Reviewer Guidance

Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

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Comments and suggestions regarding this draft document should be submitted by January 31, 1997, to the Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rm 1-23, Rockville, MD 20857. Comments should be identified with the docket number 96N-0443. Comments and suggestions received after that date may not be acted upon by the Agency until the document is next revised or updated. For questions regarding this draft document, contact Paul A. David at (301) 594-5530.

U.S. Department of Health and Human Services
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Draft — Not for implementation

REVIEWER GUIDANCE [1]

CONDUCTING A CLINICAL SAFETY REVIEW OF A NEW PRODUCT APPLICATION AND PREPARING A REPORT ON THE REVIEW

INTRODUCTORY NOTE

This is an annotated version of an outline for the clinical review of a New Drug Application (NDA), with a focus on the review of safety data [2]. Although the focus of this document is on the safety review, the document also provides some advice on other aspects of the review that are necessary precursors to the safety review (e.g., characterization of the database). This version provides narrative information to describe the contents and, in some cases, to provide the rationale for the various sections of the review.

One goal of this guidance is to provide some level of standardization in clinical reviews of NDAs without inhibiting the reviewer in any way from going beyond what might be considered the minimum elements of the review process and the review product.

In keeping with the need for standardization, this guidance proposes a standard numerical outline for the safety review, with the suggestion that this structure be applied to all reviews. One obvious advantage to such a standard structure is that secondary and tertiary reviewers may always know where to find certain standard information about the safety of a drug.

In general, the goals of a safety review are (1) to identify important adverse events that are causally related to the use of the drug, (2) to estimate incidence for those events, and (3) to identify factors that predict the occurrence of those events, e.g., patient factors such as age, gender, race, comorbid illnesses, and drug factors such as dose, plasma, level, duration of

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[1]This guidance has been prepared by Integrated Summary of Safety group which is a subcommittee of Track 8. The Track 8 Committee has been charged with developing a guidance for the clinical review of a marketing application under the Good Review Practices (GRP) initiative. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on clinical safety review of a NDA. An electronic version of this guidance is available via Internet using the World Wide Web (WWW). To access the document on the WWW, connect to the CDER Home Page at http://www.fda.gov/cder and go to the "What's Happening" section. A copy of this document may also be obtained via fax by calling the CDER Fax-on-Demand at 1-800-342-2722, under the index document no. 0506.

[2]Guidance for the safety review is presented in the context of a proposed outline for the entire clinical NDA review. It is acknowledged that once agreement is reached on a structure for the clinical review, the safety elements addressed in this document may need to be incorporated into that broader structure.

exposure, concomitant medications. The safety review is useful not only in making a risk/benefit decision, but also in drafting labeling for a drug that is going to be approved.

It is useful to distinguish between the process of doing the review and the creation of a review product for regulatory use. The review process can be thought of as involving two parts, i.e., (1) an assessment of the adequacy of the clinical experience with the new drug and the methods employed to detect adverse events occurring during or after exposure, and (2) an assessment of the adverse events discovered in this exposed population. The review product is the logically written, well-organized, user friendly document that presents and interprets the findings. This guidance may provide advice pertinent to both review process and product, and it is hoped that this it may encourage the production of clinical reviews that facilitate both the risk/benefit decision for a new product as well as the drafting of rational labeling for products that are destined for approval.

If there is one principle that underlies this guidance it would be the inadequacy of an approach involving only the review of individual studies in an NDA without any attempt to integrate the findings. Consequently, this guidance focuses on approaches to organizing and integrating the findings across studies in a manner that facilitates the regulatory tasks. However, many of the methods described may be usefully applied to the review of safety data within an individual study as well[3].

Sections proposed in this guidance may be deleted if inappropriate for a particular product, or medical device under review. In addition, it is acknowledged that, while the specific advice offered in this guidance may often represent the optimal approach for reviewing a particular product application, in other cases the suggested approach may be irrelevant or suboptimal and an entirely different approach may be more appropriate. Thus, the extent to which the specific advice offered in this guidance needs to be followed with a particular application may be determined at the level of center, office, review division or review team.

This guidance references as attachments standard guidance for certain data displays and tables and also selected materials from clinical reviews and other sources that illustrate the approaches that are suggested. Multiple other examples are needed, and it is hoped that this draft document should stimulate the submission of additional examples that can be incorporated into future versions of this guidance. Many of the suggested tables have already been created by sponsors,

[3]It is important to distinguish between the concept of doing an integrated review of safety for a drug and the separate question of whether or not to pool or combine data across studies in the conduct of that review. For the purposes of this document, an integrated safety review refers to the principle of bringing together and discussing in one place in the review all information pertinent to a particular safety issue, e.g., liver toxicity. Whether one looks at data from individual studies or from datasets resulting from pooling of certain studies to address a particular safety concern is not relevant to the concept of an integrated review. Either approach may be appropriate for a review that can be considered an integrated review.

and often can be attached as appendices with little or no editing. It is important for reviewers to acknowledge which of the materials included in the review have come directly from the product application, as well as specifically where they have come from, i.e., volume and page numbers, and to clearly distinguish such documents from the reviewer's independent work. In certain instances it may be preferable to simply refer to the sponsor's tables without actually including them in the review document.

There were a number of resources relied upon in developing this guidance document, including several previous guidance documents, in particular, the Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications. In addition, it is based on the advice of many experienced reviewers within the agency.

This guidance is being developed in parallel with the development of a software package to provide reviewers with analytical tools to facilitate the safety review (CARS, Computer Assisted Review of Safety). Both processes should be viewed as evolving to keep pace with changes in technology and in our collective views on what is appropriate for a safety review.

PROPOSED REVIEW FORMAT AND CONTENT

-Title Page

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1.0 Materials Utilized in Review

[**Note:** The focus in this outline is on safety; however, once a fully integrated clinical review outline is developed, this section would be expected to describe both the safety and the efficacy data sources for the clinical review.]

1.1 Materials from NDA/IND

It may be useful to list in this section all the materials from the NDA that were used in the review, i.e., the specific volumes utilized (dates and volume numbers). It would be appropriate to list volumes from the original submission plus any later submissions (e.g., safety update, responses to information requests). Any electronic resources utilized in the review may also be described in this section. Source medical documents obtained independently of the NDA (e.g., films, scans, discharge summaries) should also be noted.

It may be useful for the reviewer to include in an appendix a list of the case report forms (CRFs) actually examined as part of the review process, or in lieu of a list, a description of which ones, e.g., CRFs for all deaths, may suffice.

Finally, it may be useful for the reviewer to check the sponsor's IND for the new drug to make sure that important information was not submitted only to the IND.

1.2 Related Reviews, Consults for the NDA

It may be useful for the reviewer to list in this section the outside reviews and consults that were considered in the conduct of this review.

1.3 Other Resources

It may be useful for the reviewer to list in this section other resources used in the review, e.g., outside experts, including advisory committee proceedings, independent literature reviews conducted by reviewer.

2.0 Background

[**Note:** As noted under section 1.0, the goal of this effort is to develop a fully integrated review guidance document for both safety and efficacy, and in keeping with that goal, this section suggests the inclusion of background information pertinent to both safety and efficacy.]

2.1 Indication

The reviewer should identify here the proposed indication and it may also be useful for the reviewer to provide information relevant to the proposed indication (e.g., currently available treatments and their efficacy, safety).

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

It may be useful for the reviewer to identify in this section related INDs and NDAs and other pharmacologically related agents, and to mention important issues associated with any such related products (e.g., known toxicities (both clinical and nonclinical), CMC problems).

2.3 Administrative History

It may be useful for the reviewer to provide in this section a brief and relevant history of the IND and the NDA, including dates for submission of key amendments and for critical meetings (e.g., end of phase II, pre-NDA). It may be particularly important to identify and briefly describe meetings at which agreement was reached on protocol design for critical studies, on primary variables to analyze, on the definition of the intent-to-treat sample. Key regulatory letters addressing such issues should also be summarized. If an earlier version of the NDA was not filed or not approved, or if this drug or another formulation has already been approved for another indication, the reviewer may want to note this as well as the basis for any such actions.

2.4 Proposed Labeling

It may be useful for the reviewer to summarize in this section the recommendations for use of the product proposed by the sponsor in labeling, e.g., recommendations for dosing, titration schedule, duration, discontinuation, treatment of special populations, use with other drugs, drug interactions, special safety concerns and monitoring needed. These are all critical issues for review and it is important to identify them before the review is begun.

2.5 Foreign Marketing

It may be useful for the reviewer to list in this section those countries in which the drug is known to be marketed and to note the indications for which it is approved, the doses recommended, etc. The reviewer may want to discuss any pending applications elsewhere and, in particular, any applications that have been rejected. It is often helpful to know why an application was rejected in a foreign country, and even if accepted, what the concerns were about the product. Such information may be helpful to the reviewer in deciding what issues to focus on, and if not available in the NDA, may be requested from the sponsor.

2.6 Miscellaneous Background

Any additional background information that is pertinent but cannot be readily included in earlier sections may be included here.

3.0 Chemistry, Manufacturing, and Controls

This section need only mention any clinical implications of chemistry, manufacturing and control problems identified in consultation with the assigned manufacturing and control reviewer. If there are none, that can be stated. An example of a potential problem would be a situation in which a sponsor had not proposed any tablet strengths low enough to permit safe dosing of patients who may be particularly vulnerable to the adverse effects of the drug. For biological products, there may be concerns about a potential for contamination with a viral agent known to be present in the producer cell line, the potential for anaphylaxis due to residual antibiotic from the tissue culture, or the potential for a retroviral vectored gene therapy without site-specific targeting to produce insertional mutagenesis.

4.0 Animal Pharmacology

This section can also be brief and may focus only on information directly relevant to the clinical review. It may summarize pharmacological findings relevant to the proposed mechanism of action. The clinical reviewer may want to note particular animal findings that were the basis for focused searches in the review of human safety data, e.g., hepatotoxicity, seizures, bone marrow suppression, renal toxicity. In addition, certain late appearing adverse events in animal studies may be a basis for a concern about such findings in clinical studies. Particularly relevant findings may also be included under the appropriate subsections of the Review of Systems (Section 8.2).

5.0 Description of Clinical Data Sources

In this section it is useful for the reviewer to identify and characterize for the reader the data

sources utilized in conducting the review. The primary source is generally the database derived from the sponsor's development program. Studies in this program may generally have full study reports and case report forms, and they may have been closely monitored. However, secondary sources may also be available, and may be of critical importance, e.g., for a drug already available in other countries. Also appropriate for this section are the reviewer's comments on the adequacy of the clinical experience with the new drug for assessing its efficacy and safety, and comments on the quality and completeness of the clinical data.

5.1 Primary Source Data (Development Program)

Tables and graphs are useful in describing the data sources for the safety review. Generally it may be useful for the reviewer to utilize the tables and graphs in this section to characterize the database overall, while individual studies and pools of relevant studies may be characterized in greater detail in later sections. Generally, the tables and other displays for this subsection may be included in an Appendix to the review, however, summary statements may be included in narrative format here.

5.1.1 Study Type and Design/Patient Enumeration

It may be useful for the reviewer to include an appendix table in a similar format to that illustrated in Attachment A - Table 5.1.1.1 that enumerates all subjects and patients across the entire development program, phases 1-3. This is a critical table that identifies critical pools and denominators for subsequent analyses, incidence estimates.

Sponsors sometimes segregate certain clinical trials from their primary source data (see 5.2, secondary source data), especially foreign data, and this may be an appropriate action, especially if there is a basis for believing that these data differ substantially in quality and completeness from the data included in the primary source database. However, this is a matter of judgement and cannot be assumed to be a valid action. An explanation should be provided in the review regarding the decision making about what data were included and what excluded from the primary source data.

It may also be useful for the reviewer to include an appendix table in a similar format to that illustrated in Attachment B - Table 5.1.1.2 . This table includes information for individual studies on 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).

An NDA generally includes data from patient samples that are at different levels of completeness in terms of data entry, information collected, and validation. This table should include patient counts (or estimates) from all studies contributing data, regardless of these factors. Data cutoff dates or database "lock dates" for the various databases comprising the NDA should be identified at this point in the review. For example, the cutoff date for the safety database derived from

completed studies might be more distant, while the cutoff date for submitting serious adverse events from all studies may generally be more recent. These dates may likely need to be updated during the course of NDA review as more data become available.

5.1.2 Demographics

It may be useful for the reviewer to include appendix tables in a similar format to that illustrated in Attachments C and D - Tables 5.1.2.1 and 5.1.2.2 that provide basic 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.

5.1.3 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. It is suggested that the review contain tables in the format illustrated in Attachments E and F - Tables 5.1.3.1 and 5.1.3.2 that enumerate patients on the basis of mean daily dose of the NDA drug and duration of administration for Phase 1 and Phase 2-3 study pools separately.

It may be useful to provide similar tables for various subgroups, e.g., males and females separately, various age groups separately, patients with various comorbid illnesses separately. There should be similar displays for active control drugs if any were included in trials for the new drug.

It may be useful to provide comparable tables based on maximum dose, modal dose, dose expressed as mg/kg or mg/m^2, or even plasma concentrations, if such data are available.

It may be appropriate to provide similar displays for subsets within these larger study pools and for certain individual studies at other points in the review.

It may also be useful for the review to include an appendix table providing person time data for the NDA drug, active control, and placebo, for the Phase 2-3 database, as illustrated in Attachment G - Table 5.1.3.3 .

5.2 Secondary Source Data

Secondary source data are considered to be (1) data derived from studies not conducted under the

sponsor's IND **and** for which CRFs and full study reports are not available [4], or studies so poorly conducted, e.g., poor ascertainment for AEs, 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 sponsor 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.

For the secondary sources, as was the case for primary source data, the intent is not that actual data and findings would be provided in this section of the review, but rather, that the sources relied upon would be briefly described. Any actual findings should be described and discussed under appropriate subsections of the Review of Systems (see Section 8.2). 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.

