Office of Generic Drugs

Review Responsibility for Bioequivalence Studies with Clinical Endpoints Submitted in an Abbreviated New Drug Application

CONTENTS

PURPOSE
BACKGROUND
REFERENCES
DEFINITION
POLICY
RESPONSIBILITIES
PROCEDURES
EFFECTIVE DATE

PURPOSE

- This MAPP describes the Office of Generic Drugs (OGD) policies and procedures on 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 the use of a clinical endpoint study. Previously, all clinical endpoint studies necessary to determine bioequivalence of a drug product submitted in an ANDA were referred to the appropriate reviewing division in the Office of Review Management (ORM). ORM review and comments would be further evaluated by the Division of Bioequivalence (DBE) and any recommendations or deficiencies would be communicated to the applicant by DBE. However, this process changed with the addition of a medical officer to the OGD staff. Currently, OGD's medical officer, the Associate Director for Medical Affairs, reviews bioequivalence studies with clinical safety or efficacy endpoints.

REFERENCES

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

DEFINITION

- **Bioequivalence Study with Clinical Endpoints**: A bioequivalence study with clinical endpoints is a comparative clinical trial 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 applies to dosage forms intended to deliver the active moiety locally or forms that are not intended to be absorbed.

POLICY

- OGD's Associate Director for Medical Affairs (ADMA) performs the initial review of bioequivalence studies with clinical endpoints submitted with an ANDA. The ADMA can request concurrence from the Division Director in the appropriate ORM review division. In cases where special expertise is needed, the ADMA will request that ORM complete both primary and secondary level reviews.

RESPONSIBILITIES

- Division of Labeling and Program Support

  When ANDAs are filed, the Project Managers in the Regulatory Support Branch, with concurrence from DBE, identify and prepare consults for bioequivalence studies with clinical endpoints. Consults are forwarded to the OGD Consult Coordinator.

  The OGD Consult Coordinator in the Division of Labeling and Program Support (DLPS) ensures that all consults are properly prepared, tracked, and routed through or to appropriate OGD/ORM personnel.

  The OGD Consult Coordinator notifies OGD management when consults have been pending review for more than 120 days.

- Division of Bioequivalence

  Reviews and determines the acceptability of traditional bioequivalence studies, including pharmacokinetic, pharmacodynamic, and dissolution studies submitted to the ANDA in addition to the clinical endpoint studies.

  At the time an application is assigned to a reviewer, the DBE Project Manager identifies and prepares consults for bioequivalence studies with clinical endpoints requiring ADMA review. Consults are forwarded to the OGD Consult Coordinator.

  Upon return of the consults, a DBE Project Manager asks the ADMA to prepare a memorandum summarizing all recommendations, including those from the ADMA, the consultant statistician, and/or ORM. The memorandum is forwarded to the Director, DBE, for concurrence.

The Director of the DBE has final signatory authority for all bioequivalence evaluations, taking into consideration recommendations of the consult review.

- Associate Director for Medical Affairs

  Determines whether the review of bioequivalence studies with clinical endpoints will be performed within OGD or will be referred to ORM. Performs the clinical review, if appropriate.

  Prepares a memorandum summarizing all recommendations obtained from OGD and ORM consultations.

  Sends completed reviews to ORM for Division and/or Office level concurrence, as needed. Forwards recommendations to the Director of DBE.

PROCEDURES

- Filing

  After an application containing a bioequivalence study with clinical endpoints is accepted for filing by DLPS, the Regulatory Support Project Manager, with the appropriate Project Manager assigned to DBE, prepares the consult form and forwards the package to the OGD Consult Coordinator.

- Review Assignments

  All bioequivalence studies with clinical endpoints are referred to the ADMA to determine whether the review can be completed in OGD or if an ORM review is necessary.

  Both the ADMA and the DBE will review bioequivalence submissions that contain a clinical/safety and a pharmacokinetic/pharmacodynamic study or dissolution data.

- ORM Concurrence

  Reviews completed by the ADMA are forwarded to the director of the appropriate Office of Drug Evaluation for the ORM reviewing division concurrence, as appropriate. After concurrence (of the secondary review), the ADMA prepares a memorandum summarizing the study and providing an overall recommendation. The memorandum is forwarded to the appropriate DBE Project Manager. The memorandum, along with the final recommendations, is forwarded to the Director, DBE, for concurrence and signature. Deficiencies are communicated to the applicant by DBE. If the study is acceptable, the Director of DBE prepares and signs the document, concluding the product is bioequivalent to the listed drug product.

- Office Level Review

The Director, Division of Bioequivalence, is responsible for final signatory approval. The ADMA also signs the final recommendation.

EFFECTIVE DATE

This MAPP is effective upon date of publication.