OFFICE OF BIOSTATISTICS

Biostatistics Biologics Licensing Application Template

CONTENTS

PURPOSE

- This MAPP establishes procedures for documenting the review of original new biologics licensing applications (BLAs) in the Office of Biostatistics of the Center for Drug Evaluation and Research (CDER).

REFERENCES

- CDER Clinical Review Template (MAPP 6010.3):

  http://cdernet.cder.fda.gov/grp/clinical.htm

- Key words used in the statistical review can be referenced from Division of Biometrics II:

  http://cdernet/ob_apps/ob/edocs/eDocs_Main_Single.cfm?id=189

- Sample reviews with varying formats are available at the Office of Biostatistics website:

  http://cdernet.cder.fda.gov/ob/Useful_Information/Review_Related/Review_Examples.htm

- CDER Reviewer Style Manual:

  http://cdernet.cder.fda.gov/guidancedoc/gsquaredindex.htm

POLICY

- All reviewers within the Office of Biostatistics will use the Statistical BLA Review Template.

- The Statistical BLA Review Template will be used to document primary statistical reviews of all original NDAs and supplements.
- Conventions of CDER's Reviewer Style Manual should be followed in completing the BLA statistical review.

RESPONSIBILITIES

- All statistical reviewers who prepare formal, written evaluations of submitted BLA applications are responsible for adhering to the Statistical BLA Review Template guidelines regarding format, organization, and structure.

- Statistical team leaders and concurring review statisticians who are charged with secondary and/or tertiary review of these reports will also be responsible for checking template adherence and recommending to the primary statistical reviewer modifications necessary to comply with template guidelines.

- The Biometrics Deputy Division Director is responsible for oversight of statistical reviews in the Biometrics Division and will ensure that statistical reviewers comply with template guidelines.

- The Office of Biostatistics Associate Director will be responsible for oversight of statistical BLA reviews for all Biometrics Divisions in the Office of Biostatistics by conducting a final screening for template adherence and reporting compliance outcomes to the Office of Biostatistics upper management.

PROCEDURES

- Reviewers in the Office of Biostatistics will use the attached statistical BLA Review Template to document their reviews of BLA and supplement applications. The template is annotated to provide additional explanations of the content for each heading and subheading.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

ATTACHMENT A

GOOD REVIEW PRACTICES

OFFICE OF BIOSTATISTICS

STATISTICAL BLA REVIEW TEMPLATE

DATE

MAPP 4000.8
COVER PAGE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	123456/N000; or 123456/1234. Both the BLA number and the serial number associated with documents reviewed should be given here. (The serial number is the sequence of Doc Type and Doc Seq # in DFS.)
Biologic Product Name:	Trade name (generic name), strength, and dosage form
Indication(s):	List indication(s) of treatment under review
Applicant:	Identify applicant of the submission
Date(s):	At a minimum, the date submitted ("letter date" in DFS). Other dates, such as date received by CDER or reviewer, PDUFA due date, or review completion date, may be given.
Review Priority:	Priority, Standard, etc.
Biometrics Division:	
Statistical Reviewer:	
Concurring Reviewers:	Statisticians who reviewed and signed this review (e.g., statistical team leader).
Medical Division:	Medical division to which this BLA is assigned.
Clinical Team:	At a minimum, the medical officer(s) reviewing this application. The medical team leader and medical division director may be listed as well.
Project Manager:	

Keywords: It is recommended that reviewers select the key words offered in DFS by DBII.

http://cdernet/ob_apps/ob/edocs/eDocs_Main_Single.cfm?id=189

Reviewers may also include additional desired key words relevant to their review.

TABLE OF CONTENTS

LIST OF TABLES (OPTIONAL)

Reviewers have an option to include a List of Tables. It should be placed after the Table of Contents. The option of "Caption…" of the "Insert" in the Menu Bar can be used to create the list. Even though the list of tables is optional, it is recommended. The rationale for inclusion of this list is similar to that of the Table of Contents. It helps the reader to quickly find the needed tables.

