
POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Review of Bioequivalence Studies with Clinical Endpoints in ANDAs

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PURPOSE

- This MAPP describes the Office of Generic Drugs’ (OGD) policies and procedures for the review of bioequivalence studies with clinical endpoints submitted in abbreviated new drug applications (ANDAs).

BACKGROUND

- For certain classes of drug products, bioequivalence to the reference listed drug (RLD) can only be established through a comparative clinical endpoint study. Before 2000, all comparative clinical endpoint 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 Bioequivalence (OB) Division of Clinical Review (DCR) now reviews bioequivalence studies with clinical endpoints.

POLICY

- DCR performs the review of bioequivalence studies with clinical endpoints submitted in ANDAs. DCR may consult with other offices and/or centers in cases where special clinical expertise is required. The final review is completed and signed by DCR’s Director, Deputy Director, or designee.

RESPONSIBILITIES

- **OGD Office of Regulatory Operations/Division of Filing Review (DFR)**
 - Performs the initial filing review of ANDAs.
 - If the ANDA contains a bioequivalence study with clinical endpoints, determines whether a threshold amount of data has been provided to enable a substantive review by DCR.
- **OGD Office of Regulatory Operations/Division of Project Management (DPM)**
 - Issues a review assignment to a DCR project manager when an ANDA containing a bioequivalence study with clinical endpoints is received for review.
- **DCR Project Manager**
 - Issues the review assignment to the primary, secondary, and tertiary reviewers in DCR.
 - Notifies a project manager in CDER's Office of Translational Science's (OTS) Office of Biostatistics that an ANDA containing a bioequivalence study with clinical endpoints has been received for review and provides the timelines for the review.
- **OGD/OB/DCR Primary Reviewer**
 - Performs the primary substantive review of the bioequivalence study with clinical endpoints.
 - Routinely consults with statisticians in OTS' Office of Biostatistics on the review of the statistical methodology and associated data submitted as part of a bioequivalence study with clinical endpoints.
 - Determines if additional consultations are necessary from other offices and/or centers.
 - Consults the appropriate offices and/or centers for input, as necessary.

- **OGD/OB/DCR Secondary Reviewer/Team Leader**
 - Performs secondary review of the bioequivalence study with clinical endpoints.
 - Routinely consults with statisticians in OTS' Office of Biostatistics on the review of statistical methodology and associated data submitted as part of a bioequivalence study with clinical endpoints.
 - Determines if additional consultations are necessary from other offices and/or centers.
 - Consults the appropriate offices and/or centers for input, as necessary.
 - **OGD/OB/DCR Director, Deputy Director, or Designee**
 - Conducts final review of the DCR reviewer's assessment of the bioequivalence study with clinical endpoints.
 - Determines if additional consultations are necessary from other offices and/or centers.
 - Finalizes DCR review if no additional consultations are necessary.
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PROCEDURES

1. Filing

- When an ANDA containing a bioequivalence study with clinical endpoints is submitted, DFR will determine whether a threshold amount of data has been provided to enable a substantive review 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 DPM's queue for assignment.

2. Review Assignments

- A regulatory project manager in DPM will issue a review assignment to a project manager in DCR when an ANDA containing a bioequivalence study with clinical endpoints is received. DCR's project manager will issue review assignments to DCR's primary, secondary, and tertiary reviewers and will notify a project manager in OTS' Office of Biostatistics that an ANDA containing a bioequivalence study with clinical endpoints has been received

for review. DCR's project manager will also provide the timelines for review to the project manager in OTS' Office of Biostatistics.

- DCR will incorporate statisticians' assessments of the study methodology and data and will make the final conclusion and recommendation on the bioequivalence study with clinical endpoints.

3. Consultative Reviews

- During the course of their review, the DCR reviewer(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 (CDRH)
 - Center for Drug Evaluation and Research (CDER):
 - Office of Surveillance and Epidemiology
 - Office of New Drugs (division(s) with relevant clinical expertise)
 - OGD/Office of Research and Standards
- DCR reviewer will incorporate the completed consult responses into the review and will forward the review 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 review of all bioequivalence studies with clinical endpoints

REFERENCES

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

DEFINITIONS

- **Bioequivalence Study with Clinical Endpoints:** 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