Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT

OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION

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CONTENT OF THE GUIDELINE

GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION

I. INTRODUCTION

This guideline is intended to assist an applicant in presenting the clinical and statistical data required as part of an application under 21 CFR 314.50. The guideline describes an acceptable format for organizing the clinical and statistical sections and presenting the clinical and statistical information and accompanying statistical documentation of a clinical trial. With respect to documenting the results of individual studies, the guideline describes a fully integrated clinical and statistical report rather than two separate reports.

Paragraphs (d)(5), (d)(6), and (f) of 21 CFR 314.50 provide a general outline for this submission:

Clinical Section [21 CFR 314.50(d)(5)]

A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g. , because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results , and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical

investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

(vi) A summary and updates of safety information, as follows:

(g) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(Q) The applicant shall , under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5) (vi)(~) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (1) 4 months after the initial submission; (~) following receipt of an approvable letter; and (3) at other times as requested by FDA. Prior to-the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

Statistical Section [21 CFR 314.50(d)(6)]

A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5) (ii) of this section concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5) (vi)(~) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(Although the regulations do not call for submission as part of the statistical section of information described under paragraph (d)(5)(v), this was an error and the integrated summary of effectiveness data (Section II.G) should be included.)

Case Report Forms and Tabulations [21 CFR 314.50(f)]

The archival copy of the application is required to contain the following case report tabulations and case report forms:

(1) Case report tabulations. The application is required to contain tabulations of the data from each adequate and well-controlled study under section 314.126 (Phase 2 and Phase 3 studies as described in section 312.1(a)(2) [designated sections 312.21(b), (c) in a subsequent revision of regulations, Form FDA-1571], tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in section 312.1(a)(2), Form FDA-1571), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in accordance with paragraph (f)(3) of this section.

(2) Case report forms. The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(3) Additional data. The applicant shall submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under section 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally. (The preamble to the final regulation notes that every attempt will be made to request additional case report forms within 30 days of receipt of the application.)

(4) Applicants are invited to meet with FDA before submitting an application to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in a form other than hard copy, for example, on microfiche or machine readable formats.

In addition to 21 CFR 314.50, several other sections of the regulations bear directly on the contents of the clinical section of the application:

1. Adequate and Well-Controlled Studies. 21 CFR 314.126 describes the characteristics of a study the agency considers in determining whether a study is adequate and well-controlled and thus can contribute to the "substantial evidence" needed for approval.

2. Refusal to Approve the Application. 21 CFR 314.125 lists the reasons, many of them related to the results reported in the clinical data section, that would cause the agency to refuse to approve an application.

3. Fixed Combinations. 21 CFR 300.50 describes the particular requirements applicable to a combination drug product.

4. La beling. 21 CFR Part 201 describes the contents of drug labeling.

This guideline supplements and expands the general outline provided in the regulations. Because it must remain broad enough to apply to all drug classes, it deals with the to ics and kinds of displays and analyses that should be considere by any applicant, and how to organize them, rather than with the specific data requirements for approval of a specific kind of drug. Guidance regarding such specific data requirements can be found in FDA's clinical guidelines, including both the "General Considerations for the Clinical Evaluation of Drugs" and the many guidelines dealing with the evaluation of individual drug classes.

The 'guideline is directed principally toward an application for a new molecular entity, i.e., an agent not previously marketed in the United States in any dosage form. While many parts of it are equally applicable to other applications (e.g., Section III, The Format and Content of the Full Integrated Clinical and Statistical Report of a Controlled Clinical Study, is useful for presenting any well-controll ed study in support of an effectiveness claim), others are not. For example, it would not be necessary to include safety data already contained to in a previously approved application in an application for a different dosage form, new salt or ester, new combinations or new claim.

