OFFICE OF GENERIC DRUGS

Productivity Documentation in the Division of Bioequivalence

CONTENTS

PURPOSE

- This MAPP describes the procedures for documentation of productivity in the Division of Bioequivalence (DBE), Office of Generic Drugs (OGD).

BACKGROUND

- The COMIS database was created, in part, to keep track of the workload of all divisions. Information on all submissions received in OGD on abbreviated new drug applications (ANDAs) is entered into this system, including the applicant's name, ANDA number, drug name, dosage form, strengths, letter date, and receipt date. The bioequivalence section of an ANDA contains data on the demonstration of bioequivalence, such as bioequivalence studies, studies with clinical endpoints, dissolution data, and waiver requests. The bioequivalence data entry screen in COMIS keeps a record of (1) the reviewer assigned to the submission, (2) the type of studies submitted in the bioequivalence section, and (3) the dates when the review was initiated and satisfactorily completed by the reviewer. Other work, such as controlled correspondence and protocols, is tracked in separate databases. The overall productivity of the Division and the reviewers is monitored using the information in COMIS and the other databases.

POLICY

- Information entered into the COMIS database on the study types in the bioequivalence section of an ANDA documents the overall productivity of the reviewers and the Division. Consistent and fair classification of these study types ensures objective evaluation of reviewers.

- Non-ANDA-related work is tracked in separate databases. That information includes a control number, name of sponsor, drug name, name of assigned reviewer, date of assignment, date of completion of the review, and dates when letters are issued.

RESPONSIBILITIES

- Document Room Personnel

  Receive ANDA submissions and forward to the appropriate discipline.

  Classify bioequivalence submissions by study type with assistance from the regulatory support staff and/or bioequivalence project managers (PMs).

  Close the submission when the review is finalized by entering the date completed and the decision codes.

  Verify that the study types provided by the reviewer and team leader are entered in COMIS.

- DBE Reviewer

  Reviews bioequivalence submissions (including correspondence and protocols) assigned by the random assignment policy.

  Uses the available format to state the study types reviewed and the acceptability of the data submitted.

- Team Leader

  Verifies study type codes and acceptability of the review. Ensures that the study type classification is consistently applied.

- Project Managers (PMs)

  Assist the Document Room in the classification of bioequivalence study types.

  Enter into the bioequivalence data entry screen the name of the reviewer assigned to the ANDA and the date the review is started.

  Enter information on non-ANDA-related work into the appropriate databases.

  Correct any mistakes made in data entry.

  Forward completed reviews related to applications to the Document Room or Review Support Branch Chief.

Prepare fax cover sheets for any application deficiencies to be transmitted to the firm, and forward comments to chemistry PM to be faxed along with any comments from other disciplines.

For other division work, prepare responses to correspondence and protocol reviews based on the reviewer's comments.

PROCEDURES

When the Document Room assigns an ANDA to the DBE, a description of the bioequivalence section is entered into the bioequivalence data entry screen in COMIS, using the study types below.

A. BIOEQUIVALENCE STUDIES

1. **FASTING STUDY** (STF). This includes replicate study designs and combined studies (e.g., combined fasting and multiple-dose studies where the same subjects are used).

2. **FOOD STUDY** (STP).

3. **MULTIPLE-DOSE STUDY** (STM).

4. **STUDY** (STU). This category is generally used for a bioequivalence study with clinical endpoints, in vitro studies for metered-dose inhalers and nasal sprays, pilot and pivotal studies for vasoconstrictors, or any pharmacokinetic/pharmacodynamic study other than a standard bioequivalence study (such as 1-3 above).

B. **DISSOLUTION DATA** (DIS). This code is usually used when dissolution data are the only basis for approval. Examples are AA drugs and supplements for which changes in formulation or manufacturing require dissolution data only. In vitro release data for topical products may also be coded under DIS.

NOTE: Dissolution data submitted for the same strength drug that was the subject of a bioequivalence study are not separately coded. The dissolution information is considered part of the study.

C. **OTHER** (OTH):

1. **STUDY AMENDMENT** (STA). This category is for responses to deficiency comments. Whether the amendment contains dissolution data or addresses a deficiency such as incomplete information on analytical methods or a study, the submission should be coded as STA unless a new study is submitted for review. In that case, the appropriate code under BE studies should be selected. If an amendment to a previously submitted BE study is included with a new, not previously submitted BE study required to establish BE, then STA should be coded for the amendment, and the new study should be coded separately.

Retesting of subjects classified as outliers in the original submission should not be classified as a separate study, but as part of the original study.

