OFFICE OF THE CENTER DIRECTOR

Clinical Review Template

CONTENTS

PURPOSE

- This MAPP establishes procedures for documenting the primary clinical review of original new drug applications (NDAs), biologics license applications (BLAs), NDA/BLA amendments in response to action letters, and efficacy supplements in the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER).

DEFINITIONS

- **Clinical Review:** A comprehensive summary and analysis of the clinical data submitted in support of a marketing application. The clinical review also includes (1) the clinical reviewer's assessment of and conclusions about the evidence of effectiveness and safety under the proposed conditions of use, (2) the adequacy of the directions for use, and (3) recommendations on regulatory action based on the clinical data submitted by an applicant. The clinical review documents the work and conclusions of the clinical reviewer and cannot be altered after it is made final. The clinical reviewer is expected to discuss his or her analyses and conclusions, and to share a draft review with the reviewer's team leader or supervisor.

  The clinical review satisfies the legal and policy requirements for documentation of the review process and completion of the review of clinical data prior to regulatory action on the application. Final scientific and regulatory determinations on the reviewed application are not necessarily reflected in the clinical review.

- **Clinical Review Template:** A structured outline and annotated table of contents for the preparation of a clinical review. The clinical review template outlines the organization of content, promotes consistency in the documentation of elements, and provides for ready retrieval of information.

- **Executive Summary:** A required portion of the clinical review that summarizes the clinical review in concise terms, with succinct explanation of recommended action from the perspective of the clinical reviewer.

POLICY

- The clinical review template is to be used by all clinical reviewers within OND.
- The clinical review template is used to document primary clinical reviews of all original NDAs and BLAs, NDA/BLA amendments in response to an action letter, and efficacy supplements.
- Conventions of the CDER Reviewer Style Manual are to be followed in completing the clinical review.
- The template may be modified by individual clinical review divisions if necessary to accommodate unique application issues or division specific procedures; however, these modifications must be standardized across the Division, documented, and processed through clearance as a revision to this MAPP. This MAPP will be revised to add as attachments each review division specific modification to the template.

RESPONSIBILITIES

- The **clinical reviewer will** complete each designated review using the clinical review template (see attachment). Clinical reviewers should engage in scientific and regulatory dialogue with clinical team leaders and other clinical supervisors to develop complete and scientifically valid review perspectives. However, the final conclusions and recommendations in the clinical review should reflect the clinical reviewer's own opinion and should emphasize that they are based solely on the review of the clinical portion of the application, not the entire application.

- The **clinical team leader will** promote consistent use of the clinical review template by clinical reviewers. Clinical team leaders should engage clinical reviewers in scientific and regulatory exchanges regarding reviews before finalization of the clinical review. When the clinical reviewer's conclusions and/or recommendations differ from those of the clinical team leader, clinical team leaders should encourage clinical reviewers to document their own conclusions and recommendations in the clinical review. In such cases, the clinical team leader is expected to write his or her own review, noting the reasons for any differences in conclusions and recommendations from those of the clinical reviewer.

- **Division and office directors will** promote consistent use of the clinical review template, provide scientific and regulatory perspective on review issues, and encourage clinical reviewers to document in the clinical review their rationale for any alternative perspectives.

PROCEDURES

- Clinical reviewers will use the attached clinical review template to document their clinical reviews. The template is annotated to provide additional explanations of the content for each heading and subheading.

EFFECTIVE DATE

This MAPP is effective upon publication.

ATTACHMENT A

CLINICAL REVIEW TEMPLATE

Application Type	{Enter NDA or BLA}
Submission Number	
Submission Code	
Letter Date	
Stamp Date	
PDUFA Goal Date	
Reviewer Name	
Review Completion Date	
Established Name	
(Proposed) Trade Name	
Therapeutic Class	
Applicant	
Priority Designation	{enter P or S}
Formulation	
Dosing Regimen	
Indication	
Intended Population	

The following general instructions apply to use of the primary clinical review template for the entire review.

- The clinical review template must be used for all original NDAs and BLAs, NDA/BLA amendments in response to an action letter (i.e., resubmissions), and efficacy supplements. Use of the template for documentation of the clinical review for labeling supplements is encouraged, but not required.

- Headings and subheadings must be named, numbered, and ordered as stipulated in the template.

- For original NDA/BLA reviews, information must be entered under all top four level headings. For example, entries for heading 7 (level 1), 7.1 (level 2), 7.1.3 (level 3) and 7.1.3.1 (level 4) are required for original NDA/BLA reviews. If the heading does not apply, a "not applicable" should be recorded for that section along with a reason why the information is not applicable to the review. However, any subheadings that do not apply to the review can be deleted without comment. For example, all subheadings under section 6 (Integrated Review of Efficacy) can be deleted if there are no clinical efficacy trials to review. (This often occurs if the application relies on the results of bioequivalence data to support efficacy. The results of the bioequivalence data are then described in section 5, Clinical Pharmacology.)

- Level 5 headings can be deleted without explanation if they do not apply to the review.

- For other submissions (e.g., amendments in response to an action letter and efficacy supplements), individual headings may be deleted without explanation if they do not apply; however, at a minimum, each document will include an executive summary (section 1) an efficacy (section 6) and/or safety section (section 7), and an overall assessment (section 9).

- For original NDA/BLA reviews, it is important to emphasize that inserting a "not applicable" for a required subheading is not justified by the absence of data in the submission alone. To support the use of a "not applicable," it must determined and stated in the review that the data are not necessary for review of the application. For example,
    - The "not applicable" is justified for section 8.4 (Pediatrics) for a product intended to treat a disease that does not include pediatric patients (e.g., Alzheimer's disease).
    - The "not applicable" is not justifiable for an original NDA or BLA submission when further data should be requested from the applicant.

- If needed, additional subheadings may be created under any of the numbered template sections.

The template may be modified by individual clinical review divisions if necessary to accommodate unique application issues or division specific procedures; however, these modifications must be standardized across the Division, documented, and processed through clearance as a revision to this MAPP. This MAPP will be revised to add as attachments each review division specific modification to the template.

Occasionally several clinical reviewers are assigned to review different parts of the application (i.e., joint reviews). The clinical review template can accommodate joint reviews with the following suggestions:

- A lead reviewer is identified early in the review process. He or she is responsible for writing an overview of the review, including the executive summary, and describing in section 4.3 the review strategy that was undertaken for the joint review (i.e., who reviewed what). There are two principal options:
  - Option 1: Multiple authors, but one final clinical review. The lead clinical reviewer integrates all other sub-reviews into the template.
  - Option 2: Multiple authors, multiple reviews incorporated into a single overview. In the appropriate sections of the review, the lead clinical review refers the reader to the other reviews. If the other review incorporates the entire contents of a high level heading, then the subheadings under that heading can be deleted from the overview. The referenced review would only contain the headings that apply to that portion of the review. For example, if section 7 in the overview refers the reader to a separate safety review, all the subheadings for section 7 in the overview would be deleted. Similarly, the safety review need only contain the headings and subheadings for section 7.