5.2.1 Other Studies

The NDA should be clear in describing 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.

5.2.2 Post-Marketing Experience

If postmarketing data are available, this section should describe briefly the type of information available for review, but not the actual findings. An example of such a description would be a comment that a line listing for 300 spontaneous reports from marketing in the UK was provided, along with narrative summaries for the serious adverse events among the 300 reports and an estimate of product use in the UK during that time period.

5.2.3 Literature

The NDA should include a literature section based on a thorough review of the world literature pertinent to the drug of interest. The sponsor should have provided a warrant that they reviewed this literature systematically, and in detail, and that any findings they discovered that would adversely affect conclusions about the safety of their drug were summarized in the Integrated Safety Summary. The literature section should have provided details regarding how the literature search was conducted (databases used, key search words, etc.), by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. A cutoff date for the literature search should have been provided. The literature section should have emphasized

[4] If CRFs are available from any such studies and the data quality is comparable to data coming from studies conducted under the sponsor's IND, these data would ordinarily be included in the primary source database.

clinical data, but new findings in preclinical reports of potential significance should also have been described. A copy (translated as required) should have been submitted for any report or finding judged by the sponsor to be potentially important.

It may be useful for this section of the review to describe in general what was provided for review, and the extent to which the above recommendations were met, but again, no actual findings should be included here. Any independent literature reviews conducted by the reviewer should be described here as well.

Any relevant findings should be included under appropriate subsections of the Review of Systems.

5.3 Comment on Adequacy of Clinical Experience

[**Note:** Are there other documents that should be referenced?]

As noted in the introduction, one of the tasks of the clinical reviewer is to make a judgement on the adequacy of the clinical experience with the new drug, i.e., demographic aspects (age, sex, race, ethnic group) and drug exposure (dose, duration). The clinical reviewer should provide comments in this section on the adequacy of the clinical experience, with reference to current guidance on these issues, e.g., ICH guidelines on duration [5], on special populations, such as geriatrics.[6] The separate question of the adequacy of the sponsor's approach to assessing safety in the exposed population is addressed under the Review of Systems (see later).

5.4 Comment on Data Quality and Completeness

The primary source data may be the most important resource for conducting the safety review, in part because these data may be most complete and of the highest quality. The clinical reviewer has an obligation to try to assess the completeness and quality of the data and this section of the review should comment on what the reviewer has done in this regard. These concerns should pervade the entire review process and examples of potential problems may be given throughout the remaining sections of this guidance document. However, a few prototypical examples are described here to alert the reviewer to what to be thinking about.

(1) Sponsors often differ in the ways they define what information should be included in the case report form (CRF). For example, if additional laboratory data are collected at unscheduled visits,

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[5]International Conference on Harmonisation, *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*, ICH-E1A, March, 1995.

[6]International Conference on Harmonisation, *Studies in Support of Special Populations: Geriatrics*, ICH-E7, August, 1994.

either between scheduled visits or following the nominal endpoint of a trial, some sponsors choose not to include this information in the CRF. In one instance, the information was exchanged between the investigator and the sponsor in the form of correspondence, and information was held in a "correspondence file" that was not submitted with the NDA. It was only upon inquiring about the lack of information for patients with abnormal laboratory findings that the sponsor admitted to having additional data and agreed to submit it. Similar situations have been observed when investigators have sought outside consultation on patients, when the patients have been hospitalized for adverse events, and information pertinent to such actions has not been submitted as part of the NDA. If there appears to be insufficient information regarding an important abnormal finding, the reviewer should make an inquiry to find out if additional information is available.

(2) In general, the reviewer should consider the adequacy of the follow up of patients who participated in the development program. Loss to follow up of patients with abnormal findings can be a serious problem for a development program if it is extensive. In other instances, investigators may not have obtained what would ordinarily be considered appropriate follow up on patients with abnormal findings, and consequently, the information is not available because it was not collected by the investigator and the sponsor. In those instances, the reviewer may request that the sponsor attempt to obtain the needed follow up information, and if this is not possible, one alternative may be for the reviewer to assume a bad outcome. This would be one example of a type of sensitivity analysis that should be done to assess the possible impact of missing information.

(3) Sponsors sometimes make changes to CRFs, generally during the process of monitoring clinical trials and with the investigator's agreement, but sometimes at later times and without the investigator's consensual agreement. For example, some sponsors review investigator categorizations of patients with regard to reason for dropping out of a trial, and may reclassify patients. Reviewers should be alert to the possibility of such changes, especially for patients experiencing serious adverse events. As with losses to follow up, reviewers should attempt to assess the impact of multiple changes in the case report forms, e.g., re-classification of reason for dropping out of a trial.

Based on the above considerations, the reviewer should include at this point in the review general comments on data quality and completeness. Other more specific problems may be noted as well at appropriate points in the review document.

6.0 Human Pharmacokinetic Considerations

It may or may not be primarily the clinical reviewer's role to review the phase 1 human PK data. In either case, however, it is important that the clinical reviewer understand the basic pharmacokinetic characteristics of a new drug before reviewing the efficacy and safety data. These findings are also useful for the reader in understanding what may follow in the review.

Consequently, it is useful to have the reviewer summarize in this section the important phase 1 pharmacokinetic findings at this early point in the review and consider the implications of these findings. Any formal interaction studies, e.g., studies in special populations (interaction studies based on gender, age, renal disease, liver disease, etc.) and any drug interaction studies should be briefly summarized in this section (both pharmacokinetic and pharmacodynamic interactions). The reviewer should also address the adequacy of the development program overall (phases 1-3) from the standpoint of pharmacokinetic assessment.

Phase 2-3 pharmacokinetic findings may be useful in explaining certain findings observed during these later trials (e.g., adverse events, lack of efficacy) and these data may be noted here but should also be reviewed and commented on in later sections of the review. In particular, findings pertinent to safety should be included under the appropriate subsections of the Review of Systems.

7.0 Integrated Review of Efficacy

[**Note:** This heading is included simply to suggest that this would be an appropriate place in the clinical review to include the efficacy findings. Given our very different approaches to analyzing efficacy and safety data, this guidance emphasizes the utility in many instances of separate sections in the review document for efficacy and safety findings. However, it is acknowledged that in other cases, e.g., drugs for which mortality is the outcome of interest, safety and efficacy are not so easily separable. In those instances where it is deemed valuable to review individual studies separately (i.e., all efficacy and safety data for each such study would be presented as an integrated package, but for each such study separately), this section of the review might be re-titled Review of Individual Studies.]

8.0 Integrated Review of Safety

This section addresses the findings pertinent to the safety of the new drug. Generally, the focus should be primarily on adverse events occurring in clinical trials or other clinical experience, but may also include certain preclinical findings of interest. The clinical data may be derived from individual studies, pools of studies of particular design (controlled, parallel group, etc.), the entire population exposed in the sponsor's development program, any of the secondary sources, or any combination of these sources.

Very often it may be most efficient to include all the safety findings, whatever the source, in this one section of the clinical review, i.e., separate from the description of individual studies. In other cases, it may be more appropriate to discuss some or all aspects of safety as part of the discussion of individual studies, e.g., (1) in mortality studies, safety and effectiveness may be hard to separate; (2) in development programs in which most of the safety data come from one or two large multicenter studies; (3) methods of data collection may be closely linked to findings; (4)

translation of investigator terms to COSTART may raise different issues in different studies; and (5) review of individual deaths may be more convenient study by study). If safety data are discussed study by study, summaries of the safety findings should be included in this section (8.0), and a reference should be provided to where in the review more details may be found.

General Methodological Issues

Before getting into the details of the review of specific safety findings, this guidance briefly discusses several methodological issues that apply to all the different categories of adverse findings (e.g., deaths, adverse dropouts, serious adverse events, all adverse events, abnormal lab data, VS, ECGs).

Differences in the Approaches to Safety and Effectiveness Data

Approaches useful for evaluating the safety of a drug under development generally differ substantially from those useful in evaluating its effectiveness. In fact, most of the studies in phases 2-3 of a development program focus on establishing a drug's effectiveness. In designing these trials, critical efficacy endpoints are identified in advance and sample sizes are estimated to permit an adequate test of the null hypothesis. For the most part, phase 2-3 trials are not designed to test hypotheses about safety. In fact, the safety endpoints are generally not known prior to the conduct of these trials, and for many of the observed safety outcomes, one can assume that the available studies are underpowered. The usual approach is to screen broadly and sensitively for adverse events, and it is hoped that this approach should reveal the common adverse event profile of a new drug and detect some of the less common and more serious adverse events associated with the drug as well. While hypothesis testing for effectiveness outcomes generally is done within individual studies, it usually is not appropriate to proceed with hypothesis testing procedures for safety outcomes. Rather, the approach to safety data may be viewed more as exploration and estimation.

Pooling Data Across Studies to Obtain Patient Samples for Estimating and Comparing Incidence

Before estimating incidence for adverse events of interest, one has to make a decision about what patient samples to focus on. For several reasons, it is often considered desirable to pool or combine data across studies. One goal of pooling data from different studies is to improve the precision of incidence estimates, i.e., to narrow the confidence intervals. This is particularly important for the less common events which may not even occur in some studies. A related goal, pertinent in particular to explorations for interactions in subgroups of the population, based on age and gender, is to improve the statistical power for detecting any subgroup differences in adverse event incidence. Finally, a more general goal of pooling is to facilitate what may be thought of as the essence of all explorations of safety data from these types of studies, namely the generation of hypotheses about risk, some of which may become the focus of future, more definitive studies.

While often useful, such pooling should be approached with forethought and caution:

(1) One general consideration is study design. It is most appropriate to combine data from studies that are of similar design, e.g., similar in dose, duration, methods of ascertainment [7], and population[8].

(2) Another general issue to explore is the range of incidence values for individual adverse events across the studies being considered for pooling. This is an important consideration if the goal of pooling is to estimate a "typical" incidence rate. If the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimates should be meaningless, and in fact, important information about predictors for that event may be lost in the pool[9]. In this case, pooling is not appropriate. In other cases, where the differences across studies are not excessive, pooling may be appropriate. There are formal tests for extreme values that may be applied, or alternatively, one might visually display the incidence by study and event to more informally check on the extent of variability and for outliers. Outliers may be very important in identifying subgroups of patients who are at particular risk for certain adverse events. Although methods for efficiently screening studies for poolability have not yet been well established for instances in which the number of outcomes is very large, as is often the case in NDA databases, the reviewer needs to carefully consider poolability and comment on what was done to establish the appropriateness for each pool utilized in the conduct of the review.

(3) If the goal of pooling is to increase the power to detect a difference between two treatment groups, e.g. drug vs placebo, a test of heterogeneity, e.g., the Breslow-Day Chi-Square test, might be useful. Alternatively, one might use a more subjective approach, e.g., determining if the direction of the difference is always the same across studies. If no differences are found, one could have some confidence in a pooled analysis of the studies [10].

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[7]Especially for common adverse events, the method for eliciting adverse events is a factor in determining the observed incidence of reporting. Patients who are prompted with checklists of adverse events should report at higher rates than patients who are prompted with general inquiries or not prompted at all.

[8]In psychiatric drug trials, for example, it is typical for obsessive compulsive patients to spontaneously report adverse events more frequently than schizophrenic patients.

[9]An example of this type of error was a drug for which phototoxicity was observed. Several studies were combined to estimate the incidence for this event, yielding a rate that was reassuringly low. However, upon examination of individual study results, it turned out that, for one of the studies in the pool, the rate of phototoxicity was substantial, a finding that had been obscured by combining the data. It was further revealed that this was the only outpatient study among those in the pool, and thus, these were the only patients who had an opportunity to have the event by virtue of having an opportunity to be exposed to sunlight.

[10]Even if the decision is made to pool studies for a particularly important adverse event, it is almost always useful to show individual study results for that finding as well.

Finally, if a decision is made to pool data for several studies, some consideration should be given to how the pooling is to be accomplished. It is probably most common to simply combine the numerator events and the denominators for the selected studies. Other more formal weighting methods are available, e.g., weighting studies on the basis of study size or inversely to their variance, and the reviewer should address the issue of how the pooling was accomplished and the rationale for selecting the method used for pooling.

The term meta-analysis is a term that has frequently appeared in the medical literature in recent years, generally referring to formal methods for combining data across independent studies. Most typically meta-analyses are focused on efficacy outcomes, but not always. While many of the principles identified as useful in the conduct of meta-analyses are similar to those discussed above in reference to combining data in a safety review, it would probably not be useful to characterize what is being described here as meta-analysis. In rare instances, a sponsor should have submitted what it might characterize as a meta-analysis for safety data, and the concept is introduced here primarily to alert reviewers to that possibility and the need to obtain expert advice in those instances.

Exploration for Predictive Factors

Once appropriate patient samples are selected for estimating incidence, it is often useful to consider exploring various drug factors (dose, plasma level, duration of treatment, concomitant medications, etc.) and patient factors (age, sex, race, concomitant illness, etc.) that may help in predicting the occurrence of certain adverse events of particular interest.

Explorations for Dose Dependency for Adverse Findings:

If data from fixed dose studies (or data from studies in which patients were randomized to fixed dose ranges) are available, it may be useful to conduct appropriate tests to detect evidence of dose dependency for certain adverse findings. If a placebo group is present and if a drug placebo difference is clearly established, it may be desirable to exclude the placebo group from such analyses, in order to focus on between dose group differences. It may be useful to refigure dose as mg/kg or even mg/mm^2 when exploring for dose response relationships. If plasma concentration data are available, it may be useful to explore for plasma concentration effect relationships as well. It may also be useful to look at certain subgroups to explore for dose/response relationships (e.g., females, elderly patients).