The objective of this guideline is to help applicants prepare a submission of the clinical and statistical sections that is complete and easily reviewable, that contains most of the summary and basic data that will be needed for evaluation, and that organizes and presents the data and analyses in a manner that is as clear, transparent, unambiguous, and accessible as possible. A lucid, well-organized, well-displayed, and complete application helps a reviewer become quickly oriented to its contents, facilitates examination of the relationships in the data that are of interest, and allows the reviewer to move easily between basic data and analyses and summary tables or verify reported results of analysis by duplicating them or carrying out alternative analyses. The guideline provides particularly extensive guidance on three critical aspects of the submission of clinical and statistical data.

1. The overall organization of the clinical and statistical sections, i.e. , where, and in what order, to present and cross-reference descriptions and analyses of the clinical studies, overall analyses, etc., is provided in Section II.

2. How to present data from an individual study, including the aspects of the protocol and conduct of the study that should be presented and discussed, the effectiveness and safety data to be displayed and how much individual data to present in the study report, and the contents of supplementary tabular listings, is explained in section III.

3. The integrated overall analyses that take data from groups of studies to provide an overview of effectiveness and safety that is broader than that of a single trial are described in Section II. The integrated summary of effectiveness is in Section II.G; the integrated summary of safety is in Section II.H.

Several principles have shaped development of this guideline:

1. It is important to distinguish presentation of data from the subsequent evaluation, interpretation, and analysis of those data, because the two uses of data require different treatment. Data ~ involve relatively little judgment or selection, other than that devoted to assuring effective data display. Thus, presentation of the results of a study should include all patients, all time points, and all endpoints, unless there has been prior indication by the agency that a particular subset of these data should be the only one considered. Similarly, reported adverse events should be presented whether they are perceived as intercurrent illness, reactions to other therapy, part of the natural history of the disease being treated, conditions present at baseline that worsened or truly related to use of the test drug. Moreover, all studies initiated, whether completed or abandoned, should be presented in sufficient detail for a reviewer to comprehend their design and outcome. On the other hand, once the data are presented in full, the interpretation and analysis of the data, and the conclusions reached, necessarily involve selection, judgment, and explanation.

2. Interrelationships among data from different studies should be examined; i.e., studies cannot be considered only in isolation. One consequence of this is rejection, for purposes of format, of the concept of the "pivotal" study, which has all too often been nothing more than the one or two of a group of similar studies that worked out best. Studies should be grouped by design and, within design, by other relevant features, such as whether case records are available and where the study was carried out. The implications of all studies, successful, non-supportive, terminated, etc., need to be considered. Differences in results may suggest differences in response among patient populations, inappropriate dose or dose interval, or may have other explanations, or be inexplicable; they do, however, warrant attention. Of course, it remains important for the sponsor to identify those studies believed to fulfill the statutory requirement for adequate and well-controlled studies supporting effectiveness.

A second consequence of this principle is that summaries are called for at a variety of levels, ranging from the broadest (overal 1 summary, integrated summary of effectiveness data, integrated summary of safety information) to more narrow summaries (summary of clinical pharmacology studies). Further, various cross-study analyses are requested, using the larger numbers of patients available in the entire NDA to look for demographic or other features that may influence effectiveness or safety, but that cannot be detected in the individual studies.

3. Studies reported in the literature should be incorporated into appropriate sections of the submission, not treated as an isolated body of data to be placed in a separate category. Published reports should be placed in the various sections of the application in accordance with the kind of data described in the reports. The reports should be discussed and analyzed as their quality and substance dictate.

4. For most analyses, tabular listings, not case report forms, are the "raw data." The revised regulations emphasize the use of tabular listings of data as the "raw data" for review, in lieu of the case report forms (CRF's). The CRF's are used to collect information on each patient studied, but they are often not the best document to use in examining the results of a study. When a particular patient's overall course is of interest, as in the case of a death or serious ADR, or a patient who had a dramatically better response to treatment than other patients, the case report form, or some single patient oriented document derived from the CRF, is the best source of information. Where the responses of a group (patients in one study or patients in a group of studies) for a single effect (e. g., blood pressure) or several effects (e. g., blood pressure, heart rate, serum potassium, and serum uric acid) are of interest, a tabular listing of patients and their results allows easy examination of the overall results of the individuals in the group for a single measurement or for a group of measurements. This also allows for ready identification of missing data elements, outliers, etc. It is also possible to examine effects in relation to demographic, historical, or other features, using data organized with a variety of data elements in the columns (patients are the rows).