The template has been structured so that foundational materials (e.g., individual study reviews) are placed toward the end of the review and higher order syntheses and summaries are placed near the front. This provides the reader with a general picture before moving on to the details. It is understood that the reviewer cannot write these higher order syntheses (e.g., the executive summary) without having first written the later sections. Internal cross-referencing is recommended to reduce the need for repetition.

Use of MS Word headings, captions, and cross-references is highly encouraged to maintain format consistency and to automate the creation and the updating of the table of contents, bookmarks, and hypertext links in the final review document.

Table of Contents

1 EXECUTIVE SUMMARY

The Executive Summary should be a brief description of the most important findings and conclusions of the review. In general, it should be written by the primary reviewer, but if more than one reviewer has been responsible for parts of the review, the executive summary should be prepared by the reviewer or team leader who is responsible for synthesizing these reviews.

The audience for this portion of the review is both internal and external to FDA, including secondary and tertiary reviewers, health care practitioners, and the sophisticated lay public. The section should be written, to the extent possible, in language accessible to all of those groups (e.g., with few abbreviations, and explanation of exotic terminology). The length should not exceed five pages, except in unusual cases. The Executive Summary is a brief, but complete, overview of the basis for FDA action, and an introduction to the more complete review that follows, guiding, for example, secondary and tertiary reviewers to subsequent sections needing closer scrutiny.

1.1 Recommendation on Regulatory Action

The recommendation on regulatory action should focus on the clinical perspective. This recommendation should reflect the reviewer's conclusions and should be explained in terms of the legal requirements for approval and the medical rationale for the conclusions.

The conclusions and recommendations should address at least the following:

- Whether there is substantial evidence of effectiveness (i.e., evidence from adequate and well-controlled studies showing that the drug will have the effect claimed in the labeling) (this could be the applicant's proposed claim or a different claim the reviewer considers more appropriate or supportable).

  If there is not substantial evidence of effectiveness, the nature of the deficiencies should be identified briefly (e.g., defects in study design, inadequate results, absence of a second study, or other confirmatory data). Details can be provided later in the review. If there is substantial evidence of effectiveness, a brief statement of what was shown and how it was shown (placebo-controlled study, non-inferiority study, number of studies) should be provided.

- Whether the drug or biologic has been shown to be safe for its intended use as recommended in the labeling (a risk/benefit conclusion) by all tests reasonably applicable to assessment of safety. Any important safety concerns should be described, as should the most common drug/biologic-caused adverse effects. If it is not apparent, the risk/benefit analysis should be described briefly.

- Whether there are data to provide adequate directions for use, including data to describe a safe and effective dose, and data to allow adjustment for demographic, metabolic, and other differences. (Note that the directions for use could be considered adequate even if some of these data were missing or incomplete, but that would need some explanation.)

- Whether there were particularly difficult problems in any areas. These should be briefly identified.

- Whether the recommendation is for accelerated approval (21 CFR 312 subpart H). If so, this should be made clear and briefly explained, with specific reference to why the surrogate endpoint used is "reasonably likely" to predict clinical effectiveness.

The assessment of the points listed above would ordinarily make the recommendation apparent, but in some cases there may be uncertainties (or more requested analyses) that affect the recommendation. In any case, the recommendation should be explicit as to the suggested regulatory action (approval, approvable, not approvable, complete response). If an approvable action is recommended, the needed clinical data and/or analyses should be described briefly. Clinical reasons for a not approvable recommendation should also be made clear.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

All recommended postmarketing risk management activities should be described, specifically identifying those that have been previously discussed and agreed upon with the applicant. Recommendations from the Office of Drug Safety (ODS) should be considered when formulating this section.

1.2.2 Required Phase 4 Commitments

Any required Phase 4 clinical study commitments should be described in this section. It should include a description of any postmarketing clinical studies or analyses, the agreed upon timeline for submission, and the date of the applicant's agreement to these commitments. Any commitments required to comply with the Pediatric Research Equity Act (PREA, http://www.fda.gov/opacom/laws/prea.html) should also be included here.

1.2.3 Other Phase 4 Requests

Any optional or recommended Phase 4 requests should go here.

1.3 Summary of Clinical Findings

This summary is intended to pull together all the assessments and conclusions made during the review. This summary serves as both an orientation to the review and as the major section of the stand-alone Executive Summary, communicating the important

findings without recapitulating the assessment process. The summary should be the "bottom line" document, with clear conclusions about the adequacy of the data and the findings, and should be written for educated lay as well as technical audiences. The information requested below should be included unless it is not relevant to the review. For some products, additional pertinent information specific to the product should also be included.

1.3.1 Brief Overview of Clinical Program

This should be a short introduction to the summary. It should include the following information:

- Product name, class, and route of administration
- Indications and populations studied
- Number of pivotal efficacy and safety trials
- Number of patients enrolled in the primary trials
- Overall number of patients in the safety database and extent of exposure
- Description of other pertinent clinical data sources (e.g., postmarketing data)

If the development program was complex, then tabulated data might be appropriate; however, it is generally best NOT to include tables in this section. Interested readers can look in section 4, Data Sources, Review Strategy, and Data Integrity, for more details.

1.3.2 Efficacy

Summarize the key efficacy findings, including:

- A description of the major efficacy trials and a description of the primary and important secondary endpoints
- Problems and/or issues with the efficacy studies, such as choice of endpoint, choice of control, adequacy of blinding, conduct of the studies, and appropriateness of statistical analyses
- The limitations of the available data, such as adequacy of dose finding, limitations of the population studied, and duration of studies
- The reviewer's efficacy conclusions
- The role of the drug or biologic in the existing treatment armamentarium with regard to efficacy, including the results of informative comparison studies with other drugs, if available (see the ICH E10 document at http://www.ich.org) (in general, informative studies would be included in labeling)

1.3.3 Safety

Summarize the most important safety findings. This section should discuss:

- The extent of safety testing, the size of the safety database, and the duration of exposure

- Highlights of findings from clinical trials and other data sources, including serious adverse events, common adverse events that appear to be caused by the treatment, and other relevant safety findings (including abuse potential, overdosage, use during pregnancy and lactation, and height and weight effects in pediatrics)
- The limitations of the available data, including important omitted evaluations
- The reviewer's safety conclusions, including areas of uncertainty that need to be resolved by further data, analyses, or postmarketing efforts
- The role of the drug or biologic in the existing treatment armamentarium with regard to safety, including the results of informative studies comparing the safety with other drugs, if available (in general, informative studies would be included in labeling)

1.3.4 Dosing Regimen and Administration

Describe the appropriate dosing regimen, noting any differences between your recommendation and the dosing regimen recommended by the applicant, and the reason for the discrepancy. The adequacy of dose-response (including regimens) evaluation for effectiveness and safety should be described.

1.3.5 Drug-Drug Interactions

Include any important drug-drug interactions that affect the product's clinical use, as well as critical omissions in the evaluation for drug-drug interactions.