LIST OF FIGURES (OPTIONAL)

Reviewers have an option to include a List of Figures. It should be placed after the List of Tables. Again, the option of "Caption…" of the "Insert" in the Menu Bar can be used to create the list. The rationale for inclusion of this list is similar to that of the Table of Contents. It helps the reader to quickly find the needed figures.

1. EXECUTIVE SUMMARY

The executive summary "serves as both an orientation to the review and a stand-alone document. The summary should be a 'bottom-line' statement without equivocation and should be written in plain language appropriate for educated lay as well as technical audiences" (Clinical Review Template). It should be a concise summation (not to exceed 10 pages) that adequately relays relevant information regarding the submission. Further details of the evaluation should be documented in the body of the review.

Tables, charts, and graphs can be included (if necessary) to provide an overview of key information on the submission.

Under the main heading, the reviewer may include some background information on the submission and/or a description of the organization of the executive summary.

1.1 Conclusions and Recommendations

This subsection should briefly describe the conclusions and recommendations of the statistical reviewer's evaluation. The conclusion should be the synthesis of evaluations of all studies under review. Recommendations should be stated within the context of strength of statistical evidence and key findings that may or may not support the claim of the applicant.

1.2 Brief Overview of Clinical Studies

This subsection should contain a brief overview of the clinical studies and should provide information on study medication(s), including the indication(s) being sought. The overview should include a list of studies relevant to the review (usually all phase 3 studies) and should explain the selection of studies for statistical review. A brief description of selected studies may include study design, treatment groups, patient population, number of patients enrolled, duration of treatment, regional location of investigational centers (country), and efficacy variables.

1.3 Statistical Issues and Findings

This subsection should describe key statistical issues and findings that affect conclusions regarding the demonstration of efficacy/safety. It should summarize and discuss the reviewer's analyses, the extent of evidence in support of claims, statistical issues that may affect the conclusion on efficacy and/or safety, and any related comments. It should be based on each study reviewed as well as on the collective evidence. In addition to the primary endpoint analysis, the reviewer may also address secondary or subgroup analyses if these are deemed important.

Where appropriate, the reviewer should provide references to text, tables, and graphs within the review to which readers can refer.

2. INTRODUCTION

2.1 Overview

The overview subsection should include background information regarding the investigational biologic product, the product class, and its intended indication. In addition, this subsection should include important clinical program milestones that were reached during the course of biologic product development and that are relevant to the statistical review.

All relevant studies in the clinical program should be listed. The reviewer should identify those studies selected for full statistical review and evaluation, and briefly explain why these were chosen.

These selected studies should be specifically highlighted with information such as study identification number/name, study type/design, number of treatment arms, indications; number of patients in each arm, location of investigational centers, and proportion of patients enrolled in domestic versus foreign investigational centers.

The reviewer may document the overview with sub-subsections numbered as 2.1.1, 2.1.2, 2.1.3, etc. Examples of these include Class and Indication, History of Biologic Product Development, Specific Studies Reviewed, and Major Statistical Issues.

2.2 Data Sources

Data sources include all material reviewed (e.g., applicant study reports), data sets analyzed, and literature referenced.

If data were provided electronically, the location/names of data sets should be documented. The full electronic path of these data should be specified according to the CDER Electronic Document Room (EDR) naming convention. Evaluations based on literature reviews should identify the source and extent of available raw data. The reviewer should also assess the quality and integrity of all submitted data. If only paper version is submitted, then reference to volume, section, page, table, and/or graph should be specified.

3. STATISTICAL EVALUATION

This section will present the detailed review of selected studies to be reviewed from the BLA and possibly from other sources, such as published literature. Depending on the format and content of the BLA and/or the information from other sources, this section can be organized in various ways.

Typically, a BLA submission has one or more studies for a single indication. However, some submissions involve multiple indications, multiple special populations, or multiple disease

etiologies. Therefore, the reviewer may organize the review by individual study, by indication, by special population, or by etiology of disease.

If there are few studies and no need for long individual reviews, each study can be described fully in this section.

If there are multiple studies that require very detailed review, the statistical reviewer may choose to discuss each individual review in an appendix. Overall results can then be presented in the main body of the review.

