OFFICE OF GENERIC DRUGS

Review of Bioequivalence Studies with Clinical Endpoints in ANDAs

CONTENTS

PURPOSE

- This MAPP describes the Office of Generic Drugs' (OGD) policies and procedures for 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 clinical endpoint study. Before 2000, all clinical endpoint studies submitted in ANDAs were referred to the appropriate review divisions in the Office of New Drugs (OND).[1] OND reviews and comments would be taken into account in making the review decision by the Division of Bioequivalence (DBE) in OGD. Any recommendations or deficiencies would be communicated to the applicant by DBE. This process was changed with the addition of a medical officer and subsequent addition of a Clinical Review Team to the OGD staff. Currently, OGD's Clinical Review Team reviews bioequivalence studies with clinical endpoints.

REFERENCES

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

[1] Formerly the Office of Review Management.

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 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.

POLICY

- The Clinical Review Team performs the review of bioequivalence studies with clinical endpoints submitted in ANDAs. The Clinical Review Team may request assistance and/or concurrence from the Division Director in the appropriate OND review division in cases where special clinical expertise is required. The final review is to be approved and signed by the OGD's lead medical officer and/or Associate Director for Medical Affairs (ADMA).

RESPONSIBILITIES

- **The Division of Labeling and Program Support will:**

  Provide the initial filing (receiving) review of ANDAs, including identification of those with bioequivalence studies with clinical endpoints.

  Seek input from the Clinical Review Team as to the acceptability of the clinical endpoint study for substantive review during this initial assessment of the application.

- **The Division of Bioequivalence will:**

  Upon receipt in the Division of Bioequivalence, transmit bioequivalence studies with clinical endpoints to the Clinical Review Team for review.

- **The Director of the Division of Bioequivalence will:**

  Accept the reviews of the clinical team and provide assurance of consistency and agreement with the overall bioequivalence assessment.

- **The Clinical Review Team and ADMA will:**

  Perform the review of the bioequivalence study with clinical endpoints.

  Consult the appropriate Division in the Office of New Drugs when necessary.

  Provide consultation on statistical methodology and data to the statisticians co-located with OGD when necessary.

The lead medical officer and/or ADMA provides secondary review of all reviews conducted by the Clinical Review Team and may determine the need for consultative secondary reviews to the relevant Division in the Office of New Drugs.

PROCEDURES

- **Filing**

  When an application containing a bioequivalence study with clinical endpoints is submitted, it is forwarded to the Clinical Review Team for a cursory review to determine whether the study appears adequate for review.

- **Review Assignments**

  All bioequivalence studies with clinical endpoints are sent from the Division of Bioequivalence (DBE) and added to the Clinical Review Team's queue for assignment by the lead medical officer and/or ADMA.

  Both the Clinical Review Team and DBE will review respective data in bioequivalence submissions that contain both a clinical endpoint study and a pharmacokinetic/pharmacodynamic study or dissolution data.

- **Consultative Reviews**

  Reviewers on the Clinical Review Team may determine during the course of their review that there is a need for one or more consultative reviews of any application. The team may seek expertise from others, including:

  - OGD Science Team (under the Director for Science)
  - Office of Biostatistics
  - Office of Surveillance and Epidemiology
  - Office of New Drugs (division(s) with relevant clinical expertise)
  - Division of Scientific Investigations

  Input from these or other groups are incorporated into the review prepared by the Clinical Review Team.

- **Office Level Review**

  The Director of DBE is responsible for final signatory approval of all bioequivalence studies, including those with clinical evaluations that have already received final review sign-off by the lead medical officer and/or ADMA.

EFFECTIVE DATE

This MAPP is effective upon date of publication.