Although it is tempting to try to extract dose/response or plasma level/response data from flexible dose studies, there are multiple problems with attempting to use such data for establishing these relationships. In particular, many adverse findings show considerable time dependency, some occurring early, some late. It is very easy to confound dose (or plasma concentration) with duration. In other instances, e.g., for anticancer drugs, dose is adjusted to toxicity, so that any

dose response relationship should be obscured since most patients should have their doses modified until they achieve an acceptable level of toxicity.

For certain adverse events, it may be possible to demonstrate a relationship between cumulative dose and the occurrence of the event, e.g., liver fibrosis and cirrhosis with methotrexate, and the possibility of using cumulative dose as a predictor should be considered with drugs that are used chronically.

Explorations for Time Dependency for Adverse Findings :

There are two ways in which time needs to be considered in assessing adverse findings, i.e., time to onset of the finding (as noted under dose dependency above) and duration of the finding.

Time of Onset

While many adverse events occur early in treatment, others may occur only after some delay of weeks, months, or even longer. A crude incidence (number of patients having the experience/number exposed) may sufficiently characterize adverse event rate for the early occurring events. For late occurring events, a life table approach giving cumulative incidence, i.e., adjusted for duration of exposure, provides a more accurate characterization of rate. An alternative approach to adjusting for duration of exposure is to express rate in terms of person-time[11]. Using overall person-time as the denominator is useful only when one can assume that the hazard rate is constant over time. A modification of this approach that permits one to look at time of onset (i.e., hazard rate) is to look at rates stratified by time. While it is not necessary to express rates for all adverse findings as cumulative incidence or hazard rates, these approaches should be considered for important adverse events that occur later in treatment.

Duration of Adverse Event

A second time issue that it is often useful to consider is the duration of an adverse event. Certain adverse events that occur during initiation of treatment may appear to diminish with continued use. There are several possible explanations for this finding, including what might be considered adaptation or tolerance, or simply decreased reporting of the event even though it is still present. Of course, any particular adverse event may not in fact be causally related to taking the drug, even though there may appear to be a causal relationship.

For drugs typically used chronically, it may be useful to try to characterize and quantify the process of adaptation. There isn't any completely satisfactory approach to address this question,

[11]Person-time is duration of exposure summed across all patients, e.g., 2 patients each exposed for 6 months = 1 patient-exposure-year.

since patients often drop out for these same events, thereby diluting the originally randomized samples. However, one approach would be to identify cohorts of patients who experience events of interest during the first week of observation and who are then able to remain in the trial to completion, despite the occurrence of the event during initial treatment. These completer drug cohorts could be compared to completer cohorts of placebo patients who also experienced that event at baseline, hopefully to distinguish real adaptation from regression to the mean, since, as noted above, not all reported events in drug treated patients are in fact drug-related. The same approach could be taken for adverse events occurring later in treatment.

An alternative approach might be to simply describe what happened to patients who experienced a particular event, e.g., some drop out for the event, some continue despite having the event and either have it or don't at later time points.

It would probably be sufficient to do such analyses for a limited number of adverse events, e.g., one might focus on events considered to be common and likely drug-related using the rules suggested later under Adverse Event Tables (8.1.5.4).

While it is potentially clinically useful to have information on the time course of certain adverse events, it should be acknowledged that it is difficult to obtain good data pertinent to this question, and it is best to proceed cautiously.

Explorations for Drug Demographic Interactions:

The sponsor should generally have included in the NDA pharmacokinetic data pertinent to age and gender interactions, and these data should have been briefly summarized earlier in the Pharmacokinetics section (see section 6.0). The NDA should also have included some analyses on the incidence of adverse events and other adverse findings on the basis of age, gender, and race, if feasible.

The best way to compare subgroups for an adverse event of interest is not well-defined. The evaluation can focus either on relative risk (RR) [cumulative risk on drug/cumulative risk on comparison drug or placebo] or on attributable risk (AR) [cumulative risk on drug - cumulative risk on comparison drug or placebo]. Especially if background rates for the adverse event differ for subgroups, the RR analysis may be the best way to begin since this kind of analysis addresses possible differences in causality based on subgroup. [12] On the other hand, the absolute rate estimates the risk the patient should experience, so that there is also reason to compare absolute

[12]While public health impact is directly reflected by the AR and not the RR, focusing on RR differences may be more efficient than that of AR. Such focus can be justified because clinically and statistically significant variation in RR may be a stronger argument of causality, because it is more difficult to statistically evaluate the homogeneity of the AR, and because, in most situations where there is significant variation in RR across a patient characteristic, there is also significant variation in AR.

subgroup incidence. Thus, it may be appropriate to use both approaches.

If one were interested in exploring differences in causality for the adverse event 'nausea' for males vs females, one might explore a pool of short-term placebo studies of similar design. It would be important to first consider the poolability of the studies with regard to the event 'nausea,' as discussed above. The next step would be to explore for subgroup differences for this event. Initially, one might calculate risk ratios (drug to placebo) for each subgroup, i.e., RR_f and RR_m. The ratio of the risk ratios, i.e., RR_f/RR_m, would give some insight into possible gender differences in the effect of the drug on nausea. A test of the heterogeneity of the risk ratios by subgroup, e.g., Breslow-Day, would be an analytical approach to testing for a subgroup difference for this event. One could then also provide the AR for each of the subgroups, however, this would be descriptive only.

It would not likely be feasible or useful to explore for gender interactions for all adverse events. One strategy for narrowing the focus might be to limit such analyses to those considered common, e.g., occurring at an incidence of at least 2%, plus any other events of particular interest.

The same approach could be used for exploring for possible age and race differences. Some standardization is needed regarding what age categories should be looked at.

True differences in adverse event rates on the basis of demographic subgrouping may be the result of pharmacokinetic or pharmacodynamic differences, or both. For important events with such demonstrated differences, it may be useful for the reviewer to attempt to explain, if feasible, such differences on the basis of whatever pharmacokinetic data are available.

Explorations for Drug Disease Interactions :

The sponsor should generally have done some formal pharmacokinetic studies in patients with hepatic and renal disease, and the results of these studies should have been briefly summarized under the pharmacokinetic summary (see section 6.0). However, the clinical reviewer should be alert to the appearance of such interactions during phase 2-3 studies as well, and it may be useful for the review to consider both pharmacokinetic and pharmacodynamic differences as explanations for observed differences in adverse event rates for subgroups on the basis of comorbid diseases. In general, the same methods described for exploring drug demographic interactions can be applied here.

Explorations for Drug-Drug Interactions :

The sponsor should generally have done some formal drug interaction studies, and the results of these studies should have been briefly summarized under the pharmacokinetic summary (see section 6.0). However, the clinical reviewer should be alert to the appearance of such interactions

during phase 2-3 studies as well, and it may be useful for the review to consider both pharmacokinetic and pharmacodynamic differences as explanations for observed differences in adverse event rates for subgroups on the basis of coadministered drugs. In general, the same methods described for exploring drug demographic interactions can be applied here.

Subsections of the Integrated Safety Review

The first subsection (8.1) is primarily focused on methods. 8.1 should give an overview of what assessments were done in the development program and what data were available for review (tables, graphs, other displays, line listings, analyses, etc.). As discussed in more detail later, some of these standard tables, displays, etc. may be usefully included as appendices to the review. These materials are useful by themselves for answering many standard questions that are frequently asked of NDAs, e.g., how many deaths overall, but are also important from a reviewer's perspective since they signal events that need greater scrutiny, and they serve as the starting material for more in depth explorations of the data.

There is an enormous amount of data available in a typical NDA, and the reviewer needs to sift through this mountain of information to decide what to focus on for the review. It may be useful for the reviewer to explain in subsection 8.1 what strategy was used in selecting the materials explored in depth and to describe the methods used for such explorations, e.g., further data analyses, individual case explorations.

[**Note:** It may be particularly helpful to have well worked up examples of further explorations for signals that commonly occur in premarketing databases, e.g., neutropenia, hepatotoxicity. What needs to be routinely done to work up such findings?]

In general, the specific adverse events themselves, including discussions of individual cases, along with the results of data analyses and discussions regarding patient factors (age, sex, race, concomitant disease, etc.) or drug factors (dose, plasma level, duration of treatment, concomitant medication, etc.) that may help in predicting the occurrence of adverse events should be included under the appropriate parts of the second subsection, i.e., the Review of Systems (8.2). This subsection is the place for the reviewer to record (1) judgements about the adequacy of the assessments, and (2) adverse findings observed, along with discussion, interpretation, and judgements about causality. It is organized by body systems, since this is a logical and convenient way to think about adverse findings, and one that is very familiar to physicians.

The last subsection of the Integrated Safety Review (8.3) is intended as a place for the reviewer to summarize the key adverse events that are important to consider in the overall risk/benefit decision and in writing labeling for the new drug. It is critically important to have a review document that facilitates the drafting of rational labeling for a new drug product, and the primary rationale for the Review of Systems approach is to meet that need.

Identifying and Assembling Source Materials for the Safety Review

A final point for the reviewer to consider before beginning the safety review is how to identify and assemble the available materials for the review. This process may be greatly facilitated if the NDA is well indexed, and may be even further enhanced by the availability of a good CANDA. Many of the standard tables and displays focusing on grouped data that are useful in safety reviews may be described and discussed in later sections of this document. It is also especially important for the reviewer to know what individual patient information is available and how to access it. Sponsors of NDAs should provide CRFs for all deaths and adverse dropouts, i.e., patients discontinuing from studies because of the occurrence of adverse events. Narrative summaries are also generally provided for deaths, other serious adverse events, and adverse dropouts. In addition, sponsors often provide individual displays of safety information by patient for selected patients (see Attachment H for an example of a format for a particularly useful individual patient safety data display). It is critical for the reviewer to be able to easily access individual patient information, whether the information is provided in hardcopy or in electronic format. For hardcopy submissions, an index that directs the reviewer to the exact location (volume and page number) of the CRF, the narrative summary, and the individual patient safety data display is essential (for sample index see Attachment I).

8.1 Background and Methodology for Safety Review

8.1.1 Deaths

Generally it may be useful to address in this section all deaths that occurred in the sponsor's development program, aggregated over all studies, as well as any other deaths reported from secondary sources, including post-marketing reports. Exceptions to this general approach might be NDAs including studies in which mortality is the endpoint or which focus on diseases with high expected mortality. All deaths should be counted, regardless of the investigator's or the sponsor's judgement about causality, including: (1) any deaths occurring during participation in any study, or any other period of drug exposure, (2) any deaths occurring after a patient leaves a study, or otherwise discontinues drug, whether prematurely or after completion to the nominal endpoint, if the death is (a) the result of a process initiated during the study or other drug exposure, regardless of when it actually occurs, or (b) occurs within 4 weeks of a patient leaving a study or otherwise discontinuing drug, or longer for drugs with particularly long elimination half-lives or from drug classes with known late occurring effects, e.g., nucleoside analogs, vaccines, gene therapies, or stem cell transplants.

These deaths should be summarized, preferably in an appendix table, as illustrated in Attachment J - Table 8.1.1.1. Often the sponsor should have provided a line listing of all deaths aggregated over the development program, plus any deaths from other experience, and this listing can generally be attached with little or no editing. It may be useful to distinguish between those

clinical trials deaths for which exposure data are available and those for which such data are not available, e.g., late occurring deaths for which the exposure data were collected but are not yet available and postmarketing deaths for which exposure data may never be available.

The reviewer should provide a judgement for each death regarding whether or not it can be reasonably considered drug related. Any such cases for which the answer is yes, a discussion should be held. It is crucial not to accept too quickly the conclusion that a death represented an intercurrent event. While such things occur, especially in older patients, in any given database of, say 2000-3000 patients, there would not be expected to be deaths of an unusual nature. Each such death should be specifically considered for the possibility that it represents an as yet unsuspected effect of the drug. The need to review deaths closely is recognized in the NDA regulations; CRFs and narrative summaries for patients who die are automatically submitted.

The judgements about which deaths can and cannot be considered drug related, and the detailed discussions of those considered drug related, should be included under the appropriate subsections of the Review of Systems. Sorting the cases into body systems regarding primary cause of death may need a judgement in each case on the part of the medical reviewer. Of course, to some extent, this classification is arbitrary, and some cases may need to be discussed under several body system categories, e.g., a patient who develops hepatic failure that is judged to be drug related but then dies from a myocardial infarction would be discussed primarily under the GI system, but would be noted as a cardiovascular death as well under the Cardiovascular System. Wherever each such case is primarily discussed, the reviewer should identify the materials utilized in reviewing the case, e.g., CRF, narrative summary, hospital records. Deaths deemed to be coincidental need only be mentioned under the appropriate body system category, and generally need not have any discussion, e.g., a patient who dies of a cancer that was present prior to entry into a study of an antidepressant.

Apart from analysis of individual cases, it may also be useful to examine overall mortality for all phase 2-3 exposures, across treatment groups, correcting, insofar as possible, for differential duration of exposure[13]. If there are sufficient deaths due to specific causes, it may be useful to look at cause specific mortality as well. Correcting for differential exposure can be done only for those deaths for which person-time data are available. However, before conducting any mortality analyses, the reviewer needs to consider the poolability of the data pertinent to deaths. If these data are not poolable, analyses may be conducted for separate databases. It may be useful to present both crude mortality and mortality expressed in person-time in an appendix table [for sample display see Attachment K - Table 8.1.1.2] . Life table approaches may be helpful in cases where there are more than a few deaths. Ideally, one would have mortality data from other databases, e.g., other drugs in the same class, for comparison, especially if rates appear

[13]Since placebo and active control patients may generally have had shorter durations of exposures, they may have had less opportunity for serious events to have occurred.

worrisome[14].

Other issues identified above under "Methodological Issues," i.e., dose response, time-dependency, and also drug-demographic, drug-disease, and drug-drug interactions, should all be addressed where feasible with regard to overall mortality and for any instances of cause specific mortality that are judged to be drug related. The results of such special analyses for cause specific mortality should be included under the appropriate subsections of the Review of Systems, however, the basis for doing such analyses and the approach used should be described in this section.