If multiple studies are of similar design, it may be most efficient to describe them as a group, noting differences (e.g., of duration, sample size) and efficacy results in tabular form. In such cases, the detailed review may be presented in an appendix, and a summary of the review presented in the main body of the review.

Sample reviews with varying formats are available at the Office of Biostatistics website:

http://cdernet.cder.fda.gov/ob/Useful_Information/Review_Related/Review_Examples.htm

Under the main heading of section 3 or under subsection headings 3.1 and/or 3.2, the reviewer may describe the organization of subsections. For example, an ordering of sub-subsections by indication may be described here.

3.1 Evaluation of Efficacy

The assessment of efficacy for each study reviewed should include a description of the study design, primary and secondary efficacy endpoints, demographic and baseline characteristics, patient disposition, statistical methodology used, applicant's results, and the reviewer's findings.

In addition to the registration studies, the reviewer should also consider the results of other relevant studies (positive or negative). These studies should be discussed in this section and considered when determining overall strength of evidence regarding efficacy in section 5.1.

The format of this section will depend on the application being reviewed. Reviewers are encouraged to organize the review by adding sub-subsections (3.1.1, 3.1.2, etc.). Examples of these subsections are described below.

Study Design and Endpoints

A description of the design, endpoints, and conduct of each relevant study should be included in the review. The reviewer should identify the aspects of the design that may be inappropriate or introduce bias to final results.

The reviewer may discuss the relevance or appropriateness of the design and endpoints. The review may also include a brief description of the current thinking of the reviewing medical division regarding the appropriateness of the endpoints studied by the applicant.

Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations should be included in the review. This can be done by tabulation of percent dropouts, reasons for dropouts, protocol violations, and assessment of balance between the treatment arms with respect to demographics and baseline characteristics imposed by randomization. In addition, the reviewer may describe the analysis populations.

This information may be used to discuss influence of covariates, missing data imputation methods, sensitivity analyses, and subgroup analyses.

Statistical Methodologies

The reviewer should describe the statistical methodologies used by the applicant, as well as the reviewer's alternative methodologies (with explanation). The reviewer may document technical discussion, mathematical derivation, or presentation of formulas in an appendix rather than in the main body of the review.

Results and Conclusions

The reviewer should provide a brief summary of the applicant's results and conclusion. For each study examined, the statistical reviewer should discuss efficacy findings, strength of the evidence, and statistical issues. The reviewer may provide tables and graphs to describe the extent to which study results support the efficacy claim.

Detailed discussion may not be necessary for those issues on which the applicant and the reviewer generally concur. However, any differences between the conclusions of the reviewer and the applicant need to be explained.

During the course of the review, the reviewer may address various statistical issues. These issues, their resolution, and any impact on efficacy assessment need to be discussed briefly in this section.

3.2 Evaluation of Safety

This section is devoted to specific safety analyses that are crucial for biologic product approval and labeling. However, if the study does not require detailed statistical safety analyses, the reviewer can refer to the medical officer's review.

Reviewers are encouraged to use sub-subsections to report specific safety issues.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The reviewer should describe efficacy (safety) results across subgroups defined by gender, race, and age. Other subgroups, such as baseline characteristics and geographical regions, may be included depending on their relevance, representation in the clinical studies, or the disease being reviewed.

Under the main section heading 4, the reviewer may give an overview of which subgroups are relevant to the application under review.

4.1 Gender, Race and Age

In this subsection, the reviewer should describe efficacy (safety) results across subgroups defined by gender, race, and age (for example less than 65 versus greater than or equal to 65 years).

The reviewer should include descriptive statistics for the defined subgroups. Inferential statistics, such as the results of tests for treatment by subgroup interaction may also be included. Significant interaction test results should be fully explained, including graphics depicting the results. The reviewer should exercise caution when pooling the data across studies. Scientifically valid methods should be employed when drawing inferences from pooled data.

The impact of a subgroup difference may be briefly addressed here and more fully explained in section 5.1 or vice versa.

If no conclusions can be drawn due to lack of representation, limited sample size, or other factors, this should be noted. If, for example, the studies were conducted in one gender only, a brief statement should indicate that gender analysis was not applicable.