1.3.6 Special Populations

Describe any important considerations that affect the product's use in special populations, including the adequacy of the assessment.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Include:

- Description of the product
- Established name and proposed trade name
- Chemical class: new molecular entity (NME), new salt or ester, new dosage form, new combination product, etc.
- Pharmacological class
- Applicant's proposed indications, dosing regimens, age groups

2.2 Currently Available Treatment for Indications

Describe the existing alternatives to the proposed product for the indications.

2.3 Availability of Proposed Active Ingredient in the United States

If the product contains an active moiety that is already marketed, provide highlights of the regulatory and marketing experience with the active moiety in the United States, including major safety concerns, labeling changes, and other factors. If the product is a new molecular entity, this section can simply state that it is not currently marketed in this country.

2.4 Important Issues With Pharmacologically Related Products

Discuss labeling changes and safety or effectiveness concerns that have arisen in other members of the pharmacologic class, whether marketed or investigational (for in-depth discussion, refer to the integrated reviews of efficacy and safety, sections 6 and 7).

2.5 Presubmission Regulatory Activity

Describe the regulatory history of the product, focusing on presubmission activities that had important effects on the current submission (e.g., study designs, endpoints, special safety studies). Describe the major milestone interactions with the applicant and highlight important agreements made at each one. In general, the outcome of all meetings held with the applicant (e.g., end-of-Phase 2, pre-NDA/BLA) should be described as should other agreements made with the applicant (e.g., major issues for clinical protocols and their resolution, including special protocol assessments).

For important decisions or agreements, describe the scientific or regulatory basis for presubmission agreements, such as:

- FDA guidances
- Prior FDA reviews
- Pediatric Written Requests

- Internal policy
- Product approvals or other actions
- Previous advisory committee determinations

2.6 Other Relevant Background Information

Include other relevant information, such as important regulatory actions in other countries or important information contained in foreign labeling.

3 Significant Findings from Other Review Disciplines

Include here the relevant findings from the reviews of nonclinical data: chemistry, manufacturing, and controls (CMC); microbiology (if applicable); and pharmacology/toxicology reviews. In some instances, the final reviews of these disciplines will not be complete by the time the clinical review is finalized. In these cases, this section should state that the findings are based on preliminary discussions with the corresponding reviewers in those disciplines.

Do not include the results of the clinical pharmacology review. Those results should go in section 5, which immediately follows the discussion of the clinical data sources. Also, do not include the results of the biometrics review, as this should be discussed in the appropriate sections of the integrated review of efficacy (and safety review, if applicable).

3.1 CMC (and Product Microbiology, if Applicable)

Include any aspects of the CMC review important to clinical interpretation of the data. Product microbiology information should also be included here, but clinical microbiology (for antimicrobials) should be included in section 6.1.5, Clinical Microbiology.

3.2 Animal Pharmacology/Toxicology

Include important findings from the animal pharmacology/toxicology review, with emphasis on toxicological findings that affect the human safety evaluation, usually carcinogenicity and reproductive toxicology studies. The results of important in vitro assays in human and/or non-human animal tissue should also be included here (e.g., the I_{kr} affinity in assessment of drug effect on the QT interval).

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

Describe the sources of data used in the review. Potential sources for the review include: trials conducted by the applicant or designee, trials conducted by a third party such as NIH, literature reports, and foreign postmarketing safety data. Also describe any other information used in the review but not contained in the application (e.g., information from existing INDs, consultations with others outside the review team, such as internal or

external consultants, other literature reports). The existence of information obtained from an advisory committee meeting can be noted, but a detailed description of this information and how it was used in the review should be reserved for section 8.5, Advisory Committee Meeting.

4.2 Tables of Clinical Studies

Include a tabular listing of all clinical studies. The trials may be grouped in a variety of ways that make sense for the review (e.g., by purpose (PK, PD interaction, clinical effectiveness), control group, size, duration, indication). The table should indicate the relevance of each trial to the safety and/or efficacy review.

4.3 Review Strategy

Describe the general review strategy used. Which sources were emphasized in the review process? Were all trials reviewed, or were certain trials omitted from the efficacy review (and why)? All trials were presumably used in the integrated safety analysis. Was literature relied upon to support safety or efficacy? A more detailed discussion of methods for the efficacy and safety review should be included in the appropriate subsections of the integrated review of efficacy (section 6) and safety (section 7).

Many review teams divide portions of the clinical review among various reviewers to address aspects such as efficacy, safety, clinical pharmacology, and biometrics. The arrangements for such joint reviews should be described in this section, including responsibilities for synthesis and documentation of the overall conclusions for the application.

4.4 Data Quality and Integrity

Were Division of Scientific Investigations (DSI) audit processes and reports or other methods used to audit or check applicant's data and/or analyses? Include here a brief mention of the significant findings of such audits. How sites were selected for DSI inspections should also be described.

In instances where the review team or others (e.g., consultants, to include special government employees (SGEs)) audited the case report forms (CRFs) or clinical source data, the methods that were used and the results of those audits should be described.

4.5 Compliance with Good Clinical Practices

This section should include comments on informed consent, protocol violations, site-specific issues, and whether the trials were conducted in accordance with acceptable ethical standards.

4.6 Financial Disclosures

Discuss whether the applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial*

Disclosure by Clinical Investigators. Also discuss whether these arrangements raise questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

The outcome of the clinical pharmacology discipline review, including highlights of pharmacokinetics, pharmacodynamics, and exposure-response relationships that support dose selection should be described. Except in unusual circumstances, the clinical review should briefly present the conclusions and findings from these studies, but it should not contain a detailed review of the studies that generated these data.

For applications that contain only results of clinical pharmacology studies (i.e., there are no separate efficacy or safety studies), the findings as described in the clinical pharmacology discipline review are summarized here, but the safety findings from these studies should be discussed in section 7.

5.1 Pharmacokinetics

The known human pharmacokinetics, including half-life, non-linearity, metabolism, and excretion should be described. In vitro and in vivo data on drug-drug interactions should also be discussed and there should be an assessment of whether the drug will be an important inhibitor or inducer of the metabolism of other drugs or will be affected by inhibitors or inducers. The pharmacokinetic effects of drug-demographic and drug-disease interactions (e.g., renal failure, liver failure) should also be described. The use of tables is particularly useful for this section.

5.2 Pharmacodynamics

The important known pharmacodynamic relationships should be included here, including the results of PD studies that relate to the mechanism of action, as well as important safety concerns (e.g., QT prolongation, orthostatic effects, PD interaction studies). In general, a detailed review of these studies will not be necessary, but in certain cases (e.g., a QT assessment), the study should be described fully.

5.3 Exposure-Response Relationships

A description of important exposure-response assessments should be provided. The implications of these studies for the adequacy of the clinical assessment should also be discussed, as should advice and discussion of dose selection that took place at the end-of-Phase 2A or end-of-Phase 2 meetings. The effect of such discussions on the subsequent development plan should be described. Clinical trials that assess dose response (safety and/or effectiveness) would be discussed in detail in sections 6 and 7.