8.1.2 Other Serious Adverse Events

Sponsors generally provide a line listing of all patients in the phase 2-3 program meeting FDA's criteria for having had a "serious" adverse event, regardless of the investigator's or sponsor's causality judgement and regardless of whether or not the event led to discontinuation [see Attachment M - Table 8.1.2.1] . The definition of *serious adverse event* includes the following: fatal; life threatening; permanently disabling; leading to hospitalization; cancer; overdose; congenital anomaly[15] [21 CFR 314.80(a)]. Serious adverse events may, in addition to signs, symptoms and diagnosable events, include changes in laboratory, vital signs, ECG, or other such parameters that are of sufficient magnitude to meet the above definition of being serious. Sponsors often expand this definition to include other events that investigators have considered serious, even if they did not technically meet FDA's or ICH's definition, e.g., patients who had seizures, whether or not they led to hospitalization.

It is useful to have a serious events line listing, since it collects in one place all patients who have had an important adverse clinical event. Deaths may or may not be included in this list, but in any case are listed separately (see Deaths above). Even if the list doesn't include deaths, it should include serious adverse events temporally associated with or preceding death. This list may overlap extensively with the list of adverse dropouts, however, it is not identical. Many patients dropping out for adverse events do not have "serious events," and not all patients having "serious" events drop out.

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[14]Having comparison data proved helpful in evaluating sudden unexplained deaths in patients treated with two seizure drugs, gabapentin and lamotrigine (see Attachment L - Table 8.1.1.3) .

[15]A recent International Conference on Harmonisation guideline (*Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*; March 1, 1995) provides a slightly different definition of serious event that includes events prolonging hospitalization, but does not include cancer or overdose. Ultimately, FDA intends to adopt the ICH Steering Committee's guideline definition and to amend its regulations to fully implement the guideline. Until such time as the Agency's regulations are amended, the existing regulations should be followed.

One potential flaw in such lists is that there are no objective definitions of what is meant by "serious." For example, "life threatening, permanently disabling, etc." are, to a degree, a matter of judgement. The reviewer should attempt to clarify how such lists were created, by whom, and by use of what criteria.

This section of the review may simply note how many patients were identified as having one or more "serious" events for each of the treatment groups, and give an overview of the types of problems identified (e.g., how many strokes, MIs, suicides). As for deaths, discussions of specific serious events judged to be drug related and patients having those events should be included under the appropriate subsections of the Review of Systems. Again, the reviewer should identify other materials utilized in the review of individual cases, e.g., CRFs, narrative summaries, hospital records. Serious events considered unlikely to be drug-related generally need only be mentioned under the appropriate subsections of the Review of Systems.

The issues identified above under "Methodological Issues," i.e., poolability, dose response, time dependency, drug-demographic, drug-disease, and drug-drug interactions, should all be addressed where feasible with regard to any serious events that are judged to be drug related. The approaches used in conducting these additional explorations should be described here, however, the results of such explorations should be included under the appropriate subsections of the Review of Systems.

8.1.3 Dropouts and "Other Significant Adverse Events"

A recent ICH guidance (Guideline on Structure and Content of Clinical Study Reports; 7-17-96) defines a new category of "Other Significant Adverse Events" to include adverse dropouts and also potentially important abnormalities not meeting the above definition of serious and not leading to death. These include (1) marked abnormalities in laboratory, VS, ECG, or other such parameters, presumably not enough to be considered serious, and (2) adverse events or laboratory changes that led to dose adjustment, or to the addition of concomitant therapy.

If the sponsor has included listings for "Other Significant Adverse Events," these may be described here, under a separate subsection. The reviewer should also note that marked laboratory changes may be described under laboratory, VS, and the later sections addressing such changes should suffice for these parameters.

8.1.3.1 Overall Profile of Dropouts

In may be useful for the review to include appendix tables enumerating dropouts by reason for the overall phase 2-3 study pool, and also for other clinically relevant study pools, e.g., all placebo controlled trials [see Attachment N - Table 8.1.3.1.1]. The basis for selecting any particular study pools needs to be addressed here. These should be mutually exclusive displays in which individual

patients are counted only once. Often the sponsor may have provided tables of this design, and these can be attached to the review with little or no editing.

Patients are generally classified with regard to reason for withdrawing from a trial, e.g., adverse event, lack of effect, administrative, loss to follow up, by the individual investigators, and in some instances patients may be reclassified by sponsors. It is useful for the reviewer to determine and indicate in the review how and by whom such classifications were accomplished. In some cases, the reviewer, upon reviewing the CRF, may have a different view regarding how certain patients should be classified. While generally these classifications are accepted as reasonably valid, if there is a concern, the reviewer may find it is necessary to reclassify dropouts. In any case, it is often useful to collapse certain categories, e.g., combining patients categorized as dropping out for intercurrent illness along with patients categorized as dropping out for adverse drug reactions under the general category of dropouts for adverse clinical events, since this category is neutral from the standpoint of causality judgement and it is often very difficult to make such distinctions. Examining this table may be useful in identifying problems with study conduct, e.g., a substantial number of dropouts due to loss to follow up should be a signal of concern. It may also signal analytic difficulties; e.g., early dropouts in general and differential early dropouts often present difficulties in the effectiveness analysis, could suggest breakdown of blinding. In any case, such deficiencies need to be noted and discussed by the reviewer.

8.1.3.2 Adverse Events Associated with Dropout

This section focuses more specifically on the adverse dropouts, i.e., those patients identified in the previous section as dropping out in association with an adverse event, regardless of whether or not attributed to drug exposure. The adverse dropouts are particularly important in the safety assessment of a new drug. First, they include the patients who found the adverse effects of the drug intolerable, even in a clinical trial context, where patients are probably inclined to "stick it out." The frequency of this occurrence is important information for the prescriber and can be important in choosing dose, selecting a method of titration, etc. Second, and this is the reason CRFs of all adverse dropouts are provided automatically, these events may be a clue to an unexpected but important adverse effect of the drug, such as sclerosing illnesses, liver or kidney diseases. The reviewer needs to consider for each adverse dropout that is not due to a known effect of the drug, whether it might reflect such an unexpected effect of the drug. In general, an assessment of the events described in the CRF should be conducted. Particular care needs to be given to avoid glib dismissal of events as intercurrent illness.

Generally the sponsor may have provided a line listing of all adverse dropouts aggregated across phase 2-3 studies, and this document should be a primary resource for identifying the specific patients to review in greater detail as illustrated in Attachment O - Table 8.1.3.2.1 . The tables of adverse events associated with dropouts (described in the next paragraph) are another resource for identifying specific adverse events to explore in greater depth. It may be useful for the reviewer to identify what additional materials were examined for those specific patients looked at

in greater detail, e.g., narrative summaries, CRFs, hospital records. As for deaths and serious events, the detailed discussions of specific events judged to be drug related causes of dropout and of the patients experiencing those events should be included under the appropriate subsections of the Review of Systems, rather than in this section which is intended to give an overview of dropouts and the methods used in exploring them.

It may be useful for the review to include, as appendices to this section, tables that provide the incidence of dropout for those specific adverse events that are associated with dropout, again for whatever pool or pools of studies that are considered useful to explore [see Attachment P - Table 8.1.3.2.2]. The review needs to address the basis for whatever study pools are utilized in this exploration. Unlike the table in section 8.1.3.1, these would not be mutually exclusive displays, since individual patients may have experienced more than one event that led to dropout. This information may provide the basis for a subsection of the Adverse Reactions section of labeling addressing dropouts for adverse events.

It may be useful for the reviewer to determine and discuss how these tables were created. If investigators identify one or more adverse events that led to dropout for a particular patient who withdrew, these tables would represent the actual incidence of specific adverse events that led to dropout. However, if, as is often the case, the events in the table represent all the adverse events that were simply present at the time of dropout, and not specifically identified as causing dropout, the table has a somewhat different meaning. The reviewer should state in the review which of these different approaches was used.

The issues identified above under "Methodological Issues," i.e., dose response, time dependency, and also drug-demographic, drug- disease, and drug-drug interactions, should all be addressed where feasible with regard to any instances of cause specific discontinuation that are judged to be drug related and of particular interest. The approaches used in conducting these additional explorations should be described here, however, the results of such explorations should be included under the appropriate subsections of the Review of Systems.

8.1.3.3 Other Significant Adverse Events

[**Note**: If information has been provided on adverse experiences, including laboratory, vital sign, etc. abnormalities, that led to dose reduction or significant additional concomitant therapy, those findings should be described here, using approaches similar to those proposed above for adverse dropouts.]

8.1.4 Other Search Strategies

In addition to deaths, adverse dropouts, and patients experiencing serious adverse events, it may be useful to utilize other specific search strategies to identify patients meeting certain pre-defined

criteria for detecting adverse events that may be expected for a drug of a particular class but are not easy to detect, e.g., serotonin syndrome. In these cases, algorithms may be constructed involving combinations of clinical findings that may be a marker for the occurrence of such events in the database. When such algorithms are used, they should be described in this section. Generally such searches should be done blindly to avoid bias in identifying cases. It may be useful to discuss the results of such searches in the appropriate subsections of the Review of Systems.

8.1.5 Adverse Event Incidence Tables

NDAs typically include numerous tables providing adverse event incidence, for individual studies, for various pools of studies, and for the database overall. The basic rule generally used in developing these tables is to count treatment emergent signs and symptoms (TESS), i.e., those signs and symptoms that emerged for the first time on assigned treatment, or if present at baseline, occurred at a greater severity on treatment than at baseline. These data are useful in establishing the common adverse event profile for the new drug, and the reviewer has several tasks as part of this overall goal in discovering this adverse event profile. One task is to evaluate the sponsor's coding of investigator terms into preferred terms. A second task is to choose among the numerous tables those that may be the focus of the review and that may be the basis for tables to incorporate into labeling. A related task is to choose a method for identifying those adverse events that may be considered common and drug related, i.e., the common adverse event profile to highlight in labeling. Once the reviewer has developed a list of common and drug related events to focus on, it may be useful to conduct secondary analyses, i.e., for dose dependency, time dependency, and for drug-demographic, drug-disease, and drug-drug interactions. Finally, for certain adverse events of particular interest, it may be useful for the reviewer to examine individual cases to attempt to characterize the events in greater detail.

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

Adverse event data are elicited either with open-ended questions or by checklists with varying degrees of specification. In either case, the result is a data set consisting of investigator and patient descriptors for adverse clinical experiences. It may be useful in this section for the reviewer to describe and summarize briefly what the approach was in the development program to eliciting and collecting adverse event data and how frequently patients were assessed during clinical trials. Rather than providing detailed comments for each of the many studies, it is preferable to find a way to generally summarize the approach for the development program overall.

8.1.5.2 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

These investigator and patient descriptors for adverse clinical experiences are generally categorized by sponsors using some standard thesaurus, e.g., COSTART, prior to creating adverse event incidence tables. Adverse event tables in the Integrated Safety Summary are constructed with preferred terms, however, the reviewer can find tables based on investigator terms in the individual study reports. In addition, sponsors are being asked by some divisions to provide a comprehensive line listing of all adverse events aggregated across all phase 2-3 studies that includes a column for the investigator term(s) coded under the preferred term for each event reported [see Attachment Q - Table 8.1.5.2.1 for sample listing] . Sponsors also generally include listings of investigator and patient terms subsumed under the preferred thesaurus terms in the NDA, i.e., the sponsor's dictionary (see Attachment R - Table 8.1.5.2.2 for sample listing) , and it is useful for the reviewer to examine these listings to assess both the preferred terms used and the sponsor's approach to categorization.

The preferred terms may be examined to determine the following: (1) Are there terms that are too narrow, resulting in an underestimation of the true incidence for a particular event (e.g., somnolence, drowsiness, sedation, and sleepiness)? Are all such events subsumed under a common preferred term, or grouped for analysis? (2) Are there terms that are too broad or over inclusive, so that important events that need to be looked at separately are mixed in with less important events, e.g., are loss of consciousness or syncope subsumed under hypotensive events? (3) A related concern is the use of completely meaningless terms (e.g., mouth disorder, tooth disorder, GI disorder) that occur in COSTART; for such terms, it may be necessary to sort out the individual events that are included and express the incidence for those events separately.

The reviewer also needs to consider the sponsor's coding practices. It is important to recognize that a system like COSTART is simply a list of preferred adverse event terms, and not a dictionary. Sponsors use such lists to code adverse event data in whatever manner appeals to them. Consequently, the reviewer needs to evaluate their coding approach with regard to the continuum of being excessively narrow or broad. Are they unnecessarily conservative in deciding what to subsume under a particular term, or too over inclusive? For example, if a sponsor includes any instance of loss of consciousness under the term seizure, they may over estimate the incidence for true seizures, while if they are too conservative in deciding what to include, they may under estimate the incidence for this event. In other instances, they may simply be wrong in what they include under particular adverse event terms.

Obviously, it may not be possible to evaluate all or even most adverse event terms in this much detail. However, the review should comment on how this issue was addressed.

8.1.5.3 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

Labeling typically includes one or more tables of adverse events occurring at an incidence of at least 1% or some other threshold value. Clearly these threshold values are arbitrary and an

argument can be made for a variety of values that might be selected. The relevant tables, whether from individual trials or from pools of relevant studies, that the reviewer thinks may be useful for characterizing the drug's adverse event profile may be included in the review, preferably as appendices [see Attachment S - Table 8.1.5.3.1] . The issue of poolability is important to consider here, and the review should comment on how this concern was addressed.