FDA's experience with tabular presentations is extensive, but it does not suggest an advantage to our specifying a particular approach or display. Appendix A provides illustrations that may assist sponsors, but these should be viewed as examples, not required formats and should be modified as situations require. Sponsors are strongly encouraged to be creative and to consult with reviewing divisions on how to make tabulations most informative and useful.

5. The data base behind a table or figure must be readily ascertained. At many points in this guideline, tables or figures are suggested as useful in data presentation. It is critical that for any table or figure there be clear identification of the data set analyzed, clear identification of what is being displayed through use of good headings, identification of units, and labeling of graph axes, and a clear statement in the accompanying text concerning any conclusions drawn from the table.

Although virtually all of the information called for in this guideline has been part of many applications in the past, and much of it has been specifically discussed under previous regulations, including the form 356h and optional expanded summary, the guideline does provide a more defined format for the application and calls for specific new analyses, data displays, and summaries. Although the guideline reflects the experience and best advice of many FDA staff reviewers and managers and draws on a proposal of some years ago by a working group of the Pharmaceutical Manufacturers Association, it will undoubtedly require refinement as attempts to use it suggest the need for additions, deletions, and other changes. If the guideline is to have its intended effect, it must be "user-friendly," i.e., easily understood, flexible enough to fit most applications, free from requests for unnecessary material yet comprehensive enough to include needed data and analyses and minimize need for supplementary submissions. Only attempts to work with it can adequately elucidate its virtues and flaws.

As is true for any guideline, this guideline for the clinical and statistical sections of an application describes one way, but not the only way, of satisfying regulatory requirements. It will undoubtedly be less appropriate in some instances than others and is not intended to inhibit an applicant's search for the best way to exhibit the data and information needed for approval of an application. Nonetheless, it should be appreciated that under 21 CFR 314.101 the Agency can, and intends to, return to applicants (i.e., refuse to file) those applications that are not sufficiently complete or well-organized to permit a substantive review. Attention to this guideline should help sponsors prepare a complete and reviewable document.

II. OVERALL FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS [21 CFR 314.50(d)(5) and (6)]

The clinical and statistical sections [21 CFR 314.50 (d)(5) and (6)] should, in general, be organized following the format and sequence described below. Parts not applicable to a particular application should be omitted (but see discussion of index in Section VI.E.). The following outline includes, in many cases, some description of the specific content of each section, alternative ways of presenting data, or general comments. Note that a description of the Full Integrated Clinical and Statistical Report of a Controlled Clinical Study is given in Section III and that a complete topical outline of the Clinical and Statistical sections of the application is given in Section VI.

A. List of Investigators and List of IND's and NDA's

A complete alphabetical list should be provided of all investigators supplied with the drug substance or drug product by the applicant or known to have investigated the drug, using any dosage form (e.g., on the basis of published or unpublished reports), including the full name and post office address and, after each name, the kind(s) of studies carried out, the study identifier(s), and the location (Volume, page reference) of the description of each study, case report tabulations, and case report forms, if any. Investigators who carried out studies of a dosage form that is not the subject of the application and that is already marketed in the United States may be omitted.

In addition, a list should be provided of all known IND's under which the drug, in any dosage form, has been studied and any other NDA of which the applicant is aware that has been submitted for the same drug substance.

