# OFFICE OF NEW DRUGS

# OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE/OFFICE OF BIOSTATISTICS

## Responsibilities and Procedures for Statistical Review and Evaluation of Animal Carcinogenicity Studies

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## PURPOSE

- This MAPP establishes for the Office of New Drugs (OND) and the Office of Biostatistics (OB) within the Office of Pharmacoepidemiology and Statistical Science (OPaSS) mutually agreed-upon procedures regarding (1) requests for statistical review of carcinogenicity studies and (2) the interaction between pharmacologists/toxicologists and statisticians during the statistical review process.

## BACKGROUND

- The three Divisions of Biometrics within OB/OPaSS in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), are responsible for conducting statistical reviews of animal carcinogenicity experiments carried out by (or for) drug sponsors and submitted to FDA as part of the sponsors' investigational new drug application (IND) or new drug application (NDA).

- To maintain consistency in the quality of statistical reviews across the three Divisions of Biometrics and all drug review divisions, this MAPP describes the procedures for conducting statistical reviews of carcinogenicity studies in collaboration with pharmacologists/toxicologists.

## POLICY

- A statistician will be assigned to every new submission that contains reports of completed carcinogenicity studies. The pharmacologist/toxicologist and the statistician will jointly determine if a statistical review is needed and when the review should be done. If the pharmacologist/toxicologist and the statistician cannot reach an agreement, appropriate team leaders from the pharmacology/toxicology group and OB will make the final determination.

- Guidance on the following factors is contained in guidelines issued by FDA (see the guidances listed in the References section of this document):

    1. design
    2. statistical analyses of the data
    3. statistical interpretation of the results of carcinogenicity studies of pharmaceuticals
    4. formats and specifications for the electronic submission of carcinogenicity study data

- The reviewing statistician will perform a standard statistical review, plus additional analyses to address questions or concerns expressed by the reviewing pharmacologist/toxicologist during the interaction phase of the review process.

- A statistical review and evaluation report, based on the findings of the above-mentioned analyses, will be written by the reviewing statistician and archived according to standard Center policies.

- The reviewing statistician will perform additional statistical analyses that are requested and deemed necessary by the reviewing pharmacologist/toxicologist or the CDER Carcinogenicity Assessment Committee (CAC) for final determination of the carcinogenic potential of the drug.

- The reviewing pharmacologist/toxicologist or the project manager should inform the reviewing statistician and Biometrics team leader when the carcinogenicity study reviewed by the Division will be discussed in a CAC meeting. The reviewing statistician should attend the CAC meeting to answer questions related to statistical issues.

## RESPONSIBILITIES AND PROCEDURES

- **OND's reviewing pharmacologist/toxicologist will:**

    1. Send, as early as possible, requests for statistical consultation to the team leader of the Division of Biometrics that supports the drug review division.

2. Inform the Biometrics team leader and reviewer of any special questions or concerns of the reviewing pharmacologist/toxicologist.

3. Inform the Biometrics team leader and reviewer of the desired completion date based on the user fee goal date and/or other deadlines, such as CAC or advisory committee meetings.

- **OND's regulatory project manager will:**

1. Inform Biometrics team leaders of upcoming IND or NDA meetings with sponsors where statistical design or analysis issues will be discussed.

2. When requested by the reviewing pharmacologist/toxicologist, send carcinogenicity study data to the Biometrics team leader for a consultative review.

3. Arrange meetings, when necessary, for reviewers, team leaders, and directors from the Division of Biometrics and the drug review divisions to discuss and resolve important concerns regarding the statistical review.

- **The Division of Biometrics staff, Office of Biostatistics, will perform specific duties:**

1. In situations where carcinogenicity studies are needed, the Biometrics team leader will work together with the drug review division to request that the drug sponsor perform appropriate statistical analyses of the study data and submit the data in the recommended format.

2. The Biometrics team leader will perform a preliminary review of the request-for-consultation package to evaluate whether the material contained in the package is adequate for a full-scale statistical review, and if adequate, will assign the request for consultation to a statistical reviewer.

3. The Biometrics team leader or a designated statistician will determine whether the data have been submitted in the proper electronic format.

4. The reviewing statistician will discuss with the Biometrics team leader the adequacy of the data and any issues or problems encountered in the statistical review process.

5. To incorporate possible modifications before the final report is issued, after statistical analyses are completed, the reviewing statistician will discuss review results with the reviewing pharmacologist/toxicologist and will send a draft report to the reviewing pharmacologist/toxicologist, including the supervisory pharmacologist/toxicologist in cc: distribution.

6. The reviewing statistician will archive the final statistical review and evaluation report in accordance with Center policies. He or she will send the report, in cc: distribution, to the OB deputy director, the Biometrics division director, the Biometrics team leader, the supervisory pharmacologist/toxicologist, the pharmacology/toxicology reviewer, and the regulatory project manager.

7. If necessary, the reviewing statistician will ask the project manager to arrange meetings for reviewers, team leaders, and directors from the Biometrics and drug review divisions to discuss and resolve important concerns regarding the statistical review.

8. The reviewing statistician should attend and participate in relevant internal or sponsor/FDA (including CAC) meetings as appropriate.

## REFERENCES

- FDA, Center for Drug Evaluation and Research, *Providing Regulatory Submissions in Electronic Format – General Considerations* (Revision 1), guidance for Industry, available on the Internet at http://www.fda.gov/cder/guidance.

- FDA, Center for Drug Evaluation and Research, *Regulatory Submissions in Electronic Format – NDAs*, guidance for industry, available on the Internet at http://www.fda.gov/cder/guidance.

- FDA, Center for Drug Evaluation and Research, *Statistical Aspects of Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*, guidance for industry, available on the Internet at http://www.fda.gov/cder/guidance

## EFFECTIVE DATE

This MAPP is effective upon date of publication.