These tables should include incidence data for the NDA drug, active controls, and placebo, if included in the design. Since investigators are often asked to rate patients with regard to severity of the event, it may be useful to consider displays that distinguish between events on the basis of severity. Investigators may also be asked to make a causality judgement about the adverse events reported, and it may be useful to have separate displays for the data on the basis of causality judgements by investigators. A typical display, for example, one often used in labeling, is of all events considered to be at least "possibly" related to the drug.

It is important to acknowledge certain weaknesses in these data. For most adverse event tables, an event is considered to have occurred for a patient whether it occurred one time or many times during an observation period, e.g., during an 8-week study. Thus, no distinction is made between a patient who has one such occurrence and one who has had multiple such occurrences. It should also be noted that these standard tables may be derived from a relatively small proportion of the total number of patients exposed to a drug during a development program.

For more common reactions, the advantages of basing tables on controlled trials may often outweigh the loss of numbers. For less common events, particularly those that are serious, the larger database may be needed, even if there is no useful concurrent control. It is, of course, this larger database in which one finds the relatively rare events of significant concern.

[**Note**: The guidance in the following paragraph regarding a phase 2-3 adverse events table can be added as footnotes to the table template when it is prepared. See labeling guidance for additional details on this table.]

It may be useful for labeling purposes to note the occurrence of adverse events over the entire phase 2-3 database, particularly for adverse events not already adequately characterized in the adverse event tables described above. This is often a very heterogeneous database, including much uncontrolled exposure for varying durations and at varying doses. Consequently, it is not possible to assess causality and it may be sufficient to present these data in gross categories of incidence rather than providing actual estimates for each event. For example, it may be sufficient to categorize these events by body system and list them in order of decreasing frequency according to the following definitions: frequent $\geq$ 1/100; infrequent 100 - 1/1000; rare, 1/1000 (see Attachment T - Table 8.1.5.3.2 for sample table) .

8.1.5.4 Identifying Common and Drug-Related Adverse Events

It may be useful to identify from these tables adverse events that can be reasonably considered common and drug related. One approach to identifying possibly drug-related events would be to do hypothesis testing on the data, e.g., using Fisher's Exact Test, but this ignores the great multiplicity involved in these analyses and, realistically, most of these "analyses" should be considered "descriptive." What makes them most persuasive is consistency across studies and, where this occurs, evidence of dose response. An alternative approach sometimes employed is to use a more informal rule, e.g., considering adverse events that meet the following criteria to be common and drug related: those occurring at an incidence of at least 5% for patients assigned to the NDA drug and for which the NDA drug incidence is at least twice the placebo incidence.

8.1.5.5 Additional Analyses and Explorations

Additional analyses should be done for some subset of the adverse events, e.g., one might focus on those identified as common and drug related by the above rule. Explorations for dose dependency should generally be limited to fixed dose studies. Explorations regarding time of onset generally need to be done only for events for which there is an indication of a delay in time to onset. Explorations for adaptation might be done for common and troublesome adverse events (e.g., somnolence, nausea) to try to develop potentially useful clinical information on the time course of such events. Explorations for demographic interactions are needed at least for the more common and important adverse events. Explorations for drug disease and drug-drug interactions should be done if there is a strong signal for an interaction or a good rationale for expecting an interaction.

In addition, it may be useful for the reviewer to selectively explore certain adverse events in an attempt to better characterize them. For example, if rash appears to be a drug related event, the reviewer may want to look more closely at individual cases of rash. Those patients who dropped out for rash or who were considered to have a serious event can be found in the respective line listings for such events. However, one may want to look at the other cases of rash as well. As noted earlier, a valuable resource for such a search is a line listing of all adverse events across the entire phase 2-3 database, especially if sorted by adverse event, since one can find all the cases in one place in the list.

As noted earlier for deaths, adverse dropouts, the results of these additional analyses should not be included in this section, but rather, under the appropriate subsections of the Review of Systems. However, the reviewer should mention here and describe what additional analyses and explorations were done, with a reference to the later sections for the results and interpretation.

8.1.6 Laboratory Findings

Laboratory findings (chemistry, hematology, and urinalysis) are generally available from a diverse array of clinical trials varying in dose, duration, population studied, controls. The review

approach suggested here is generally similar to that suggested for the other categories of safety data, i.e., describe what is available for review and provide a rationale for what was selected for more in depth review. This section should be primarily a methodology section, giving an overview of laboratory data and describing the more detailed analyses and explorations done for findings of particular interest. The results of these more detailed explorations should be included under appropriate subsections of the Review of Systems.

8.1.6.1 Extent of Laboratory Testing in the Development Program

Here the reviewer should provide an overview of what laboratory testing (chemistry, hematology, and urinalysis) was done in the development program. Details should be provided on what was planned (what tests, at what frequency, etc.) and what was accomplished. It would be useful to describe the procedures utilized for following up on abnormal values, e.g., were patients always followed until the values normalized, were any patients rechallenged? Also, what was the procedure for getting samples analyzed, e.g., were central or local labs used? Rather than providing detailed comments for each of the many studies, it is preferable to find a way to generally summarize what the plan was for laboratory testing. It would be helpful to have a summary table that provides accurate numbers for how many patients exposed to test drug actually had baseline and follow up assessments (1 or more) for all the different assessments done, e.g., of 3000 patients exposed to new drug, how many had a baseline and at least one follow up ALT? (See Attachment U - Table 8.1.6.1.1 for sample table) .

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

Controlled comparisons are often the best source for deciding whether or not there is a signal for a finding that is worth exploring in greater depth. As noted, a typical NDA often contains multiple controlled trials, and a reviewer needs to decide where to focus in order to obtain the kind of overview that these data provide. If there are placebo controlled trials, one approach might be to focus on these trials for this comparative view. It is important to consider poolability issues in deciding what studies to specifically consider. This subsection should provide details on the decision making in regard to the selection of study subsets for review.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

This subsection should address the standard approaches used in analyzing and exploring laboratory data. The first two parts to this section should focus on approaches to comparative trials data, and the third part on dropouts is intended to refer to the entire phase 2-3 experience.

For the comparative trials data, it is recommended that p-values be obtained for most of these analyses, even if there is the obvious problem of multiplicity. This exercise should not be thought of as hypothesis testing, but rather as descriptive.

8.1.6.3.1 Analyses Focused on Measures of Central Tendency

Unlike the generally discrete and qualitative sign and symptom data found in typical adverse event tables, much of the laboratory data are continuous and lend themselves to parametric analyses. It is common practice to compare mean or median changes from baseline across treatment groups for such data, and this section of the review should include some findings from relevant analyses of drug effect on central tendency. From the standpoint of safety, the outliers are generally of greater interest. However, there are times when a potentially important effect is revealed only in analyses looking at differences in mean change from baseline. For example, several psychotropic drugs have been shown to be associated with decreases in serum uric acid, within the normal range, but to a degree that raises a concern about the possible consequences of this mild uricosuric effect in more vulnerable populations (see Attachment V - Table 8.1.6.3.1.1) .

It may be useful for the reviewer to include as appendices tables providing data on central tendency [see Attachments W, X, and Y - Table 8.1.6.3.1.2, Table 8.1.6.3.1.3, and Table 8.1.6.3.1.4]. Detailed discussion is not needed at this point, but rather, the reviewer should simply note what signals emerged from these tables for further exploration.

8.1.6.3.2 Analyses Focused on Outliers

Outliers on laboratory parameters, i.e., patients whose values deviate substantially from the reference range, may be of particular clinical interest, and the sponsor should have included some tables, displays, and analyses that are designed to detect outliers. It may be useful for this section of the review to provide, as appendices, findings pertinent to outliers. The relevant data for this section would come from shift tables, scatter plots, box plots, cumulative distribution functions, and tables providing incidence of patients across treatment groups who met criteria for having gone from relative normality at baseline to a potentially clinically important deviation from normality on one or more laboratory parameters at some time on treatment [see Attachments Z, AA, and BB - Tables 8.1.6.3.2.1, 8.1.6.3.2.2, and 8.1.6.3.2.3] .

Since it is not possible to know in advance what criteria are optimal for detecting between group differences, it may be useful to look at and compare across treatment groups distributions of data in addition to proportions meeting some arbitrary criteria (see Attachment CC - Table 8.1.6.3.2.4 for sample display). In addition, it may be useful to look not only at patients with values outside the normal reference ranges, but possibly also at patients with large shifts within the reference range. It may also be useful to look at patients who meet criteria for being outliers on more than 1 variable simultaneously, e.g., transaminases and bilirubin.

Detailed discussion of the findings resulting from such exploration is unnecessary in this section of the review. As for analyses of central tendency, these analyses of outliers should serve as a source of signals for events to explore in more depth. The results of these explorations, including

discussions of individual cases, should be included under the appropriate subsections of the Review of Systems.

While the focus in this discussion has been in looking at grouped data, selected individual patients with changes of potential importance need to be looked at in detail. To facilitate this effort, it is useful for the sponsor to provide a list that identifies patients meeting one or more of the PCS criteria and indicates which of the criteria have been met [see Attachment Table DD - Table 8.1.6.3.2.5].

8.1.6.3.3 Dropouts for Laboratory Abnormalities

Discontinuation for a laboratory abnormality may be considered a marker of possible clinical importance of the finding, and it may be useful for the reviewer to compare treatment groups for relevant study pools on rates of discontinuation for certain laboratory abnormalities. Given the potential importance of looking at dropouts for laboratory changes, this exploration should extend beyond the controlled trials data to the entire phase 2-3 population. Once these cases are identified, it may be useful for the reviewer to examine and comment on each individual patient identified as dropping out for any significant laboratory abnormalities. Even isolated marked abnormalities, e.g., of liver function, WBC count, may signal major problems. The results of these explorations of individual cases should be included under appropriate sections of the Review of Systems.

8.1.6.4 Additional Analyses and Explorations

As for the other categories of safety data, 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. This section should provide the rationale and specifics of whatever additional analyses were done, however, results that are generated should be included under the appropriate subsections of the Review of Systems.

8.1.7 Vital Signs

An essentially identical approach to that taken for laboratory data can be applied to vital signs data [see Attachments EE and FF - Tables 8.1.7.1 and 8.1.7.2] .

8.1.8 ECGs

Similarly, an essentially identical approach to that taken for laboratory data can be applied to ECG data [see Attachments GG and HH - Tables 8.1.8.1 and 8.1.8.2] .

8.1.9 Special Studies

Not uncommonly, studies may be done to explore for certain pharmacological effects that may be expected because of a drug's membership in a particular class of drugs. For example, special studies are often conducted with benzodiazepine hypnotics to look at effects on respiration, memory, next day psychomotor functioning. This subsection should describe any special studies conducted to address these kinds of concerns. However, any pertinent findings from these studies should be included under the appropriate subsections of the Review of Systems.

8.1.10 Withdrawal Phenomena/Abuse Potential

While special studies focusing on abuse potential and withdrawal phenomena are generally done only for certain drug classes, e.g., sedative/hypnotics and anxiolytics, the question of discontinuation emergent adverse events applies to drugs more broadly, and thus, this subsection may be appropriate for a wider variety of drug classes. It may be useful for the reviewer to discuss the sponsor's approach to this issue, e.g., was there a specific prospective effort to detect withdrawal emergent signs and symptoms during drug taper or following discontinuation, or was it more of a post hoc effort to gather whatever data were available for patients during taper or following discontinuation. Since withdrawal symptoms, if they occur, may include several body systems, it would be reasonable to give an overview of any such findings in this section. However, any major withdrawal effects, e.g., seizures, should also be noted under the appropriate subsections of the Review of Systems.

8.1.11 Human Reproduction Data

Typically there is little or no human reproduction data in most drug development programs. In the event there are no data, that fact should be acknowledged in this subsection. However, it is not uncommon for a few pregnant women to have inadvertently been exposed to a new drug during development, and for completeness, that experience should be summarized here. Whatever data might be available from secondary sources, e.g., post-marketing surveillance, should be summarized and discussed here as well. Any such findings should also be noted under the Genitourinary subsection of the Review of Systems.

8.1.12 Overdose Experience

From the standpoint of writing labeling, it is useful to have all the experience with human overdose for a new drug summarized in one place in the review. This subsection should summarize and discuss all the overdose data, whether it comes from the sponsor's development program or from secondary sources. Phase 1 data should be considered as a possibly useful source for data pertinent to overdose, since subjects may have received higher doses than those utilized in later phases of study. In addition, it may be useful to consider patients with certain

physiological differences that would compromise their ability to clear a drug, e.g., renally or hepatically impaired, or limited P450IID6 activity for a drug cleared by this isozyme, as a possibly useful source of data pertinent to overdose. A summary should be provided here of the constellation of signs, symptoms, and other abnormalities one might expect to see in association with overdose. In addition, any particularly remarkable findings not observed during dosing in the recommended range, e.g., QT prolongation may be observed only in association with overdose, should be noted under the appropriate subsections of the Review of Systems.

8.2 Review of Systems

As noted, section 8.1 is for describing what safety data were available for review, for providing a rationale for why the reviewer chose to focus on certain data in greater depth, and for describing what the reviewer's approach was to the more focused review. This section is for providing, within the structure of a review of systems, commentary on the adequacy of the safety evaluation pertinent to each body system and the detailed safety findings that may be the basis for a risk/benefit decision and labeling, if the drug is to be approved.

The following are the body systems proposed for the review of systems:

8.2.1 Cardiovascular
8.2.2 Gastrointestinal
8.2.3 Hemic and Lymphatic
8.2.4 Metabolic and Endocrine
8.2.5 Musculoskeletal
8.2.6 Nervous
8.2.7 Respiratory
8.2.8 Dermatological
8.2.9 Special Senses
8.2.10 Genitourinary
8.2.11 Miscellaneous

Initially, within each body system, the reviewer should comment on the adequacy of the development program in evaluating the new drug with regard to the body system in question. This gets at the question of whether or not "all tests reasonably applicable" were conducted to assess the safety of the new drug. Were all the appropriate animal tests done? Were all the appropriate clinical tests done? Were all potentially important findings adequately explored, e.g., to what extent was psychomotor impairment specifically assessed in a drug that is sedating? If not, this could be the basis for a non-approval action, or alternatively, a phase 4 study for additional testing.