6 INTEGRATED REVIEW OF EFFICACY

The integrated review of efficacy should contain review information related to efficacy only (e.g., dose-finding for efficacy, the adequate and well-controlled trials for efficacy,

and supportive trials). The section should also include negative trials (i.e., adequate and controlled trials that failed to show an effect).

If there are a few principal trials, it is generally preferable to describe each one fully in this section of the review. If there are multiple trials of similar design, it may be most efficient to describe them as a group, giving the description of one study in detail, then noting differences between the trials in one table (e.g., differences in duration, sample size, exclusion criteria), and giving the results in another table. Detailed description of individual trials, if necessary, can then be provided in the appendix.

This section should not include noncontributory studies (e.g., active controlled trials not formally designed to show either superiority or non-inferiority/equivalence, unless they were trials the applicant intended to depend upon for demonstrating effectiveness).

This section should not generally include a discussion of safety findings, even from the efficacy trials, unless these findings involve major study endpoints. Safety should be discussed in section 7.

In addition to a description of how the data submitted in the application support the reviewer's efficacy conclusions, this section should identify any relevant data that were not provided and areas in which there was insufficient information to reach a decision. The consequence of any conflicting data should be weighed, and there should be a discussion of the clinical significance of the efficacy findings.

This section is organized to accommodate applications that contain efficacy data to support multiple indications. The review of the efficacy data is grouped and discussed by indication. When a single indication is considered, the headings shown here would apply. When multiple indications are being considered, they can be considered in order under new and separate subheadings (e.g., a new section 6.2, 6.3, etc.).

6.1 Indication

This section should describe the proposed indication. The heading for this section can be modified to include a brief one- or two-word description of the indication being sought, with a more detailed description of the indication appearing in this section.

6.1.1 Methods

Describe which clinical data were used in the efficacy review to support the proposed indication. Section 4.1 may be referenced for completeness, but the relative importance of the major efficacy trials should be described in this section.

6.1.2 General Discussion of Endpoints

The basis for choice of endpoints for the proposed indication should be described, including their regulatory history, past practices, development and validation history, clinical interpretation, and their ability to provide a reasonable assessment of clinical

benefit. Describe any limitations of the endpoints (e.g., unvalidated surrogate). Other sections of the review may be referenced. A discussion about how efficacy endpoints were adjudicated by the applicant (e.g., using CT scans or other clinical source data), including a description and assessment of an Independent Review Charter (IRC), should be included. If applicable, any re-adjudication of endpoints conducted by the FDA or its consultants should also be described.

6.1.3 Study Design

The design of the studies supporting effectiveness for the proposed indication should be described with reference to (1) the regulations on adequate and well-controlled studies (21 CFR 314.126), and (2) whether the design provides a reasonable assessment of benefit.

With respect to adequate and well-controlled studies, the review should consider:

- Minimization of bias (blinding, randomization, endpoint committees, prospective statistical analytic plan, and identification of endpoints)
- Choice of control group and the limitations of various choices, especially for historical controls or non-inferiority studies

With respect to assessment of benefit, the review should consider:

- Adequacy of duration of controlled studies
- Entry criteria (exclusions, stage/severity of disease), especially the implications for generalization
- Adequacy of dose finding in Phase 2 as a basis for doses and dose regimens used in major effectiveness studies

6.1.4 Efficacy Findings

A detailed review of the results and analyses of the clinical studies that support (or fail to support) efficacy for the proposed indication should be presented. A discussion of the demographic, baseline characteristics and inclusion/exclusion criteria pertinent to the efficacy evaluation should also be included. Detailed review of the individual trials may be placed in section 10.1, but this section should provide sufficient information to describe the important efficacy findings.

The findings from the statistician's analysis of the data should be integrated into the discussion.

It is important to reemphasize that the existence and results of adequate and well-controlled studies that did not show an effect should not be ignored. It is important to take these into account when considering whether the drug or biologic is effective. All studies that support effectiveness (Phase 2 or Phase 3) should be described in detail, as

should any studies that are considered "confirmatory evidence" in support of a single controlled trial.

This section should also include a review of effectiveness data for gender, age, and racial subgroups.

The section should address limitations of the efficacy studies and describe how they have been resolved. For example, if a single study is considered persuasive, this should be explained, generally with reference to the FDA guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (http://www.fda.gov/cder/guidance/1397fnl.pdf). Similarly, flaws or problems in design and conduct of the studies (concern about blinding, unplanned subset analyses, use of secondary endpoints, unclear choice of non-inferiority margin, imbalance of baseline characteristics, handling of dropouts, etc.) should be described and their resolution discussed. Section 4 may be referenced for issues related to study conduct and data integrity.

A comparison of efficacy to other available products can be included in this section, and should rely on the review of direct comparative data. In the absence of comparative data, any comparative statements must be made with caution, and the review must state that it is based solely on the reviewer's clinical opinion.

6.1.5 Clinical Microbiology

For antimicrobials, a summary of the outcome of the clinical microbiology review should be included, together with the implications for the clinical review, if applicable.

6.1.6 Efficacy Conclusions

Include:

- Conclusions from the available information to support the proposed indication
- Limitations of the available data
- Additional information needed

7 INTEGRATED REVIEW OF SAFETY

This section addresses the findings pertinent to the safety of a new drug or biologic.

7.1 Methods and Findings

This section should describe the relevant data sources, the safety assessments that were carried out, and the major findings of the detailed safety review. Each of the subsections is organized somewhat differently, depending on the content.

When there are important adverse effects that involve judgment on the likelihood of drug causation, reviewers should consider whether the case review should be blinded.

7.1.1 Deaths

All deaths that occurred in the development program should be identified, as should any other reports of deaths from secondary sources (e.g., postmarketing or literature reports), without regard to investigator or applicant judgment about causality. It is critical to consider deaths on control treatment for comparison.

7.1.2 Other Serious Adverse Events

All non-fatal serious adverse events that occurred during development or were reported from secondary sources (e.g., postmarketing or literature reports) should be identified without regard to the applicant's causality judgment. Serious adverse events may, in addition to signs, symptoms, and diagnosable events, include changes in laboratory parameters, vital signs, ECG, or other parameters of sufficient magnitude to meet the regulatory definition of a serious adverse event (see 21 CFR 312.32(a); 314.80(a)).

7.1.3 Dropouts and Other Significant Adverse Events

Patients who discontinue treatment in association with an adverse event receive special attention in regulations (their CRFs must be submitted) and their analysis is a critical part of the safety evaluation.

7.1.3.1 Overall profile of dropouts

Include an overall profile of dropouts from clinical trials. The profile should classify dropouts from the overall Phase 2 and 3 study pool by reason for dropping out (e.g., adverse event, treatment failure, lost to follow-up).

7.1.3.2 Adverse events associated with dropouts

The incidence of more common adverse events should be presented, preferably in a table or set of tables, and there should be an assessment of whether the events can reasonably be considered treatment-related (usually based on rates in treatment and control groups). Any dose-response or time dependency of the dropout, and any drug-demographic, drug-disease, and drug-drug interactions should be described.

