
POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Assessment of Bioequivalence Studies with Clinical Endpoints in ANDAs

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PURPOSE

- This MAPP describes how the Office of Generic Drugs (OGD) will assess bioequivalence (BE) studies with clinical endpoints (i.e., comparative clinical endpoint bioequivalence studies) submitted in abbreviated new drug applications (ANDAs).

BACKGROUND

- For certain drug products, BE to the reference listed drug (RLD) is recommended to be established through a comparative clinical endpoint BE study. Before 2000, all comparative clinical endpoint BE studies submitted in ANDAs were referred to the appropriate review divisions in the Office of New Drugs (OND) for review. Currently, OGD’s Office of Safety and Clinical Evaluation (OSCE) Division of Clinical Review (DCR) assesses comparative clinical endpoint BE studies submitted in ANDAs.
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POLICY

- DCR performs the assessment of comparative clinical endpoint BE studies submitted in ANDAs.¹ DCR may consult with other offices and/or centers in cases where special expertise is required. The final assessment is completed and signed by DCR's Director, Deputy Director, or designee.

RESPONSIBILITIES

- **OGD Office of Regulatory Operations (ORO)/Division of Filing Review (DFR)**
 - Performs the initial filing review of ANDAs.
 - Determines whether a threshold amount of data has been provided for the comparative clinical endpoint BE study to enable a substantive assessment by DCR.
- **OGD/OSCE/DCR Project Manager**
 - Triage information from shared queue and informs DCR management for assignment.
 - Issues the assessment assignment to the primary, secondary, and tertiary assessors in DCR.
 - Notifies a project manager in CDER's Office of Translational Sciences' (OTS) Office of Biostatistics (OB) that an ANDA containing a bioequivalence study with clinical endpoints has been received for assessment.
 - Issues information requests as needed.
 - Ensures the clinical information is included in the appropriate Discipline Review Letter.
 - Uploads the clinical site information in CDER Informatics Platform and informs OTS' Office of Study Integrity and Surveillance (OSIS) project manager (PM).

¹ There are instances where OSCE may work with OGD's Office of Bioequivalence (OB) on issues not related to comparative clinical endpoint BE studies (e.g., irritation and sensitization studies for transdermal products) that could lead to a joint assessment. In these instances, the two offices will follow their communications practices to reach alignment on the joint assessment.

- **OGD/OSCE/DCR Primary Assessor**
 - Performs the primary substantive assessment of the comparative clinical endpoint BE study.
 - Routinely consults with statisticians in OTS/OB on the assessment of the statistical methodology and associated data submitted as part of a comparative clinical endpoint BE study.
 - Determines if additional consultations are necessary from other offices and/or centers.
 - Consults the appropriate offices and/or centers for input, as necessary.
 - Consults the DCR Secondary Assessor/Team Leader when necessary. Collaborates with OTS/OB assessors as necessary when issues arise with the assessment.

 - **OGD/OSCE/DCR Secondary Assessor/Team Leader**
 - Performs secondary assessment of the comparative clinical endpoint BE study.
 - Routinely consults with statisticians in OTS/OB on the assessment of statistical methodology and associated data submitted as part of a comparative clinical endpoint BE study.
 - Determines if additional consultations are necessary from other offices and/or centers.
 - Consults the appropriate offices and/or centers for input, as necessary.
 - Ensures appropriate communications have occurred with OTS/OB as needed.

 - **OGD/OSCE/DCR Director, Deputy Director, or Designee**
 - Conducts final assessment of DCR's assessment of the comparative clinical endpoint BE study.
 - Determines if additional consultations are necessary from other offices and/or centers.
 - Finalizes DCR assessment if no additional consultations are necessary.
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PROCEDURES**1. Filing**

- When an ANDA containing a comparative clinical endpoint BE study is submitted, DFR will determine whether a threshold amount of data has been provided to enable a substantive assessment by DCR. If such threshold amount of data has been provided, then the ANDA may be filed, provided all other filing considerations have been adequately addressed. Once the ANDA is found acceptable for filing, the ANDA will be placed in ORO's Division of Project Management's queue for assignment.

2. Assessment Assignments

- When an ANDA containing a BE study with clinical endpoints is received, ORO's Division of Project Management assigns the ANDA to DCR. Upon receipt of the ANDA in DCR's shared queue, a DCR project manager informs management and issues an assessment assignment to DCR's primary, secondary, and tertiary assessors.
- The DCR project manager also notifies a project manager in OTS/OB that an ANDA containing a comparative clinical endpoint BE study has been received for assessment. DCR's project manager provides the timelines for assessment to the project manager in OTS/OB.
- In addition, DCR's project manager provides the clinical site information to OSIS.
- DCR will incorporate statisticians' assessments of the study methodology and data and will make the final conclusion and recommendation on the comparative clinical endpoint BE study. DCR will also incorporate the results of the OSIS clinical site inspection (if conducted).

3. Consultative Assessments

- During the course of their assessment, the DCR assessor(s) may determine that there is a need to seek additional expertise and issue consults to other offices and/or centers including, but not limited to, the following:
 - Center for Devices and Radiological Health
 - Center for Drug Evaluation and Research:
 - Office of Surveillance and Epidemiology
 - OND (division(s) with relevant clinical expertise)
 - OGD/Office of Research and Standards

- The DCR project manager issues the consult.
- DCR assessor(s) will incorporate the completed consult responses into the assessment and will forward the assessment to the DCR Director, Deputy Director, or designee for review and concurrence.

4. Division Level Review

- The DCR Director, Deputy Director, or designee is the final signatory for assessment of all comparative clinical endpoint BE studies.

REFERENCES

- Federal Food, Drug, and Cosmetic Act – Section 505(j)
- Code of Federal Regulations – 21 CFR 320.24

DEFINITION

- **Bioequivalence Study with Clinical Endpoints** (comparative clinical endpoint BE study): A bioequivalence study with clinical endpoints is a comparative clinical study in humans that can determine the bioequivalence of dosage forms 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.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
12/18/00	Initial	N/A
12/12/06	1	Revised to reflect the current organizational structure and processes in OGD
06/26/17	2	Revised to reflect the current organizational structure and processes in OGD

MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH

MAPP 5210.4 Rev. 3

5/2/23	3	Revised to reflect the current organizational structure and processes in OGD
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