Within each body system, the reviewer should then provide all findings pertinent to safety within that body system. This might include findings from animal studies, phase 1 studies, phase 2-3

studies, postmarketing reports, literature reports. It would be appropriate to include any clinical findings pertinent to that body system: deaths, adverse dropouts, serious events, labs, VS, ECGs, any other adverse events. The results of any supplementary analyses conducted for important events should be summarized here as well, e.g., analyses for dose dependency, time dependency, and various interactions (drug demographic, drug disease, and drug-drug).

Both events considered drug related and those considered not drug related should be included. This is the place for the reviewer to provide judgements about which events should be considered drug related (definitely, probably, or possibly) and which not. Obviously, the most detailed discussion would focus on important events considered drug related. However, one value of this approach is that it provides a structure for mentioning all other serious events considered not drug related, perhaps with explanations in some cases about why they are judged to be not drug related.

Clearly some clinical events may refer to more than one body system, e.g., some may be recognizable as syndromes manifested in several body systems, and in those instances, the reviewer needs to decide where to primarily include the event, with reference to this primary body system from the associated body systems in which the event should be more briefly mentioned.

There is an expanding checklist of adverse events that we now routinely think about when reviewing new drugs, e.g., sedation, anticholinergic effects, vasodilator effects, QT prolongation, tachycardia, beta agonist effects, hepatotoxicity, hematological effects, such as neutropenia. All of these standard concerns should be specifically addressed within the appropriate body systems.

It is critical for the reviewer, whenever describing events for a specific patient, to fully identify that patient (study #, investigator #, patient #, etc.) so that the reader can follow up the case if interested.

The following is a suggested organizational structure for the reviewer to utilize under each body system category, e.g., the structure for cardiovascular would be as follows:

8.2.1 Cardiovascular
8.2.1.1 Adequacy of Development Program in Assessing Cardiovascular Risk for New Drug
8.2.1.2 Cardiovascular System Adverse Events Considered Possibly, Probably, or Definitely Related to New Drug
8.2.1.3 Cardiovascular System Adverse Events Considered Unlikely to be Related to New Drug

The organization of the 8.2.*.2 subsections ordinarily would be on the basis of the important and drug related events in that body system for the new drug. Ordinarily the 8.2.*.3 subsections would consist of a list of serious adverse events that occurred in association with new drug use and are classified in that body system, but that are considered unlikely to be drug related. In certain instances, some explanation may be needed regarding why the events are considered not

likely drug related.

8.3 Summary of Key Adverse Findings

Since the review of systems is likely to be a lengthy section of the review, it may be useful to have the reviewer summarize more briefly the adverse events considered important, from the standpoint of approval and labeling, and drug related. The reader should be referred to the appropriate subsections of the Review of Systems for more details on the listed events. The subheadings for this section should be the various event categories, e.g., hepatotoxicity, seizures, agranulocytosis, meeting the above criteria.

9.0 Labeling Review

This section of the review should provide a critical review of the clinical sections of the labeling provided by the sponsor, but only for drugs that are headed for approval. The review should suggest alternative language in those sections in which the reviewer does not agree with the proposed language. Foreign labeling, if available, should be considered in this review.

10.0 Conclusions

[**Note:** This guidance addresses efficacy as well as safety in anticipation of the final integration of the safety and efficacy guidance documents.]

This should be a brief statement summarizing the reviewer's risk/benefit assessment for the NDA. Has the sponsor demonstrated (1) effectiveness for the claimed indications and (2) reasonable safety for the product under the conditions of use recommended in the labeling. While no details need be provided here, the reviewer may note major issues that were foremost in the review, e.g., important safety findings, deficiencies in the efficacy studies.

11.0 Recommendations

This section should also generally be brief. It should state the reviewer's recommendation regarding approvability. If the recommendation is for non-approvability, it should mention what additional work might fix the application. No details should be provided here, but rather, the reader should be referred to earlier sections for supporting details. If the recommendation is for approvability, this section should provide any recommendations for additional analyses, needed for approval and any recommendations for Phase IV commitments.

INDEX OF ATTACHMENTS

Attachment S: Table 8.1.5.3.1 - Sample adverse event incidence table for controlled trials

Attachment T*: Table 8.1.5.3.2 - Sample adverse event incidence table for overall phase 2-3 program

Attachment U*: Table 8.1.6.1.1 - Enumeration of laboratory testing experience for phase 2-3 program

Attachment V*: Table 8.1.6.3.1.1 - Mild uricosuric effect for psychotropic

Attachment W: Table 8.1.6.3.1.2 - Sample table providing data on mean changes for effects on serum chemistry

Attachment X*: Table 8.1.6.3.1.3 - Sample table providing data on mean changes for effects on hematology

Attachment Y*: Table 8.1.6.3.1.4 - Sample table providing data on mean changes for effects on urinalysis

Attachment Z: Table 8.1.6.3.2.1 - Sample table providing data for incidence of patients having serum chemistry changes of possible clinical significance for controlled trials

Attachment AA*: Table 8.1.6.3.2.2 - Sample table providing data for incidence of patients having hematology changes of possible clinical significance for controlled trials

Attachment BB*: Table 8.1.6.3.2.3 - Sample table providing data for incidence of patients having urinalysis changes of possible clinical significance for controlled trials

Attachment CC*: Table 8.1.6.3.2.4 - Sample display providing distributions of change from baseline for laboratory variables for controlled trials

Attachment DD*: Table 8.1.6.3.2.5 - List identifying patients meeting 1 or more PCS criteria

Attachment EE*: Table 8.1.7.1 - Sample table providing data on mean changes for effects on vital signs

Attachment FF*: Table 8.1.7.2 - Sample table providing data for incidence of patients having vital sign changes of possible clinical significance for controlled trials

Attachment GG*: Table 8.1.8.1 - Sample table providing data on mean changes for effects on ECGs

Attachment HH*: Table 8.1.8.2 - Sample table providing data for incidence of patients having ECG changes of possible clinical significance for controlled trials

*To be added in a subsequent version of the guidance.

Attachment A

Table 5.1.1.1
Enumeration of Subjects/Patients for
New Drug Development Program [1,2,3,4]
Cutoff Date[5]:

Study Groups	Treatment Groups		
	New Drug	Active Control[6]	Placebo
Completed Phase 1 (Clinical Pharmacology)			
Single Dose	120	30	30
Multiple Dose	60	30	30
Ph 1 Subtotal	180	60	60
Completed Phase 2-3 (Studies of Proposed Indication)			
Placebo Control[7]			
Fixed Dose	500	150	150
Flexible Dose	100	100	100
Active Control			
Fixed Dose	200	100	0
Flexible Dose	100	100	0
Uncontrolled			
Short Term	100	0	0
Long Term	700(500)	0	0
Ph 2-3 Subtotal	1200[8]	450	250
Ongoing Phase 2-3 Studies (Studies of Proposed Indication)			
Placebo Control			
Flexible Dose	150[9]	0	150[8]
SD Subtotal	120	30	30
MD Subtotal	1410	480	430
Grand Total	1530	510	460

[1]This table provides a count by study type of the subjects/patients exposed to New Drug, active control, and placebo across the entire set of studies in the development program that contributed safety and efficacy data for New Drug. It should include all subjects/patients known or assumed to have received even a single dose of assigned treatment. It should exclude subjects/patients who are known not to have received any of the assigned treatments or for whom no follow up information is available subsequent to the assumed receipt of assigned treatment. A separate listing of all such patients should be provided. [Note: If this list includes more than a few patients, this may indicate a potentially important problem in the conduct of studies.]

In creating this table, it is necessary to classify and group studies on the basis of several characteristics. For the purposes of this table, the following characteristics and distinctions were deemed important:

-Phase 1 vs Phases 2-3
-Completed vs Ongoing and Unblinded
-Single Dose vs Multiple Dose
-Controlled vs Uncontrolled
-Short-Term vs Long-Term
-Placebo-Controlled vs Active-Controlled
-Fixed Dose vs Flexible Dose

Obviously, there are other features that may be important as well, e.g., different indications, inpatient vs outpatient status, differences in the quality and completeness of data collected across different studies, foreign vs domestic. The characteristics to be used in classifying studies for the purpose of this table should be decided in consultation with the designated reviewing division at FDA.

In addition to this table that enumerates patients by category of study, it would be useful to have a table that enumerates patients by each individual study in the development program. This would be an expanded version of the above table that enumerates patients for each study, i.e., each of the categories in the above table would provide data for the individual studies comprising that category.

[2]Patients participating in crossover trials should be counted in each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be counted in all three columns.

[3]Footnotes to this table should identify by study number all those studies comprising the various study groupings for this table. For example, in the sample table, the fixed dose placebo controlled trials contributing to the counts for that category should be listed in a footnote, and similarly for all other categories.

[4]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[5]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table To likely need to be updated during the course of NDA review as more data become available.

[6]In the sample table, only 1 column is provided for an “active control” group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients should be made in consultation with the reviewing division.

[7]In this table, a decision was made to pool all studies having a placebo arm, whether or not an active control arm was also included. Thus, the active control category includes only those active control studies that did not have a placebo control arm. Other approaches to grouping studies may be equally appropriate.

[8]The intent of this table is to provide a count of unique subjects/patients exposed to New Drug, etc. in the development program. Since patients often participate in more than 1 study in a development program, it is necessary to have an approach to avoid counting patients more than once for the subtotals and grand totals. The approach used in this table is to include in parentheses in the pertinent cells of the table a count of the patients in that cell total who have already been counted by virtue of having participated in a previous study (e.g., a patient in an open extension trial should have been previously counted in an acute, controlled phase). The subtotals of unique individuals exposed to the assigned treatment can then be calculated by subtracting the sum of all numbers in parentheses from the sum of all the cell totals for each column (e.g., in this table, the completed ph 2-3 subtotal for New Drug is 1700 less the 500 patients already counted in short-term controlled trials, or 1200).

[9]Frequently, some studies may be ongoing and blinded at the time of NDA submission, even though some individual patients having experienced serious adverse events may have been unblinded. In these instances, the table should include estimates of the numbers of patients exposed to New Drug, etc. from these studies, since exact counts may not be available. Footnotes should indicate when the table entries are based on estimates rather than exact counts.

Attachment D

Table 5.1.2.2
Demographics Profile for Phase 2-3 Studies with New Drug [1,2,3,4,5]
Cutoff Date[6]:

Demographic Parameters	Treatment Groups[7,8]		
	New Drug N =	Placebo N =	Active Control N =
Age (years)			
Mean			
Range			
Groups			
< 40	**%**	**%**	**%**
40-64	**%**	**%**	**%**
> 65	**%**	**%**	**%**
Sex			
Female	**%**	**%**	**%**
Male	**%**	**%**	**%**
Race[9]			
Caucasian	**%**	**%**	**%**
Non-Caucasian	**%**	**%**	**%**
Weight (kg)			
Mean			
Range			

[1]This table should be based on a pool of all trials in the phase 2-3 development program. Similar tables may be appropriate for other subgroups within the phase 2-3 program and also for certain individual trials of interest.

[2]Patients participating in crossover trials should be included in the calculations for each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be included in the calculations for all three columns.

[3]Numbers for this table should be rounded to the nearest integer.

[4]This sample table includes 4 demographic categories of obvious interest, however, others may be of interest as well, e.g., height, severity on baseline measures of disease severity, and decisions about what to include should be made in consultation with the reviewing division.

[5]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[6]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[7]In the sample table, only 1 column is provided for an "active control" group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients should be made in consultation with the reviewing division. Similarly, for this table, only 1 column is provided for New Drug, with the implication that all New Drug patients, regardless of dose, should be included in the calculations for that column. Other approaches, e.g., distinguishing patients on the basis of dose, may be equally appropriate. The N's in these column headings should match the N's in Table 5.1.1.1.

[8]If, as is often the case, the N's available for calculating any particular demographic parameter are less than the N's in the column headings, these N's should be provided, along with an explanation, in footnotes.

[9]Other approaches to racial categorization may be substituted for that proposed in this sample table.

Attachment F

Table 5.1.3.2
Number (Percent) of Patients Receiving New Drug According to Mean [1,2,3,4,5,6,7] Daily Dose and Duration of Therapy in Phase 2-3 Studies (N=2500)
Cutoff Date[8]:

Duration (Weeks)	Dose[9] (mg)							
	0<Dos≤5	5<Dos≤10	10<Dos≤20	20<Dos≤30	30<Dos≤50	50<Dos	Total (AnyDos)	(%)
0<Dur≤1	6	19	31	31	25	13	125	(5%)
1<Dur≤2	6	19	31	31	25	13	125	(5%)
2<Dur≤4	13	37	62	63	50	25	250	(10%)
4<Dur≤12	31	94	156	156	125	63	625	(25%)
12<Dur≤24	25	75	125	125	100	50	500	(20%)
24<Dur≤48	25	75	125	125	100	50	500	(20%)
48<Dur≤96	13	37	62	63	50	25	250	(10%)
96<Dur	6	19	31	31	25	13	125	(5%)
Total (AnyDur)	125	375	623	625	500	252	2500	(100%)
(%)	(5%)	(15%)	(25%)	(25%)	(20%)	(10%)	(100%)	

[1]This table is calculated by first categorizing patients on the basis of the interval of exposure for each, e.g., a patient exposed for 6 weeks would be counted in the 4<Dur ≤12 row. The mean daily dose is then calculated for each patient for dose categorization, e.g., a 6-week patient with a mean daily dose of 15 mg would be counted in the 10<Dos ≤20 column. Patients are enumerated in only 1 cell of the matrix, i.e., this is a mutually exclusive display. The dose and duration intervals need to be designed specifically for the drug of interest.