For rarer events that could represent an important adverse event, a critical assessment of whether any of these may represent treatment-induced injury should be included. These events should be considered individually with narratives and reference to other data as appropriate.

7.1.3.3 Other significant adverse events

The International Conference on Harmonisation (ICH) defines a new category of "Other Significant Adverse Events." It includes:

- Marked hematological or other lab abnormalities not meeting the definition of serious

- Any events that led to an adverse dropout or any other intervention such as dose reduction or significant additional concomitant therapy (an expansion of the adverse dropout concept)
- Potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy (e.g., a single seizure, syncopal episode, orthostatic symptoms)

Those adverse events that did not lead to discontinuation but otherwise meet the definition above should be described in this section.

7.1.4 Other Search Strategies

In addition to reviewing deaths, serious adverse events, and adverse events associated with dropouts, it may be useful to construct algorithms involving combinations of clinical findings that may be a marker for a particular toxicity (e.g., cough, chest congestion, and shortness of breath that may constitute drug-related or drug-induced bronchospasm). When such algorithms are used, they should be described in the review and results of the search provided.

Another special search could be for possible consequences of a safety signal from any source (e.g., nonclinical toxicology, postmarketing, or literature reports; or concerns that have arisen with pharmacologically related drugs). Results of any such searches should be described.

The results of unique or special safety studies can be mentioned here for completeness, but should be described fully in section 7.1.12, Special Safety Studies.

7.1.5 Common Adverse Events

This section of the review should focus on establishing the common adverse event profile for the drug and determining the content of the adverse reaction tables to be included in labeling.

7.1.5.1 Eliciting adverse events data in the development program

The applicant's methods of eliciting adverse event data in clinical trials should be described, noting whether checklists were used, how frequently patients were assessed, and whether the approach differed among studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Applicants will usually group closely related investigator or patient reported terms using a so-called *dictionary* of preferred terms such as COSTART or MedDRA. These dictionaries leave considerable discretion to the classifier for choosing the term that best describes what has been reported. The applicant's categorization of events should be assessed by comparing the preferred terms to the terms used by investigators and patients, focusing on the events leading to dropouts or other changes in treatment.

7.1.5.3 Incidence of common adverse events

Applicants typically prepare a wide variety of tables of ADR rates for individual studies and pools of various studies. Those tables generally include investigator causality assessments and severity ratings. The tables considered useful should be included in the review. Incidence rates for common adverse events are best estimated from the relatively small portion of the overall database contained in the controlled (especially placebo-controlled) trials. For these more common reactions, the ability to compare rates on drug with a control outweighs the disadvantage of basing the rate estimates on fewer subjects. In determining incidence rates for common adverse events, the subset of trials in the Phase 2 and 3 database that provides the best estimate of rates should be identified and used to develop tables of ADR rates based on that judgment.

7.1.5.4 Common adverse event tables

A table (or tables) that presents the best overall display of commonly occurring adverse events, generally those occurring at a rate of 1% or more (although lower rates can be presented for very large databases) should be provided. This table or tables will be the basis for the ADR table in labeling, which may, however, use a higher cutoff if this does not leave out important information, and will eliminate ADRs that are equally common on drug and placebo. The frequency cutoff for inclusion of adverse events in the table (e.g., > 1%) is inherently arbitrary. If one is used, the review should explain how the threshold was determined. It may also be informative to include tables that distinguish between common adverse events on the basis of severity.

7.1.5.5 Identifying common and drug-related adverse events

Those events that can reasonably be considered drug-related should be identified. Although it is tempting to use hypothesis-testing methods, any reasonable correction for multiplicity would make a "finding" almost impossible and studies are almost invariably underpowered for statistically valid detection of small differences. The most persuasive evidence for causality is a consistent difference from control across studies and, where there is such consistency, evidence of dose response.

7.1.5.6 Additional analyses and explorations

For adverse events that seem clearly drug-related, the following additional analyses should be performed, as appropriate:

- Exploration for dose dependency, exploration of time to onset (for those that show a delay in onset)
- Exploration of adaptation (for common, troublesome events such as somnolence or nausea)
- Explorations of demographic interactions (gender, age, racial subgroups), explorations of drug-disease and drug-drug interactions (if there is a strong signal for an interaction or a good rationale for expecting an interaction)
- Selective exploration of individual cases in an attempt to better characterize the events

7.1.6 Less Common Adverse Events

In general, a fairly large database is needed to evaluate less common adverse events. To identify relatively rare events of significant concern, the occurrence of adverse events over the entire Phase 2-3 database will usually be necessary, including data for which there is no useful concurrent control. Since the overall database is generally heterogeneous, it is unlikely to lend itself to meaningful estimations of rates or assessments of causality. Thus it may be sufficient to group these events by incidence and by body system. For example, it may be useful to categorize less common adverse events in order of decreasing frequency within certain ranges (e.g., ≤1%, between 0.1% and 1%; ≤0.1%).

7.1.7 Laboratory Findings

The approach to a review of laboratory findings (chemistry, hematology, and urinalysis) is generally similar to that suggested for the other categories of safety data. Laboratory tests performed in the clinical studies should be identified and the dataset from which laboratory findings information is obtained described. The methods used to assess findings, discuss pertinent findings, and review the more important findings in depth should also be described. Laboratory findings discussed in detail in other sections of the review (e.g., Section 7.1.2—Other Serious Adverse Events, Section 7.1.3—Dropouts and Other Significant Adverse Events) need not be discussed in detail in this section, but this section should refer to the more detailed discussions of such findings elsewhere in the review.

7.1.7.1 Overview of laboratory testing in the development program

An overview should be provided of the laboratory testing (chemistry, hematology, and urinalysis) carried out. It is best to summarize the overall approach, rather than provide detailed comments about laboratory testing for each study. Any discrepancies between planned analyses and those actually conducted should also be described, as should the procedures used to evaluate abnormal values. Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. Placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities; therefore, longer-term data need to be examined also. If there is no concomitant control, there may need to be a comparison with similar populations outside the NDA. In identifying the sample population for comparison of laboratory values, the reviewer should pool relevant studies. The review should explain how the pooled studies were selected.

7.1.7.3 Standard analyses and explorations of laboratory data

This section should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the Phase 2-3 experience. The analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these do not represent real probabilities.

7.1.7.3.1 Analyses focused on measures of central tendency

The central tendency analysis generally compares mean or median changes from baseline across treatment groups. The results of these analyses for all laboratory measurements should be provided.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

This section should focus on patients whose laboratory values deviate substantially from the reference range. The criteria used to identify outliers should be described.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Individual patients with large changes in laboratory values should be analyzed. Discontinuation of treatment for a laboratory abnormality may be considered a marker of perceived clinical importance of a finding.

7.1.7.4 Additional analyses and explorations

Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. The rationale for additional explorations, the methods used, and the results and interpretations should be described.

7.1.7.5 Special assessments

Certain laboratory assessments are so critical that they deserve special attention in any review. For example, hepatotoxocity has been an important cause of market withdrawal since the 1950s and may deserve a special assessment in this section.