Frequently, the Division telephones sponsors to request information needed to finalize the review. These requests should be made for information the sponsor can respond to within 10 working days, and should be coded as STA. If the sponsor submits incorrect information or partial data, the submission should be coded as new correspondence (NC). Once the correct information is received, the submission should be coded as STA.

2. **WAIVER** (WAI). This category is used for injectable, ophthalmic, otic, oral, and topical solutions. A formulation in the same concentration packaged in different sizes is not coded separately, but different concentrations of the same product are coded separately.

3. **DISSOLUTION WAIVER** (DIW). This code is used for lower strengths that can be approved based on proportionality of the formulation and an acceptable study on the highest strength or the strength of the reference listed drug. A dissolution waiver should be coded for each strength for which dissolution data are submitted, except the strength for which bioequivalence studies have been conducted.

4. **OTHER** (OTH). This category is used for correspondence or addenda revising the original review.

   The Division of Scientific Investigations (DSI) inspection reports may generate an addendum to the review. If a significant statistical analysis is needed based on the recommendation of the DSI, or if the issuance of a Form 483 (Inspectional Observations) indicates serious violations by the laboratory, then the review of the DSI report may be coded as OTHER. If the DSI report is acceptable, the DSI report should be filed in the ANDA, and no addendum to the review is necessary. Addenda to the reviews are entered as US documents (FDA generated), because these reviews are not prompted by industry submissions, but are due to internal policy changes or inspection reports.

   Diskettes containing the data already coded in a previous submission will not be coded separately.

D. PROTOCOLS

1. Protocol (PRO). This is used for protocols submitted as part of an investigational new drug application (IND) or an ANDA. An example of a protocol submitted as part of an ANDA would be a skin irritation study protocol.

2. Protocol Amendment (PRA). Amendment to a protocol.

3. Other protocols. There are also protocols sent to the DBE for review to obtain comments on the proposed study design prior to the submission of

ANDAs. Pilot studies submitted with a protocol to justify a particular study design are not coded separately. A review is generated and comments are provided to the firm by letter. This is not recorded in COMIS. It is tracked in a separate database and is counted as part of the overall productivity of individual reviewers.

Occasionally, sponsors submit protocols for studies that are not necessary (i.e., a waiver request for in vivo testing). In this case, the additional protocol does not have to be reviewed and credit will not be given.

E. CONTROLLED CORRESPONDENCE

Bioequivalence information requests sent as correspondence are also randomly assigned to DBE reviewers for evaluation and generation of a review. These reviews are not recorded in COMIS, but are tracked in a separate database and counted as part of the overall productivity of individual reviewers. A citizen petition is counted as controlled correspondence. If additional information is submitted for pending correspondence and/or citizen petitions prior to the completion of the response to the original piece, the issues raised by the additional supplement to the submission should be addressed in the review underway. If a review has been finalized and an additional supplement is submitted raising new issues, another review can be generated.

Processing of Work

- The reviewers sign their names in the assignment logbook. When an assignment is available, the bioequivalence PM assigns it to the next reviewer and enters the reviewer's name and date of assignment in the appropriate database (COMIS, protocols, controlled correspondence) and the assignment logbook. The PM also verifies study codes at this time. The reviewer obtains the submission from the document room.

- When the review is completed, the reviewer states on the last page of the review the study types reviewed in the submission and comments on the acceptability of the data provided by the firm. The following decision codes should be used when determining the acceptability of each study type.

  AC – Acceptable. The submission was complete and all data were found acceptable.

  UN – Unacceptable. A study failed to meet standard criteria for bioequivalence (e.g., 90% CI for fasting study, incorrect dissolution methods).

  IC – Incomplete. Information was missing from the submission.

  NC - No Action. No action or review was necessary.

- The Team Leaders verify that study codes and decision codes are accurate. Once the review is finalized and has the Division Director's concurrence, it is forwarded to the bioequivalence PM, who forwards acceptable comments to the chemistry PM or prepares fax cover sheets for deficiencies to be transmitted to the firm. The bioequivalence PMs then deliver acceptable completed reviews to the Document

Room. Reviews containing deficiencies to be transmitted to the firm are delivered to the Review Support Branch Chief, who gathers any comments from other disciplines (chemistry, labeling, microbiology), and faxes all deficiencies and comments together.

- The Document Room staff enters data into the bioequivalence data entry screen in COMIS, including the completion date (the date when the Director of Bioequivalence signed the review). The Document Room staff also verifies study codes and enters decision codes. This closes the submission, indicating that the review has been completed. Once the submission is closed, reviewers are credited for their work.

EFFECTIVE DATE

This MAPP is effective upon date of publication.