The unexplained omission of any report of investigations made with the new drug by, or on behalf of, the applicant, or of any pertinent reports of clinical experience received or otherwise obtained by the applicant from published literature or other sources, may constitute grounds for refusing to approve the application [(21 CFR 314.125(b)(14)]. Studies of a dosage form that is not the subject of the application and that is already marketed in the United States need not be included.

B. Background/Overview of Clinical Investigations

The general approach and rationale used in developing clinical data should be described in narrative form, including a description of the following areas, as appropriate (but not necessarily in the order listed).

1. How information about the drug derived from the clinical pharmacology studies led to critical features of the clinical studies (starting and maximum dose-interval, kind and frequency of monitoring, titration procedures, etc.).

2. The basis for the critical design features of the clinical trials, such as numbers of patients involved, patient selection criteria, duration of studies, choice of type(s) of control for controlled studies (placebo, active), and a discussion of their suitability, ethical constraints leading to a particular choice, etc., and selection of major clinical endpoints.

3. Reference to existing FDA drug-class clinical guidelines and the General Considerations guideline, explaining any important differences between guideline recommendations and the actual study plan. For example, the sponsor may consider the guideline outmoded or superseded by new or better information, as would be indicated by particular FDA Advisory Committee recommendations or FDA decisions on other agents, or the sponsor might simply believe he has developed a superior or equally satisfactory plan, based on his own expertise or discussions with expert consultants. The clinical guidelines are guidelines, not rules, and need not necessarily be followed. However, divergences from the guidelines should be addressed.

4. Reference to any FDA/sponsor discussions of major issues, such as an end of phase 2 conference, and a discussion of any agreements reached and any important differences between those agreements and the ultimate conduct of the NDA.

5. Selection of areas of special interest for study and analysis, such as studies in elderly or pediatric populations, studies in particular clinical environments, or particular drug-demographic or drug-drug interactions studied prospectively or examined retrospectively through evaluation of phase 3 data.

6. Particular effectiveness or safety issues raised by other drugs of the same pharmacologic or therapeutic class, such as withdrawal effects, important adverse effects (including long-term effects), or important drug-drug interactions, as suggested in the literature or by other data.

7. Specific questions raised by the results of clinical trials or by experience with related drugs and not answered by the clinical trial program. The status of such questions should also be described, for example:

    to be answered by ongoing studies or studies to be planned, noting particularly those questions for which additional data are anticipated while the application is under review.

can only be answered by post-marketing surveillance.
question recognized but no planned evaluation.

This section should include a discussion of any planned evaluation of additional potential indications, such as those approved for related drugs but not yet evaluated for the drug that is the subject of the application, as well as uses of the new drug or related drug that are fairly widespread but not approved for any agent.

C. Clinical Pharmacology [21 CFR 314.50(d)(5)(i)]

1. Types of studies to be included in this section are:

a. Studies of absorption, distribution, metabolism, and excretion (ADME studies). The full reports of bioavail ability and pharmacokinetic studies are included in the Human Pharmacokinetic and Bioavailability Section [21 CFR 314.50(d)(3)], but the Clinical Pharmacology section should summarize those results, emphasizing findings of particular importance to the design of clinical trials, the basis for dosage selection, and optimal use of the drug. The section should include investigations of drug-drug interactions (effects on the pharmacokinetics of the new drug by another drug or on the pharmacokinetics of any other drug by the new drug) and investigations of effects of other diseases or conditions (renal disease, hepatic disease, hypochlorhydria) or demographic characteristics (age, race, sex) on pharmacokinetics. Pharmacokinetic implications of blood level determinations carried' out during controlled or uncontrolled trials, including phase 3 "pharmacokinetic screen" measurements, should be considered in this section.

b. Pharmacodynamic dose range and dose-response studies including:

1) Early dose-tolerance studies
2) Short-term studies of therapeutic response or of a principal pharmacodynamic effect thought to relate to therapeutic response (e.g., effects of a beta blocker on heart rate during exercise), including dose response and blood-level response studies.

c. Studies of pharmacodynamic properties of the drug in humans other than the specific property thought to relate to clinical effectiveness, such as:

- hemodynamic studies
  electrophysiologic studies
  studies of effects on renal function

studies of effects on G.I. motility or gastric acid secretion
studies of effects on the immune response
studies of autonomic effects
studies of endocrine effects
studies of CNS effects, such as sedation or impairment of driving ability
studies of effects on coagulation

d. "Special studies," defined here as all clinical pharmacologic studies not described above. Clinical studies intended to demonstrate the effectiveness and/or safety of the drug should not be included here.