7.1.8 Vital Signs

Vital signs can be reviewed using an approach essentially identical to that taken for laboratory data.

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

ECG data can be reviewed using an approach that is essentially identical to the one taken for laboratory data. The adequacy of the assessment may be especially important in this case, given recent experience with drugs that prolong the QT interval. This section should be organized in a manner similar to the laboratory section.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Describe the number of baseline and on-study ECGs obtained, who read the ECGs, using what methodology.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

All therapeutic proteins may potentially elicit an immune response. Data on the impact of immunogenicity (if applicable) on safety, efficacy, clinical pharmacology, and pharmacokinetics may be summarized in this section and referenced throughout the review. An assessment of the adequacy of the immunogenicity data provided to address these issues should also be included.

7.1.11 Human Carcinogenicity

Although formal studies in humans of the carcinogenic effects of drugs and biologics are uncommon, reflecting the expectation that induction of cancer would occur over a very long period of exposure, a systematic assessment of all human tumors reported during drug development can provide useful safety information in some cases. Such assessments would be appropriate where controlled trials are of long duration (e.g., more than a year), especially for drugs or biologics that have positive genotoxicity or animal carcinogenicity findings or are known immune modulators.

7.1.12 Special Safety Studies

Include a summary of any studies designed to evaluate a specific safety concern or concerns. These studies may include:

- Studies to assess whether a drug has safety concerns common to its pharmacological class
- Studies in topical products to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity
- Studies to characterize the effect on the QT interval (part of most modern development efforts)
- Studies intended to demonstrate a safety advantage over therapeutic alternatives

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The review should contain a discussion of abuse potential and any apparent withdrawal symptoms. This section should contain a summary of findings from any nonclinical and clinical abuse liability studies, problems in medication accounting encountered while monitoring the investigational supply of medication, chemistry and pharmacology issues that relate to abuse potential, and relevant adverse events and epidemiologic data. The findings of consultations with the Controlled Substances Staff should be included in this section. Scheduling recommendations under the Controlled Substances Act should be consistent with information recommended for inclusion in the product label.

For therapeutic classes with a history of abuse potential and withdrawal phenomena (e.g., sedative/hypnotics and anxiolytics), studies are usually performed to assess these issues. The review should comment on the adequacy and findings of these studies. For other drugs, adverse events that emerge after discontinuation of the drug should be assessed to

determine whether they may indicate a withdrawal phenomenon. If the applicant evaluated the potential for withdrawal phenomena, the review should indicate whether there was a prospective or post hoc assessment of withdrawal emergent signs and symptoms (during drug taper or following discontinuation) and should discuss the implications of the approach used on the reliability of the findings.

7.1.14 Human Reproduction and Pregnancy Data

Although formal studies in humans of the effects of drugs on reproduction or pregnancy are uncommon, any available information on drug exposure in pregnant women, including any inadvertent exposure during the drug's development and exposure identified from secondary sources (e.g., postmarketing surveillance) should be described. If there is no information on drug exposure in pregnant women, that fact should be acknowledged. Both positive and negative findings should be discussed.

7.1.15 Assessment of Effect on Growth

Increasingly, clinical reviewers are presented with analyses of height and weight data collected during studies of pediatric subjects. These data are generally inadequate to allow for definitive conclusions about an effect of a drug on growth for several reasons, which are not discussed here. Nonetheless, review of height and weight data for possible effects on growth makes use, in part, of approaches described in the laboratory data section. Analysis of changes in central tendency and outlier analysis, for example, applies to the evaluation of the effect of a drug on growth. Any review of height and weight data should also include a description of the measurement methodology. Adjustment of growth for age and sex can be made by conversion of a child's height and weight to a z-score, which is the number of standard deviations that an individual's measurement is from the mean for age and sex matched children in the general population.

7.1.16 Overdose Experience

All overdose experience with a drug or biologic in humans (including both information provided by the applicant and information obtained from secondary sources) should be summarized. It is important to describe the signs and symptoms that might be associated with overdose. Phase 1 data should be reviewed to identify subjects who may have received higher doses than those used in later phases of study. Patients with certain physiological differences that would compromise their ability to clear the drug (e.g., renal impairment, limited CYP450 2D6 activity for a drug cleared by this isozyme) may provide relevant data on the clinical implications of overdose.

7.1.17 Postmarketing Experience

Relevant findings from U.S. and foreign postmarketing experience, if any, should be described briefly here, including the results of any postmarketing safety assessments conducted by the Office of Drug Safety (ODS).

7.2 Adequacy of Patient Exposure and Safety Assessments

Section 7.1 is an assessment of the adverse events seen during the development program. Section 7.2 provides an assessment of the adequacy of drug exposure and the safety evaluations performed as part of the development program. This section addresses the regulatory question of whether or not "all tests reasonably applicable" were conducted to assess the safety of the new drug. Was there adequate experience with the drug in terms of overall numbers of patients and in appropriate demographic subsets of patients? Were doses and durations of exposure appropriate? Were all (or not all) appropriate tests performed in the exposed patients? Were all necessary and appropriate animal tests performed? Were all the appropriate clinical tests carried out (e.g., electrocardiographic assessment of effects on QT interval)? Was the drug adequately worked up metabolically? Were appropriate in vitro studies of drug-drug interaction carried out according to current guidelines? Were all potentially important findings adequately explored (e.g., to what extent was psychomotor impairment specifically assessed in a drug that is sedating)?

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In this section the reviewer should identify and characterize the primary safety data sources used in conducting the review. If these are described elsewhere in the review (e.g., section 4), those sections can be referenced here.

Tables and graphs are useful in describing the data sources for the safety review. Generally, the reviewer should use the tables and graphs in this section to characterize the overall database. The detailed tables and other displays for this subsection may be included in an appendix to the review, but summary tables and narrative statements should be included here. The reviewer should also characterize the per patient data (narratives, CRFs, CRTs, and electronically accessible databases) for baseline information. See section 7.4 for a discussion of the ability to link databases.

7.2.1.1 Study type and design/patient enumeration

A table that enumerates all subjects and patients across the entire development program, Phases 1-3, should be included here (or by reference). This table identifies the important patient pools and denominators for subsequent analyses and incidence estimates.

A table that provides brief descriptive information for all individual studies, including study design (fixed dose vs. flexible dose, parallel vs. crossover), dosing schedule, study location (foreign vs. domestic), treatment groups and doses, N's, patient population (elderly) should generally be included in an appendix and referenced here. Studies that were designed to assess a particular aspect of safety (ECG, ophthalmic, etc.) should be noted. Because a table of all studies is called for in the guidance for industry on *Format and Content of the Clinical and Statistical Sections of an Application* and in the ICH Common Technical Document, most NDAs and BLAs will include such a table.

Other sections (e.g., section 4 and/or an appendix) may be referenced.

7.2.1.2 Demographics

Tables should be included (or referenced) that provide overall demographic information for Phase 1 and Phase 2-3 study pools separately. It may be appropriate to provide demographic displays for subsets within these larger pools at other points in the review.