4.2 Other Special/Subgroup Populations

Other subgroups could be defined by baseline characteristics, geographical regions such as the United States, Europe, and/or Asia. These should be included depending on their relevance, on representation in the clinical studies, or the disease being reviewed.

If no subgroups other than those in subsection 4.1 are reviewed, the reviewer should indicate here that "No other subgroups were analyzed."

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical issues that affect the overall conclusions should be described here. The main statistical issues should be summarized study by study, as well as collectively, for all studies in the review. It may be necessary to refer to other sections of the review or to appendices to

provide sufficient detail. Resolution of these issues and their impact, if any, on overall efficacy assessment need to be briefly discussed.

Discussion of the statistical issues serves to justify the comments and conclusions of the reviewer
and brings attention to these issues for future trials.

The following are examples of important statistical issues that may affect the results.

- Breaking the blind
- Unblinded or unplanned interim analyses
- High percentage of dropouts
- Inappropriate imputation for missing values
- Change of primary endpoint during conduct of the trial
- Dropping/adding treatment arms
- Sample size modification
- Inconsistency of results across subgroup
- Type I error inflation due to multiplicity

The reviewer's summary of the collective evidence of effectiveness is a compilation of the main findings from all studies reviewed. This summary may include treatment estimates obtained by combining studies where appropriate. As with special/subgroup populations, the reviewer should exercise caution when pooling data across studies. Scientifically valid methods should be employed when drawing inferences from pooled data. Well-controlled studies that do not demonstrate biologic product effect should be considered when determining the strength of evidence.

The reviewer should provide easy to read yet fully informative tables, graphs, and text to collectively describe the overall extent to which study results support the efficacy claim. If the review includes a statistical examination of safety, a summary of the safety findings should be included in this section.

5.2 Conclusions and Recommendations

The statistical reviewer's conclusions should be based on collective evidence provided by the entire application, as described in section 5.1. They should be made within the context of whether the statistical results do or do not provide adequate evidence to support the claims proposed in the BLA, particularly in the labeling. If the reviewer's conclusion differs from that of the applicant, the reviewer needs to briefly mention the reasons for these differences.

This section should include clear and succinct statements regarding the strength of the statistical evidence to support the applicant's claims. Any recommendation as to whether the biologic product should or should not be approved is beyond the scope of the statistical review and should not be stated as such in the review. The need for additional studies and labeling recommendations may be included in this section.

APPENDICES (ADD WHEN NEEDED)

Appendices may be included when necessary. Appendices may incorporate, for example, bibliography, references, detailed discussion of statistical/technical issues, derivation of formulas, statistical programs, excerpts from the BLA that may be of interest to the reader (e.g. listing of all the center investigators, sections of the protocol), and list of patients included or excluded from analyses. If there are multiple studies that require very detailed reviews, the statistical reviewer may choose to discuss each individual review in an appendix and present summary results in the main body. If more than one appendix is used, the reviewer can label them as Appendix I (or 1), Appendix II (or 2), etc.

SIGNATURES/DISTRIBUTION LIST (OPTIONAL)

The reviewer may officially identify the primary and concurring reviewer(s), as well as the Biometrics Deputy Division Director and Office Associate Director who will ensure adherence to template format. The distribution list provides reference to the medical review division, medical officer, and project manager. Even though the review is stored in the Division File System (DFS), the reviewer may also include as an additional reference marker the final identifier of actual physical review file name. An example of this optional documentation is as follows:

Primary Statistical Reviewer:
Date:

Concurring Reviewer(s):

Statistical Team Leader:

Biometrics Deputy Division Director:

cc:
HFD-Number/Project Manager
HFD-Number/Medical Officer
HFD-Number/Medical Team Leader
HFD-Number/Primary Statistical Reviewer
HFD-Number/Statistical Team Leader
HFD-Number/Biometrics Deputy Division Director
HFD-Number/Biometrics Division Director
HFD-Number/Office of Biostatistics Associate Director
HFD-Number/Office of Biostatistics Deputy Director

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