# OFFICE OF GENERIC DRUGS

## Productivity Documentation in the Division of Bioequivalence

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## PURPOSE

- This MAPP describes the procedures for documentation of productivity in the Division of Bioequivalence (DBE), Office of Generic Drugs (OGD), and how that productivity is credited to individual reviewers.

## BACKGROUND

- The COMIS database was created, in part, to keep track of the workload of all divisions. The information entered into COMIS on all abbreviated new drug applications (ANDAs) received in OGD includes 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) 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, as well as the other databases.

## POLICY

- Information entered into the COMIS database on the study types in the bioequivalence section of an ANDA documents the productivity of the reviewers and the Division. Consistent and fair classification of these study types will ensure objective evaluation of reviewers based on credit earned for certain review activities.

- Non-ANDA related work products are 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, and date when the letters are issued.

## RESPONSIBILITIES

- **Document Room Personnel will:**

  Receive ANDA submissions and assign to the appropriate bioequivalence discipline with assistance from the regulatory support staff and/or bioequivalence project managers (PMs).

  There are three disciplines and discipline codes:

  (1) BPH = Division of Bioequivalence
  (2) BCE = Clinical Team
  (3) BDI = Dissolution data review of solid orally administered dosage forms

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

  Close the submission once the review is finalized by entering date completed.

- **The DBE Reviewer will:**

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

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

- **The Team Leader will:**

  Verify study type and decision codes stated in the last page of the review, and ensure that the study type and decision code classifications are consistently applied.

- **Project Managers (PMs) will:**

  Enter into the bioequivalence data entry screen the name of the reviewer assigned to the ANDA, the date the review is started, and the study types that apply to that submission.

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

  Correct any mistakes made in data entry.

  Prepare and forward fax cover sheets and deficiency comments for any application to the Document Room to be transmitted to the firm.

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

## PROCEDURES

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

### A. BIOEQUIVALENCE STUDIES (BE)

The following study types fall under this category:

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

2. **FED 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 vasoconstrictor studies, or any pharmacokinetic/pharmacodynamic study other than a standard bioequivalence study (such as 1-3 above). In vitro data submitted for nasal sprays and metered dose inhaler products receive only one credit.

### B. OTHER (OTH)

1. **STUDY AMENDMENT** (STA). This category is for responses to deficiency comments or additional information the sponsor wishes to provide after the original application is submitted. 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. If a complete new study is submitted, the appropriate code under BE studies should be selected

   Re-dosing studies of subjects with results suspected as aberrant when submitted in an amendment are classified as STA.

   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 without charge (WC) and no credit is given. If the amendment contains new data or information, the reviewer gets credit for the evaluation of complete data. If the amendment contains corrections to the application, or information that should have been part of the original submission

(such as long-term stability data, diskettes, SOPs, chromatograms, potency, expiration dates, lot numbers, or typographical errors), the amendment should be coded WC, and no credit is given.

**2.** **WAIVER** (WAI). This category is used for injectable, ophthalmic, otic, oral, and topical solutions. A formulation in the same concentration that is packaged in different sizes will not be coded separately. 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 reference listed drug strength. 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. This code is also generally 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 data for topical products may also be coded as DIW.

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

**4.** **MISCELLANEOUS** (MIS). Miscellaneous is usually the code for correspondence or addenda to revise the original review.

The Division of Scientific Investigations (DSI) inspection reports may generate an addendum to the review. If a significant reevaluation of the data is needed based on the recommendation of DSI, or if the issuance of a Form 483 indicates serious violations by the laboratory, then the review of the DSI report may be coded as MIS, and regular credit is given. 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 need to be 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. An addendum to the review generated due to policy changes is not given additional credit.

## C. DISSOLUTION DATA (DIS)

This category is generally used for preliminary reviews of the dissolution data. Every month applications are assigned to reviewers to determine the dissolution method to be used in the stability and quality control testing. Early review of the dissolution data ensures that firms are able to work on their stability testing sooner, avoiding the risk for changes to this method at a much later time during the review process. Credit for dissolution reviews is documented in a separate report. If the dissolution amendment is received before assignment to the bioequivalence reviewer (BPH), the amendment should be assigned to the dissolution reviewer, who will receive dissolution credit in the dissolution report. If the application is assigned to a BPH reviewer before the dissolution amendment is received, the BPH reviewer should review the dissolution amendment and will receive regular credit for it.

## 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 before the submission of ANDAs. Pilot studies submitted with a protocol to justify a particular study design are not counted 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 products that do not require bioequivalence testing (i.e., a waiver request of 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.

## PROCESSING WORK

- The reviewers sign their names in the electronic assignment logbook when ready to receive additional work. The bioequivalence PM assigns the next assignment from the random queue to the next reviewer, and enters the reviewer's name and date of assignment in COMIS and the assignment logbook. The PM will also enter study type codes into COMIS at this time. The reviewer will obtain the submission from the document room or electronic document room.

- When the review is completed, the reviewer will state, 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 is missing from a submission.

**WC** – Without charge. No credit is given, usually for missing information, diskettes, correction of typographical errors.

- The Team Leaders verify that the study codes and the decision codes are accurate. Once the review is finalized and has the Division Director's concurrence, it is forwarded to the bioequivalence PM, who again verifies the decision codes and enters corrections into COMIS. The PM prepares fax cover sheets for deficiencies to be transmitted to the firm. The PM forwards the reviews to the Document Room for faxing and entry into the Division File System (DFS).

- The Document Room staff will enter data into the bioequivalence data entry screen in COMIS, to include completion date (the date the Director of Bioequivalence signed the review). This will close the submission, indicating that the review has been completed. Once the submission is closed, reviewers receive credit for their work.

## EFFECTIVE DATE

This MAPP is effective upon date of publication.