7.2.1.3 Extent of exposure (dose/duration)

There are many ways to summarize the dose and duration experience with a new drug. Either can be expressed as mean, median, maximum, with histograms or other displays that give the numbers exposed at various doses or for various durations. A particularly useful approach is to provide combined dose and duration information.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary source data are (1) data derived from studies not conducted under the applicant's IND and for which CRFs and full study reports are not available, or studies so poorly conducted (e.g., poor ascertainment for adverse events) that they cannot be reasonably included in the Primary Source Database, (2) postmarketing data, and (3) literature reports on studies not conducted under the IND. Often the applicant may have made the distinction between the data considered primary source data and other data, and the reviewer needs to examine the rationale for this distinction.

The secondary data sources should be briefly described. It is worth emphasizing that secondary source data may be a critical source of information for review, despite the generally lower quality of these data, because they often provide the larger database needed to look for less common serious events, and may be reliable with respect to deaths and serious adverse events.

7.2.2.1 Other studies

The NDA or BLA should clearly describe exactly what other studies provided data and what the basis was for not integrating such data with the primary source data (e.g., no CRFs, no study reports, not adequately monitored).

7.2.2.2 Postmarketing experience

If postmarketing data are available, this section should describe briefly the type of information available for review. Important events should be described in appropriate sections (e.g., 7.1.1 and 7.1.2, Deaths and Other Serious Events; 7.1.16, Postmarketing Experience).

7.2.2.3 Literature

This section of the review should describe what information from the literature search was provided for review, the extent to which the applicant’s literature search was ideal, and whether any missing information is important (and/or was obtained by the reviewer). Independent literature reviews conducted by the reviewer should be described here as

well. Individual literature references can be listed at the end of the review in the References section.

Actual safety findings should be described in appropriate sections of the safety review. A complete review of the literature (i.e., including non-safety related literature findings) can go in section 8.6, with appropriate cross-references, as necessary.

7.2.3 Adequacy of Overall Clinical Experience

In evaluating the adequacy of clinical experience with the drug, the reviewer should refer to current ICH guidance on extent and duration of exposure needed to assess safety. The following should be specifically addressed:

- Whether an adequate number of subjects were exposed to the drug, including adequate numbers of various demographic subsets and people with pertinent risk factors
- Whether doses and durations of exposure were adequate to assess safety for the intended use
- Whether the design of studies (open, active-control, placebo-control) was adequate to answer critical questions
- Whether potential class effects were evaluated (e.g., for anti-arrhythmic effects, evaluation of the potential for pro-arrhythmic effects) and whether problems suggested by preclinical data were assessed
- Whether patients excluded from the study (e.g., diabetics, people over 75, people with recent myocardial infarction, people with renal or hepatic functional impairment, or people on particular other therapy) limit the relevance of safety assessments. This may depend on the signals of toxicity that were observed in the patients who were studied.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

A general assessment of the preclinical program should not be provided, but rather, there should be comment on whether preclinical testing was adequate to explore certain potential adverse events, using preclinical models based either on a drug's pharmacology or on clinical findings that emerged early in clinical development. For example, for a drug anticipated to cause QT prolongation because of its drug class or because QT prolongation was seen in Phase 1 studies, there are in vitro models to evaluate this potential. It should be noted whether such studies were done. If such studies were performed, the results should be summarized in the Pharmacology Review.

7.2.5 Adequacy of Routine Clinical Testing

The adequacy of routine clinical testing of study subjects, including efforts to monitor laboratory parameters, vital signs, ECGs, and efforts to elicit adverse event data should be assessed, considering the adequacy of the methods and tests used and the frequency of testing. The adequacy of specific testing intended to assess certain expected or observed events should be discussed under subheading 7.2.7.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Knowledge of how a drug is metabolized and excreted is critical to anticipating safety problems in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions.

Drug-drug interaction assessment is a critical part of a modern drug development program and should evaluate the drug both as a substrate for interactions (interference with its clearance) and as an inducer or inhibitor of the clearance of other drugs.

The adequacy of in vitro and in vivo testing carried out by the applicant to identify the following should be assessed:

- The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins
- The effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds
- The major potential safety consequences of drug-drug interactions

The details of these assessments may be in section 5 and the Clinical Pharmacology Review, in which case this section can refer to them.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adequacy of the applicant's efforts to detect specific adverse events that are potentially problematic and might be expected with a drug of any class (e.g., QT prolongation or hepatotoxicity) or that are predicted on the basis of the drug class (sexual dysfunction with SSRI antidepressants) should be discussed. It should be noted whether the applicant should have made efforts to assess certain events that it did not assess. Pertinent negative findings (absence of findings) for a drug should also be discussed in this section of the review.

7.2.8 Assessment of Quality and Completeness of Data

A general overall assessment of the quality and completeness of the data available for conducting the safety review should be provided, with a description of the basis for this assessment. Attention to completeness and quality of assessment is important throughout the review, recognizing that quality for the primary source data may differ from quality for data over which the applicant had less control.

7.2.9 Additional Submissions, Including Safety Update

The initial NDA/BLA submission may not contain all information pertinent to the safety evaluation. Further data submissions may be planned at the time of initial submission and filing (e.g., results of additional long-term follow-up), may represent responses to specific questions or discipline review letters, or may be part of the safety update

required under 21 CFR 314.50(d)(5)(vi)(b). It is critical to review these data to determine whether safety conclusions are affected, particularly with respect to serious or fatal events.

This section should:

- Describe safety submissions, noting whether the results have been incorporated into the rest of the review or are considered in this section.
- For those safety matters not incorporated into the rest of the review, discuss any safety data with important implications for safety. In general, this will involve deaths, adverse dropouts, and other serious events, and these should be considered (as in sections 7.1.1, 7.1.2, 7.1.3) as appropriate to the (usually) small number of events. Only if these events alter the overall safety picture will a more detailed discussion of the entire area (deaths, liver injury, etc.) be needed.

Any reports of important changes in foreign labeling or new studies that give insight into more common events should also be noted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Each of the adverse events considered important and treatment-related should be briefly summarized (i.e., this should be a "problem list" for the treatment). For each event, include a separate subheading that contains a brief summary of the event and references to other sections of the review that contain more detailed information about the event.

7.4 General Methodology

This section is a general discussion of methodology and will not necessarily be reflected in the previous sections of the safety review. The section does provide a location, however, for any general discussion of methodological issues not discussed elsewhere, organized by the subsections listed here, with additional sections as needed. It is important to consider early in the review whether the available patient level data will allow the analyses the reviewer intends. For example, in examining whether particular baseline risk factors are related to an adverse event, the baseline characteristics will need to be extracted from case report tabulations if they are otherwise not readily available elsewhere. Similarly, it may be important to link individual safety observations with other on-therapy data, such as dose, duration of treatment, concomitant therapy, other adverse effects, lab data, or effectiveness results (it is obviously best if such issues are considered at pre-NDA/BLA meetings).