[2]Similar tables can be calculated for median, for modal, and for maximum dose.

[3]The same table can be generated for any individual study or for any pool of studies.

[4]The same table can be generated for any subgroup of interest, e.g., on the basis of age, sex, race, comorbid condition, concomitant medications, or any combination of these factors.

[5]Similar tables should be provided for active control drugs and placebo.

[6]If the total N for this table does not match the total N from Table 5.1.1.1, as may be the case, e.g., if dose or duration data are not available for all exposed patients counted in Table 5.1.1.1, a footnote should provide an explanation for the discrepancy.

[7]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[8]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[9]Dose may also be expressed as mg/kg, mg/m^2, or in terms of plasma concentration if such data are available.

Attachment I

Index for Linking Identified Patients with Supplementary Patient Information in the NDA (CRFs, Narrative Summaries, and Patient Data Listings)[1]							
Study Number[2]	**Patient Number[3]**	**Case Report Forms**		**Narrative Summaries**		**Patient Data Listings**	
		Volume[4]	**Pages[5]**	**Volume**	**Pages**	**Volume**	**Pages**

[1]Separate indices should be provided for patients exposed to New Drug, Active Control Drugs, and Placebo

[2]Study numbers should be numerically ordered and tabbed as separate sections within the index.

[3]Patient numbers should be numerically ordered within each study section.

[4]The volume number provided in this index should be the unique volume number assigned to the volume as part of the complete NDA, and not a separate volume number assigned to the volume as part of a section of the NDA.

[5]The page numbers provided in this index should be the unique page numbers assigned for the entire volume, and not separate page numbers assigned to the separate sections that might be included in any particular volume.

Attachment J

Table 8.1.1.1
Deaths Listing [1,2,3]
Treatment = New Drug [4]
Cutoff Date [5]:

Trial	Center	Patient	Age (yrs)	Sex	Dose (mg)	Time (Days)	Source [6]	Person Time [7]	Description [8]

[1]A footnote should describe the rule for including deaths in the table, e.g., all deaths that occurred during a period of drug exposure or within a period of up to 30 days following discontinuation from drug and also those occurring later but resulting from adverse events that had an onset during drug exposure or during the 30-day follow up period. Other rules may be equally appropriate.

[2]Deaths occurring outside the time window for this table should be listed elsewhere.

[3]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[4]Similar lists should be provided for patients exposed to placebo and active control drugs.

[5]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[6]This listing should include all deaths meeting the inclusion rule, whether arising from a clinical trial or from any secondary source, e.g., postmarketing experience. The source should be identified in this column, i.e., 1 [0] for deaths arising from primary source clinical trials and 2 [0] for those arising from secondary sources.

[7]This column should identify patients for whom person-time data are available, so the reviewer can know which patients were included in the mortality rate calculations.

[8]Since narrative summaries should be available for all deaths, the description can be very brief, e.g., myocardial infarction, stroke, pancreatic cancer, suicide by drowning.

Attachment K

Table 8.1.1.2 **Incidence of Mortality by Treatment Group** **for Pool of Phase 2-3 Studies with New Drug [1,2,3]** **Cutoff Date [4]:**					
Treatment Group [5]	**Total Number of Patients [6]**	**Patient Exposure Years (PEY) [7]**	**Number of Deaths [8]**	**Crude Mortality Incidence [9]**	**Mortality per 100 PEY [10]**
New Drug					
Active Control					
Placebo					

[1]This table provides data comparing the incidence for overall mortality across treatment groups for the pool of all phase 2-3 studies in the development program. Similar tables may be appropriate for other subgroups within the phase 2-3 program, e.g., a table may be provided for a pool of all similarly designed short-term placebo controlled trials. Similar tables may be appropriate for certain individual trials of interest. All deaths should be counted, regardless of the investigator's or the sponsor's judgement about causality, including: (1) any deaths occurring during participation in any of the studies in the target pool, (2) any deaths occurring after a patient leaves any of the targeted studies, whether prematurely or after completion to the nominal endpoint, if the death is (a) the result of a process initiated during the study, regardless of when it actually occurs, or (b) occurs within 4 weeks of a patient leaving a study, or longer for drugs with particularly long elimination half-lives or from drug classes with known late occurring effects. However, this table should be limited to patients for whom person-time data are available. In case there are substantial deaths of specific causes, it may be appropriate to provide incidence data for cause specific mortality as well.

[2]Patients participating in crossover trials should be enumerated for each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be included in all three columns.

[3]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[4]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[5]In the sample table, only 1 row is provided for an “active control” group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients should be made in consultation with the reviewing division. Similarly, for this table, only 1 row is provided for New Drug, with the implication that all New Drug patients, regardless of dose, should be included in the calculations for that column. Other approaches, e.g., distinguishing patients on the basis of dose, may be equally appropriate.

[6]The N’s in these rows should match the N’s in Table 5.1.1.1., and if not, an explanation should be provided in a footnote.

[7]This column should provide person-time in patient exposure years (PEY). This table assumes a constant hazard rate, however, in certain situations it may be appropriate to stratify by increments of exposure.

[8]As noted above, only patients with person-time data available should be included in these counts.

[9]This is simply the number of deaths divided by the number of patients exposed in each group.

[10]This is the number of deaths divided by PEY for each group.

Attachment M

Table 8.1.2.1
Serious Adverse Event Listing[1,2,3]
New Drug Clinical Trials
Source: Phase 2-3 Trials[4]
Sorting A: Randomized Treatment, Trial #, Investigator/Center #, Patient # [5]
Treatment = New Drug[6]
Cutoff Date[7]:

Trial	Center	Patient	Age (yrs)	Sex	Dose[8] (mg)	Time[9] (days)	Body System	Prefrrd Term	Adverse Event[10]	W/D[11]	SAE Type[12]

[1]This is a line listing of all reported adverse events that met the sponsor's definition of being a "serious" adverse event, regardless of whether or not considered drug related, for all patients participating in the phase 2-3 trials in the development program. This listing is a critical component of the Integrated Safety Summary.

[2]The variables included in this listing include:

-Trial #
-Center #
-Patient # (a unique number that identifies this patient in the NDA database)
-Age
-Sex
-Dose (in mg) at time of event onset
-Time, i.e., duration, of exposure (in days) at time of event onset
-Body system category for event (using COSTART or other thesaurus)
-Preferred term for event
-Adverse event as reported by investigator and/or patient
-An indication of whether or not the event led to withdrawal
-Serious Adverse Event Type (e.g., fatal, life-threatening).

The following additional variables may be considered for inclusion as well:

-Race
-Weight
-Height
-Dose expressed as mg/kg, mg/mm ^{2}, or even plasma concentration, if available
-Other drug treatment
-Severity of adverse event (mild, moderate, severe)
-Action taken (none; decrease dose; discontinue treatment; etc.)
-Outcome
-Causality assessment by investigator (related; not related)
-Location in NDA of CRF, patient narrative summary, etc.)

[3]This table should be provided by the sponsor in hardcopy. The exact design of the table and whether or not it needs to be provided in electronic format should be established in discussions between the sponsor and the reviewing division.

[4]Similar listings may be provided for individual studies as part of Full Reports for such studies, and possibly for other pools that are subsets of this larger pool.

[5]It is essential to provide this listing in two different forms, i.e., sorting A (by patient) and sorting B (by adverse event). This listing is for sorting A, by patient, and permits the reviewer to explore all the serious adverse events reported for each individual patient. Sorting B (by adverse event) should be as follows: Randomized Treatment, Body System, Preferred Term, Adverse Event, Trial, Center, Patient #, Age, Sex, Dose, Time, W/D. Sorting B permits the reviewer to explore all the reported serious adverse events of a similar type.

[6]This sample listing is for all New Drug patients across all studies in the phase 2-3 development program. Similar listings should be provide for active control and placebo patients.

[7]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[8]This column should include the dose being administered (in mg/day) at the time the event occurred.

[9]This column should include the time, i.e., duration of exposure (in days), at the time the event occurred.

[10]This column should include the adverse event in the language reported by the investigator and/or patient, i.e., before coding.

[11]This column should include an indication of whether or not the adverse event led to discontinuation of the assigned treatment.

[12]This column should indicate which one of the 7 criteria for serious adverse event was met, as follows:

FatalFor a death
LTFor a life threatening adverse event
PDFor a permanently disabling adverse event
HospFor an adverse event resulting inpatient hospitalization
CancerFor an instance of cancer
ODFor an overdose
AnomFor a congenital anomaly

Attachment N

Table 8.1.3.1.1
Dropout Profile: Incidence of Dropout by Treatment Group and Reason for Phase 2-3 Studies with New Drug [1,2,3]
Cutoff Date[4]:

Reasons for Dropout[5]	Treatment Groups[6]		
	New Drug N =	Placebo N =	Active Control N =
Lack of Efficacy	%[7]	%	%
Adverse Event	%	%	%
Lost to Follow up	%	%	%
Other	%	%	%
Total Dropouts	%	%	%

[1]This sample table should be based on a pool of all trials in the phase 2-3 development program. Similar tables may be appropriate for other subgroups within the phase 2-3 program, e.g., a table should be provided for a pool of all similarly designed short-term placebo controlled trials. Similar tables may be appropriate for certain individual trials of interest.

[2]Patients participating in crossover trials should be enumerated for each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be included in all three columns.

[3]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[4]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[5]This sample table includes 4 categories for dropout, however, a more detailed breakdown may be of interest as well.
-The adverse event category here would include all patients identified as dropping out for adverse events, regardless of whether or not the events were judged by the investigator or sponsor to be drug related and regardless of what other reasons may have been identified in association with dropout. Patients identified as dropping out for intercurrent illness would ordinarily be included under this adverse event category. Similarly, a patient identified as dropping out for an adverse event and lack of efficacy would also ordinarily be included under this adverse event category.
-Lost-to-follow up is considered an important outcome to track, since it reflects on the overall conduct of the studies.
-The "other" category is intended to include all other reasons which may generally be considered non-treatment related. This category is often identified as "administrative," and includes such reasons as patient refused further participation, patient moved away, patient improved, patient not eligible, protocol violation, unknown.
-Decisions about what categories to include should be made in consultation with the reviewing division.

[6]In the sample table, only 1 column is provided for an "active control" group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients

should be made in consultation with the reviewing division. Similarly, for this table, only 1 column is provided for New Drug, with the implication that all New Drug patients, regardless of dose, should be included in the calculations for that column. Other approaches, e.g., distinguishing patients on the basis of dose, may be equally appropriate. The N's in these column headings should match the N's in Table 5.1.1.1., and if not, an explanation should be provided in a footnote.

[7]Numbers for this table should be rounded to the nearest integer.

Attachment O

Table 8.1.3.2.1
Adverse Event Dropout Listing[1,2,3]
New Drug Clinical Trials
Source: Phase 2-3 Integrated Primary Database[4]
Sorting A: Randomized Treatment, Trial #, Investigator/Center #, Patient #[5]
Treatment = New Drug[6]
Cutoff Date[7]:

Trial	Center	Patient	Age (yrs)	Sex	Dose[8] (mg)	Time[9] (days)	Body System	Prefrrd Term	Adverse Event[10]	Serious[11]	Outcome[12]

[1]This is a line listing of all reported adverse events that were identified as leading to discontinuation, regardless of whether or not they were considered drug related, for all patients participating in trials identified as sources for this listing. Thus, all events categorized as "intercurrent illness" leading to discontinuation would, neverless, be included in this listing, and any judgements about attribution can be included in the narrative summary. This listing is a critical component of the Integrated Safety Summary.

[2]The variables included in this listing include:
-Trial #
-Center #
-Patient # (a unique number that identifies this patient in the NDA database)
-Age
-Sex
-Dose (in mg) at time of event onset
-Time, i.e., duration, of exposure (in days) at time of event onset
-Body system category for event (using COSTART or other thesaurus)
-Preferred term for event
-Adverse event as reported by investigator and/or patient
-An indication of whether or not the event met definition for serious
-Outcome

The following additional variables may be considered for inclusion as well:
-Race
-Weight
-Height
-Dose expressed as mg/kg, mg/mm ^{2}, or even plasma concentration, if available
-Other drug treatment
-Severity of adverse event (mild, moderate, severe)
-Action taken (none; decrease dose; discontinue treatment; etc.)
-Causality assessment by investigator (related; not related)
-Location in NDA of CRF, patient narrative summary, etc.)

[3]This table should be provided by the sponsor in hardcopy. The exact design of the table and whether or not it needs to be provided in electronic format should be established in discussions between the sponsor and the reviewing division.

[4]Similar listings may be provided for individual studies as part of Full Reports for such studies, and possibly for other pools that are subsets of this larger pool.

[5]It is essential to provide this listing in two different forms, i.e., sorting A (by patient) and sorting B (by adverse event). This listing is for sorting A, by patient, and permits the reviewer to explore all the adverse events reported as leading to discontinuation for each individual patient. Sorting B (by adverse event) should be as follows: Randomized Treatment, Body System, Preferred Term, Adverse Event, Trial, Center, Patient #, Age, Sex, Dose, Time, Serious. Sorting B permits the reviewer to explore all the adverse events of a similar type reported as leading to discontinuation.

[6]This sample listing is for all New Drug patients across all studies in the phase 2-3 development program. Similar listings should be provide for active control and placebo patients.

[7]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[8]This column should include the dose being administered (in mg/day) at the time the event occurred.

[9]This column should include the time, i.e., duration of exposure (in days), at the time the event occurred.

[10]This column should include the adverse event in the language reported by the investigator and/or patient, i.e., before coding.

[11]This column should include an indication of whether or not the adverse event met the criteria for "serious" as defined for the development program overall.