2. Format/content

The following information should be presented in this section:

a. A table of all studies, grouped by the study types described above and, within type, as preferred by the sponsor. The table should list investigators, provide study identifiers (including protocol number and publication citation, if any), give the starting date of the study., give the location in the application of the full report of each study (if the study is both a clinical pharmacology and effectiveness trial, it will need to appear in more than one location; in that case the location of all reports involving the study should be included), tabulations, and case report forms, if any, and give the number, age range; and sex distribution of subjects, study design (randomized, double-blind, parallel, crossover, etc.), the specific formulation and dosage strength used, the control treatment, if any, and the dose range, dose regimen, and duration of dosing. See Table 1 in Appendix A for an illustration of such a table.

b. For each group of studies:

1) A brief synopsis, one to two pages in length, of each study within the group describing the study population and results, including critical numerical data. A narrative description of the outcome without numerical data or a statement only of the "statistical significance" of an effect is not useful. The use of tables is crucial to efficient presentation. Abstracts commonly prepared for scientific meetings illustrate how a description of a study and a reasonable display of critical data can be presented in a small space, but the extreme brevity and very extensive use of abbreviations common to these documents is unnecessary here and should be avoided.

2) A full report of each study, except that human pharmacokinetics and bioavail ability studies included under 21 CFR 314.50(d)(3) need not be represented in full here and may be summarized. The synopsis called for in the previous paragraph may be sufficient if it includes critical pharmacokinetic parameters and appropriate graphical representations. Section 111 below describes the data that should be included in a full integrated clinical and statistical report of a controlled study but the description must be adapted to suit the particular case. If the clinical pharmacology study is a well-controlled trial that is important to the evaluation of the application, it deserves the complete analysis. In many cases, these studies are not so rigorously designed and can be described more briefly. The report should reference the volume and page numbers where the additional tabulations [21 CFR 314.50(f)(1)] and case report forms, if any, are located.

   The report should include a statement [314.50 (d)(5) (ix) I that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

3) An overall summary and evaluation of each group of studies, including a brief narrative or tabular comparison of the results of the human studies with the animal pharmacology and toxicology data. Particular attention should be paid to important animal findings not confirmed in humans or human findings not suggested by animal studies. Comparative ADME study results should be incorporated into evaluations of the relationship between animal and human pharmacology and toxicology findings.

c. An overall summary of the clinical pharmacology data, emphasizing findings especially relevant to clinical use of the drug, such as dose-response or blood level response data, duration of action data, and potential problems that could be associated with the observed patterns of metabolism or excretion (e.g., high first-pass effect, dependence on renal function, etc.). While the main pharmacologic effects are of greatest interest, other pertinent properties of the drug identified from human or animal studies should also be discussed. For example, vasodilation, ECG effects, sedation, effects on seizure threshold, and anticholinergic effects would always be pertinent. Documented or potential age-related effects should be highlighted.

D. Controlled Clinical Trials [21 CFR 314.50(d)(5)(ii) and (6)(i)]

The presentation of results of controlled clinical trials should be included in both the clinical and statistical sections.

1. Overview

a. Adequate and well-controlled studies

Approval of a new drug requires substantial evidence of effectiveness. Substantial evidence is defined under the Federal Food, Drug, and Cosmetic Act as "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." The studies presented in this section thus are those that will be used to determine whether there is substantial evidence that the drug is effective.

