE studies and OSIS evaluations of the findings for potential impact on acceptability of data from CEP-BE studies are illustrated in the following three CEP-BE case studies.

Each case study discusses:

- Study Design
- Objectionable Finding
- OSIS Evaluation

CEP-BE Case Study 1

Study Design:

A randomized, double-blind, placebo-controlled, parallel-design, multiple-site bioequivalence study with clinical endpoints

Objectionable Finding:

The clinical site didn't retain reserve samples for the third shipment of products for the study.

OSIS Evaluation:

We recommended not to accept data from subjects dosed with kits from the third shipment of products.

CEP-BE Case Study 2

Study Design:

A randomized, double-blind, multicenter, three-arm, active and placebo controlled, parallel study to evaluate the bioequivalence with clinical endpoint

Objectionable Finding:

The baseline data from 48% subjects enrolled for the study were reported to have the same inflammatory lesion counts, the sum of inflammatory papules and pustules on the subjects' skins.

OSIS Evaluation:

We recommended that data from the study conducted at the clinical site are not reliable to support regulatory decision.

CEP-BE Case Study 3

Study Design:

A double-blinded, randomized, placebo-controlled, parallel-group treatment bioequivalence study with clinical endpoint

Objectionable Findings:

The clinical site did not maintain a complete sealed blinding code and reserve samples were not retained at either the inspected clinical site or an independent third party.

OSIS Evaluation:

We recommended that the identity and accuracy of the study medication administered cannot be verified.

Summary

Failure to meet requirements specified in BIMO Compliance Program 7348.003 may:

- Result in objectionable findings at inspection site and
- Affect data acceptability for clinical endpoint bioequivalence (CEP-BE) studies.

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Challenge Question #1

True or False?

There is no documentation requirement for clinical endpoint bioequivalence (CEP-BE) studies.

A. True

B. False

Challenge Question #2

Under which of the following situations would a clinical endpoint bioequivalence study be conducted?

A. When a pharmacokinetic study alone cannot reliably establish bioequivalence

B. With locally acting dosage forms

C. With dosage forms with minimal systemic absorption

D. All of the above

References

- Code of Federal Regulations (CFR) Title 21, Part 320 – Bioavailability and Bioequivalence Requirements
  (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320)
- FDA BIMO program
  www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring- program-bimo-compliance-programs
- BIMO Compliance Program 7348.003: In Vivo Bioavailability-Bioequivalence Studies – Clinical
  (www.fda.gov/media/112538/download)
- Review of Bioequivalence Studies with Clinical Endpoints in ANDAs
  (www.fda.gov/media/72554/download)


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