[12]This column should categorize the outcome upon follow up evaluation for the adverse event leading to discontinuation, as follows:

(R) Resolved
(P) Persisting
(U) Unknown

Attachment Q

Table 8.1.5.2.1
Adverse Event Listing[1,2,3]
New Drug Clinical Trials
Source: Phase 2-3 Integrated Primary Database[4]
Sorting A: Randomized Treatment, Trial #, Investigator/Center #, Patient #[5]
Treatment = New Drug[6]
Cutoff Date[7]:

Trial	Center	Patient	Age (yrs)	Sex	Dose[8] (mg)	Time[9] (days)	Body System	Prefrrd Term	Adverse Event[10]	Serious[11]	W/D[12]

[1]This is a line listing of all reported adverse events, regardless of whether or not they were considered drug related, for all patients participating in trials

identified as sources for this listing.

[2]The variables included in this listing include:
-Trial #
-Center #
-Patient # (a unique number that identifies this patient in the NDA database)
-Age
-Sex
-Dose (in mg) at time of event onset
-Time, i.e., duration, of exposure (in days) at time of event onset
-Body system category for event (using COSTART or other thesaurus)
-Preferred term for event
-Adverse event as reported by investigator and/or patient
-An indication of whether or not the event met definition for serious
-An indication of whether or not the event led to withdrawal

The following additional variables may be considered for inclusion as well:
-Race
-Weight
-Height
-Dose expressed as mg/kg, mg/mm ^{2}, or even plasma concentration, if available
-Other drug treatment
-Severity of adverse event (mild, moderate, severe)
-Action taken (none; decrease dose; discontinue treatment; etc.)
-Outcome
-Causality assessment by investigator (related; not related)
-Location in NDA of CRF, patient narrative summary, etc.)

[3]This table should be provided by the sponsor in hardcopy. The exact design of the table and whether or not it needs to be provided in electronic format should be established in discussions between the sponsor and the reviewing division.

[4]Similar listings may be provided for individual studies as part of Full Reports for such studies, and possibly for other pools that are subsets of this larger pool.

[5]It is essential to provide this listing in two different forms, i.e., sorting A (by patient) and sorting B (by adverse event). This listing is for sorting A, by patient, and permits the reviewer to explore all the adverse events reported for each individual patient. Sorting B (by adverse event) should be as follows: Randomized Treatment, Body System, Preferred Term, Adverse Event, Trial, Center, Patient #, Age, Sex, Dose, Time, Serious, W/D. Sorting B permits the reviewer to explore all the reported adverse events of a similar type.

[6]This sample listing is for New Drug patients, i.e., for all patients exposed to New Drug in the phase 2-3 studies that are part of the Integrated Primary Database. Similar listings should be provide for active control and placebo patients.

[7]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[8]This column should include the dose being administered (in mg/day) at the time the event occurred.

[9]This column should include the time, i.e., duration of exposure (in days), at the time the event occurred.

[10]This column should include the adverse event in the language reported by the investigator and/or patient, i.e., before coding.

[11]This column should include an indication of whether or not the adverse event met the criteria for "serious" as defined for the development program overall.

[12]This column should include an indication of whether or not the adverse event led to discontinuation of the assigned treatment.

Attachment S

Table 8.1.5.3.1 **Treatment-Emergent Adverse Event Incidence** **for Pool of 6-Week Placebo-Controlled Trials [1-10]** **Cutoff Date[11]:**			
Body System/ **Adverse Event [12-14]**	**Percentage of Patients Reporting Event [15]**		
	New Drug **N[16]=**	**Active Control** **N=**	**Placebo** **N=**
Body as a Whole			
Headache			
Etc.			
Cardiovascular System			
Postural Hypotension			
Etc.			
Gastrointestinal System			
Constipation			
Etc.			
.			
.			
.			
Urogenital System **Impotence[17]**			
Etc.			
.			
.			
.			

[1]This table compares the incidence of treatment emergent adverse events across treatment groups for a pool of similarly designed placebo-controlled trials of New Drug. Generally an arbitrary threshold incidence for New Drug patients is used as a criterion for selecting adverse events to include, e.g., $\geq$ 1% for New Drug is a commonly used rule, but others may be equally appropriate.

[2]Study pools other than that described for this sample table may be equally appropriate, and similar tables useful for individual trials may also be of interest.

[3]In the sample table, only 1 column is provided for an "active control" group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients

should be made in consultation with the reviewing division.

[4]Similarly, for this table, only 1 column is provided for New Drug, with the implication that all New Drug patients, regardless of dose, should be included in the calculations for that column. Other approaches, e.g., dividing patients on the basis of dose, may be equally appropriate. If the studies utilized were fixed dose studies, it is generally most informative to preserve the dose categories in constructing this table. However, dose categories that are not relevant to the doses that are being recommended for use may reasonably be omitted from this table. It is generally not useful to try to artificially construct dose categories from dose titration studies, since there is often confounding of dose and time.

[5]Data are often available on the investigator's opinion regarding whether or not any particular adverse event was in fact related to the drug being taken. Some observers consider this useful information and may construct tables that include only those events considered possibly, probably, or definitely drug-related by the investigator. Others may ignore such judgements and include all reported adverse events, with the view that the control groups, especially placebo if present, may permit one to make causality decisions, regardless of the investigators' judgements about drug-relatedness. Either approach is acceptable, however, it is critical that a footnote indicate clearly when adverse events are not included due to investigators' judgements that they were not drug-related, since this approach may reduce the adverse event rates that appear in the table.

[6]Data are also often available on the intensity of the reported adverse events, generally including categories of "mild, moderate, or severe." Adverse event tables may ignore such classifications and pool all events together, or some attempt may be made to focus only on a subset of reported events, e.g., only those classified as "severe." Again, either approach is acceptable, but it is important to describe in a footnote what approach was taken.

[7]Not uncommonly, a New Drug is developed for more than one indication. If adverse event rates appear to be comparable across the indications, it may be reasonable to pool the data in creating an adverse events table, possible one providing greater precision. However, it is not inconceivable that adverse event rates may vary depending on the population studied, and if this appears to be the case, pooling may not be appropriate.

[8]Adverse events that occur at a rate for placebo that is $\geq$ to the rate for New Drug should be removed from the table and noted only as a footnote.

[9]Patients participating in crossover trials should be included in the calculations for each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be included in the calculations for all three columns.

[10]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[11]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[12]Adverse events should be organized under body system categories.

[13]Within each body system category, adverse events should be ordered according to decreasing frequency.

[14]Adverse events during exposure are generally obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. Generally a table of this type should utilize these preferred adverse event terms, and a footnote should identify the system used for coding investigator terms. Adverse event terms that convey no useful information, e.g., joint disorder, should be replaced by more clinically useful terms or deleted.

[15]Percentages should be rounded to the nearest integer. While not strictly hypothesis testing, p-values should be produced for all New Drug/placebo pairwise comparisons and any p-values meeting a $p < 0.05$ level of significance should be noted by an asterisk (*) as a superscript to the %.

[16]The N for each column should be provided at the column heading, so that only the percent of patients having that adverse event need be included in the table, and not the actual number.

[17]The rates for gender specific adverse events, e.g., impotence, should be determined using the appropriate gender specific denominator, and this fact should be indicated with a footnote.

Table 8.1.6.3.1.2
Mean Change from Baseline for Serum Chemistry Parameters [1]
in Pool of Placebo-Controlled Studies [2,3,4]
Cutoff Date[5]:

Serum Chemistry Parameters and Units of Measure[6]	Treatment Groups[7,8]								
	New Drug			Placebo			Active Control		
	N[9]	$\bar{X}_{BL}$[10]	$\bar{X}\triangle_{BL}$[11]	N	$\bar{X}_{BL}$	$\bar{X}\triangle_{BL}$	N	$\bar{X}_{BL}$	$\bar{X}\triangle_{BL}$
Albumin (g/dl)									
Alkaline Phosphatase (U/L)									
Bilirubin, total (mg/dl)									
BUN (mg/dl)									
CK (U/L)									
Calcium (mg/dl)									
Cholesterol (mg/dl)									
Creatinine (mg/dl)									
GGT (U/L)									
Glucose (mg/dl)									
LDH (U/L)									
Phosphorus (mg/dl)									
Potassium (mmol/L)									
Sodium (mmol/L)									
Triglycerides (mg/dl)									
Uric Acid (mg/dl)									

[1]This table provides data comparing the mean change from baseline across treatment groups for serum chemistry parameters. An acceptable alternative would be to provide median change from baseline.

[2]This sample table is based on a pool of similarly designed placebo controlled trials. Other pools, as well as individual trials may also be of interest.

[3]Patients participating in crossover trials should be enumerated for each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be included in all three columns.

[4]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[5]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[6]The parameters included in this list are for illustration. In general, the list should include all those serum chemistry parameters measured in whatever pool of studies is the focus of the table. Similarly, the units of measure are for illustration, and these details should be worked out in consultation with the reviewing division.

[7]In the sample table, only 1 column is provided for an "active control" group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients should be made in consultation with the reviewing division.

[8]Similarly, for this table, only 1 column is provided for New Drug, with the implication that all New Drug patients, regardless of dose, should be included in the calculations for that column. Other approaches, e.g., dividing patients on the basis of dose, may be equally appropriate. If the studies utilized were fixed dose studies, it is generally most informative to preserve the dose categories in constructing this table. However, dose categories that are not relevant to the doses that are being recommended for use may reasonably be omitted from this table. It is generally not useful to try to artificially construct dose categories from dose titration studies, since there is often confounding of dose and time.

[9]N repesents the number of patients who had the serum chemistry parameter of interest assessed at baseline and at least one follow up time.

[10]This column should provide the baseline means for all the serum chemistry parameters of interest.

[11]This column should provide the mean change from baseline for each of the serum chemistry parameters of interest. While not strictly hypothesis testing, p-values should be produced for all New Drug/placebo pairwise comparisons and any p-values meeting a $p < 0.05$ level of significance criterion should be noted by an asterisk (*) as a superscript to the %.

Attachment Z

Table 8.1.6.3.2.1
Incidence of Potentially Clinically Significant Changes in Serum Chemistry Parameters [1] for Pool of Placebo Controlled Studies for New Drug [2,3,4]
Cutoff Date[5]:

Serum Chemistry Parameters and PCS Criteria [7] L=Low; H=High; ULN=Upper Limits of Normal	Treatment Groups[6]								
	New Drug			Placebo			Active Control		
	Total Pts[8]	Abnormal		Total Pts	Abnormal		Total Pts	Abnormal	
		Nbr[9]	%[10]		Nbr	%		Nbr	%
Albumin-L (< 2.5 g/dl)									
Alkaline P'tase-H (> 400 U/L)									
Bilirubin, total-H (> 2 mg/dl)									
BUN-H (> 30 mg/dl)									
CK-H (> 3XULN)									
Calcium-L (< 7 mg/dl)									
Calcium-H (> 12 mg/dl)									
Cholesterol-H (> 300 mg/dl)									
Creatinine-H (> 2 mg/dl)									
GGT-H (> 3XULN)									
Glucose-L (< 50 mg/dl)									
Glucose-H (> 250 mg/dl)									
LDH-H (> 3XULN)									

Phosphorus-L (< 2.0 mg/dl)									
Phosphorus-H (> 5.0 mg/dl)									
Potassium-L (< 3.0 mmol/L)									
Potassium-H (> 5.5 mmol/L)									
SGOT/AST-H (> 3XULN)									
SGPT/ALT-H (> 3XULN)									
Sodium-L (< 130 mmol/L)									
Sodium-H (> 150 mmol/L)									
Triglycerides-H (> 300 mg/dl)									
Uric Acid (F)-H (> 8.0 mg/dl)									
Uric Acid (M)-H (> 10.0 mg/dl)									

[1]This table provides data comparing the incidence across treatment groups of patients who were normal at baseline meeting criteria of having had a change on any of the listed serum chemistry parameters of potential clinical significance (PCS). Separate listings should be provided for patients who were abnormal at baseline and met these PCS criteria.

[2]This sample table is based on a pool of similarly designed placebo controlled trials. Other pools, as well as individual trials may also be of interest.

[3]Patients participating in crossover trials should be enumerated for each of the pertinent columns of the table, e.g., a patient receiving treatment in each of the three arms of a 3-way crossover study comparing New Drug, active control, and placebo would be included in all three columns.

[4]This table should be provided by the sponsor in both hardcopy and in an electronic format. The exact design of the table and the preferred electronic format should be established in discussions between the sponsor and the reviewing division.

[5]This is the data lock date for entering data into this table, i.e., the date beyond which additional exposed patients were not available for entry. Generally this date should be no more than several months prior to the submission date for an NDA. This date as well as this table may likely need to be updated during the course of NDA review as more data become available.

[6]In the sample table, only 1 column is provided for an "active control" group. One such category may suffice for certain NDAs, but may not for others, and the decision regarding how to categorize active control patients should be made in consultation with the reviewing division. Similarly, for this table, only 1 column is provided for New Drug, with the implication that all New Drug patients, regardless of dose, should be included in the calculations for that column. Other approaches, e.g., distinguishing patients on the basis of dose, may

be equally appropriate.

[7]The parameters included in this list are for illustration. In general, the list should include all those serum chemistry parameters measured in whatever pool of studies is the focus of the table. Similarly, the proposed criteria for "potentially clinically significant" are for illustration, and these details should be worked out in consultation with the reviewing division.

[8]The total number of patients for each parameter should represent the number of patients for the treatment group who (1) had that parameter assessed at baseline and at least one follow up time and (2) for whom the baseline assessment was normal.

[9]The number abnormal represents the subset of the total number who met the criterion in question at least once during treatment. A separate listing should provide patient identification for those patients meeting the criterion.

[10]Percentage of the total number meeting the criterion should be rounded to the nearest integer. While not strictly hypothesis testing, p-values should be produced for all New Drug/placebo pairwise comparisons and any p-values meeting a $p < 0.05$ level of significance should be noted by an asterisk (*) as a superscript to the %.