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Before estimating the incidence of adverse events, the patient sample of interest must first be selected. Pooling data from different studies can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size). Better precision is particularly important for lower frequency events, which can be difficult to detect and may not occur in some studies. Pooling can also provide a larger database that will permit explorations of possible drug-demographic or drug-disease interactions in population subgroups. However, pooling can also obscure real and potentially meaningful differences between studies. The review should explain the choice of any pooling used in the review.

7.4.1.2 Combining data

In pooling data, usually the numerator events and denominators for the selected studies are simply combined. Other more formal weighting methods can be used (e.g., weighting studies on the basis of study size or inversely to their variance). How the pooling was performed should be described, as well as the rationale for selection of the method used.

7.4.2 Explorations for Predictive Factors

Adverse reaction rates may differ considerably from one patient population to another and may change over time. Factors that may affect the safety profile of a drug should be sought during the review. Common predictive factors include plasma level, duration of treatment and concomitant medications, and patient-predictive factors such as age, sex, race, and concomitant illnesses. In general, these explorations are meaningful only for adverse reactions that appear to be drug-related (see section 7.4.3)

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

In assessing the critical question of whether an adverse event is caused by a drug or biologic, whether the treatment is capable of causing that adverse event in the population is usually of greater interest than whether the treatment caused the event in each patient who reported the event. However, the approach to causality is distinctly different for relatively common events and relatively rare, serious events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This section should address all of the following that are of concern:

- Level of confidence for the dose/regimen
- Dose-toxicity and dose-response relationships
- Dose modification for special populations
- Unresolved dosing/administration issues

The recommended dose/regimen should be discussed, including how well supported the dose recommendations are. If dose-response trials have been reviewed elsewhere (e.g., in the efficacy section), those sections can be referred to here. An attempt should be made to integrate dose-response for toxicity and efficacy and to indicate how much uncertainty remains about optimal dosing. Discuss dose interval and the timing of administration (including relation to meals).

8.2 Drug-Drug Interactions

Discuss important drug-drug interactions and recommendations for dosing adjustments in these settings.

8.3 Special Populations

Include in this section:

- Special dosing considerations based on demographics: race, gender, age for adults, age for pediatrics
- Special dosing considerations base on coexisting states (e.g., hepatic, renal insufficiency)
- Special dosing considerations in pregnancy or lactation

The adequacy and quality of the studies used to assess use in special populations should be discussed.

8.4 Pediatrics

Given the unique legal, regulatory, and public health interest in pediatrics, discuss here any issues specifically related to the pediatric population. Include, as appropriate, the

result of consultations with the Division of Pediatric Drug Development, a discussion of the pediatric development plan, pediatric waivers, deferrals, or written requests, and the application's compliance with the Pediatric Research Equity Act (PREA).

8.5 Advisory Committee Meeting

The results of an advisory committee meeting may be considered in a separate review and referred to here. If included in this section, a discussion of the questions addressed by the advisory committee, other input that the advisory committee provided, and the implications of the advisory committee input to the recommendations should be provided.

8.6 Literature Review

Literature related to the application ordinarily would be referenced throughout the review (e.g., literature related to the development or interpretation of endpoints would be described in section 6.1.2). When applicable, a comprehensive review of the literature can be included here. Any specific references can be listed in the References section at the end of the review.

8.7 Postmarketing Risk Management Plan

If one has been submitted, a review of the applicant's postmarketing risk management plan should be included here. Any recommendations for postmarketing risk management (regardless of whether the applicant has submitted a plan) should go in section 9.3.1.

8.8 Other Relevant Materials

The review of any other relevant material not included in other sections should be covered here. This can include:

- Actual use and labeling comprehension studies, marketing studies
- Results of other consultations with clinical implications that have not been described elsewhere, such as those from the Division of Drug Marketing, Advertising, and Communication (DDMAC)
- Reviews from the Office of Drug Safety (ODS) on proposed and completed epidemiologic studies

9 OVERALL ASSESSMENT

9.1 Conclusions

Conclusions and analyses in other sections of the review should be summarized and referenced but need not be repeated in detail in this section. This section should identify the primary differences between the reviewer's conclusions and those of the applicant.

9.2 Recommendation on Regulatory Action

The recommendation on regulatory action should focus on the clinical perspective. The recommendation should be supported by a brief discussion of the risk-benefit analysis. For any review where the recommended action is other than approval, a complete and

detailed list of all the deficiencies that preclude approval of the application should be provided. A summary of any recommendations developed in this section should be included in the Executive Summary.

9.3 Recommendation on Postmarketing Actions

The need for risk management activities (including restricted distribution programs) and/or Phase 4 studies should be considered. The need for postmarketing activity to achieve compliance with PREA, if necessary, should also be assessed. A summary of any recommendations developed in this section should be included in the Executive Summary.

9.3.1 Risk Management Activity

Include all recommended postmarketing risk management activities. Specifically identify those that have been previously discussed and agreed upon with the applicant. This section should also include the rationale for the recommended risk management activities. Recommendations resulting from appropriate consultation with the Office of Drug Safety (ODS) should be considered when formulating these recommendations.

9.3.2 Required Phase 4 Commitments

Include any required Phase 4 commitments in this section. It should include a description of any postmarketing clinical studies or analyses, the agreed upon timeline for submission, and the date of the applicant's written agreement to these commitments. This section should also include the basis for each Phase 4 commitment, as well as other potential alternatives to garner the information. Any commitments required to comply with PREA should also be included here.

9.3.3 Other Phase 4 Requests

Any optional or recommended Phase 4 requests should go here, along with the scientific basis for the requests.

9.4 Labeling Review

Include here a summary of the major changes needed in the applicant's proposed labeling. Refer to the appendix for a line-by-line review.

This section should also include:

- A review of the trade name, including the results of consultation from the Division of Medication Errors and Technical Support (DMETS)
- A discussion of whether a Medication Guide or Patient Package Insert should be developed or, if already proposed, a review of these materials, including the results of appropriate consultation with the Office of Drug Safety (ODS)

9.5 Comments to Applicant

Include here all comments that should be conveyed to the applicant. Comments the applicant must address to correct important deficiencies that preclude the approval of the application during this review cycle should be distinguished from any other comments that may not pertain to specific deficiencies. The comments should be numbered for easy reference.

10 APPENDICES

10.1 Review of Individual Study Reports

If performed, the review of individual study reports should go in this section. Suggested subheadings for each study report review include:

- Protocol
- Amendments
- Post Hoc Changes
- Results
    - Disposition
    - Demographics
    - Baseline Characteristics
    - Efficacy
        - Primary
        - Secondary
    - Safety
- Conclusions
- Summary

10.2 Line-by-Line Labeling Review

Include a detailed line-by-line review of labeling here (if performed). For clarity, underlined text for recommended additions to the applicant's proposed text and strike-through text for recommended deletions should be used.

REFERENCES

List any literature references used in the review. The use of MS Word endnotes in the body of the review is encouraged for automatic reference entry in this section.