OFFICE OF GENERIC DRUGS

Procedures for Review of Bioequivalence Study Protocols

CONTENTS

PURPOSE

- This MAPP describes the procedures to be followed when bioequivalence study protocols are received for review in the Division of Bioequivalence (DBE), Office of Generic Drugs (OGD).

BACKGROUND

- Bioequivalence studies are frequently needed to support the filing and approval of abbreviated new drug applications (ANDAs). To conduct an adequate study and avoid unnecessary human research, any sponsor planning to conduct a bioavailability or bioequivalence study should submit the proposed study protocol to the Office of Generic Drugs (OGD) for review prior to the initiation of the study. OGD reviews the protocol and provides advice on appropriate study design, reference material, and the proposed analytical and statistical methods to be used. Sponsors or contract research organizations (CROs) can submit protocols.

REFERENCES

- 21 CFR 320.30, Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration

- 21 CFR 10.90, Food and Drug Administration regulations, recommendations, and agreements

POLICY

- The DBE will review submitted bioequivalence protocols.

- The protocols will be randomly assigned to bioequivalence reviewers, unless a protocol requires the expertise of a particular reviewer.

- The reviewers will perform a search of the literature and the Agency's databases and prepare the review.

- After the protocol review, comments will be provided in a letter to the generic firm.

RESPONSIBILITIES

- **DBE Reviewer**

  Searches available pharmacokinetic information and provides recommendations on appropriate study design, reference material to be used, and analytical and statistical methods.

  Prepares a review with guidance on protocols for the product. Includes in the review a list of databases checked, appropriate references, and a list of submitted protocols and/or ANDAs for that product. Notes in the review whether it is the first protocol reviewed for a particular product.

  If it is found that conflicting or outdated information has been provided to another sponsor or CRO, prepares a memorandum listing the sponsors and/or ANDA affected, specifying the guidance provided.

- **Team Leader, Division Director, or Deputy Director**

  Ensures that consistent recommendations are provided to industry.

  Resolves any controversial issues through discussion in the appropriate forum (internal meetings within the DBE, OGD, or other groups as indicated).

- **Project Manager (PM) and/or Technical Information Assistant (TIA)**

  Enters in protocol tracking system all protocols received, including the control number, drug name, firm name, date of receipt, reviewer assigned, date the protocol was assigned, date the review was finalized, and date the letter was issued.

  Ensures all comments are communicated to the firm completely and clearly. Drafts letter to the sponsor or CRO and routes through reviewer, team leader, and Division Director. Forwards protocol and final letter to Document Room for mailing and filing.

  If outdated information has been provided to any sponsor or CRO, prepares a letter to the sponsor/CRO providing the correct information.

  Ensures that protocols are electronically filed in the appropriate local area network drive and directory.

PROCEDURES

- When a protocol is received in the DBE, the PM assigns it randomly to the next available reviewer. All protocols received are entered in the protocol tracking system and assigned a control number. The protocol receipt date, firm name, drug name, reviewer assigned, and date of assignment are recorded.

- The reviewer searches the literature and the Agency's databases (e.g., Excalibur, WinBio, drug files (hard copy and electronic)). If a protocol has been previously submitted and found acceptable by the Division, this should be used as a model in the preparation of responses to subsequent protocols for the same drug. The reviewer should state in the review whether other protocols for the same drug have been previously reviewed. If no other protocols have been reviewed for the product, a statement to that effect should be included in the review.

- The reviewer prepares a review with recommendations to the requestor. The review must have the concurrence of the team leader and Division Director.

- If the reviewer discovers discrepancies in bioequivalence criteria or appropriate study design in recommendations provided to industry in previous protocols or correspondence for the same drug product, the reviewer prepares a memorandum to the team leaders and Division Director. The memo should specify the name of the sponsor or CRO that received conflicting information/guidance in protocol responses. ANDAs affected by this information should also be noted.

- Once the review is finalized and has the concurrence of the Division Director, it is forwarded to the PM.

- The PM or TIA drafts a letter based on the reviewer's recommendation. The PM ensures that all recommendations are provided to the firm. The letter will be routed through the team leader for corrections and endorsement, and to the Division Director for signature.

- Once the letter is signed by the Division Director, the PM or TIA enters into the protocol tracking system the date the review was finalized and the date the letter was issued. The protocol is then forwarded to the Document Room. Document Room personnel mail the letter and store the protocol in the designated area.

- The PM drafts letters to sponsors or CROs that have received outdated information to ensure that consistent information is provided to industry.

EFFECTIVE DATE

This MAPP is effective upon date of publication.