The requirement for well-controlled clinical investigations has been interpreted to mean that the effectiveness-of a drug should be supported by more than one well-controlled trial and carried out by independent investigators. This interpretation is consistent with the general scientific demand for **replicability.** Ordinarily, therefore, the clinical trials submitted in an application will not be regarded as adequate support of a claim unless they include studies by more than one independent investigator who maintains adequate case histories of an adequate number of subjects.

There have, however, been instances in which a single particularly persuasive study has been accepted in support of a claim because the study was considered unrepeatable on ethical grounds. In the case of the approval of timolol for reduction of post-infarction mortality, for example, a major effect on mortality was demonstrated in a single study. The timolol study was very persuasive because of excellent design, minimal or no problems during execution of the study, and a high degree of statistical significance associated with the critical finding. Such cases are unusual and an applicant seeking to invoke these exceptional circumstances must provide strong support for this position.

In general , a study for which case reports are not available will not be relied upon as a well-controlled study contributing to substantial evidence of effectiveness. Special circumstances have permitted exceptions to this policy, especially when such a study is used to support at least one other study with fully available case records. Extreme rarity of a disease, for example, may argue for reliance on published data collected over a long period, even if case records cannot be obtained, when comparable data could not be assembled prospectively in well-controlled studies over a reasonable time. In addition, when a drug is already approved for a major claim, secondary claims have sometimes been approved based on published data. when published studies are used as support for a claim, they should be analyzed in light of the reporting requirements for a study set forth below in Section III.

b. Combination drug products

If a drug product is a fixed combination, the adequate and well-controlled studies requirement applies to those studies intended to show that each component of the combination contributes to the claimed effect. (See 21 CFR 300.50 for the complete regulation on combination drug products.)

c. Submission of all data

All controlled clinical studies, including incomplete or abandoned studies, and all pertinent data, whether developed with support of the sponsor or obtained from any other source should be presented in this section. For any study intended to support effectiveness the discussion of each study should include the full report described in Section III, but in others an abbreviated report omitting some of the details of study design and effectiveness analyses will be sufficient [See II.D.2.c.5)].

The regulation is perhaps ambiguous on where to present a controlled trial available to the sponsor only as a report in the literature, i.e., in the section on controlled trials or in the "other information" section, but it seems best to include all controlled trials pertinent to the claimed effects of the drug in the controlled trials section. Although the absence of case records, an original protocol, and other information would ordinarily limit reliance on these studies, they should be considered as part of the available controlled data base.

2. Format/content

The following information should be presented:

a. A table of all studies included, grouped as described below. The table should list investigators, provide study identifiers (including protocol number and publication citation, if available), give the starting date of the study, give the location in the application of the full report of each study and its tabulations and case report forms, if any, and give the number, age range, and sex distribution of subjects , study design (randomized, double-blind, parallel , crossover, etc.), the specific formulation and dosage size used, the control treatment(s), the dose range, and the duration of dosing. See Table 1 in Appendix A for an illustration of such a table.

b. Reports of individual studies - order of presentation

For each claim of effectiveness, studies should be grouped by study design (see 21 CFR 314.126 for definitions of the cited study designs), and within design, by other pertinent characteristics, as follows:

1) Studies with a concurrent placebo control, including studies that include both placebo and active control

a) Completed studies

i. Domestic, with full case reports available
ii. Foreign, with full case reports available
iii. Published reports and other reports for which full case reports are not available.

b) Ongoing studies with interim results

i, ii, iii as above

c) Incomplete studies no longer active

i, ii, iii as above

A study should be considered incomplete only if it was terminated with very few patients. If it was stopped short of the projected population yet has a substantial number of patients, it should be analyzed as a complete study. If an applicant is undecided as to whether a particular study should be considered complete, and analyzed as such, the reviewing division should be consulted. When the sponsor considers a study incomplete, the basis for considering it incomplete should be provided.

2) Studies with dose-comparison concurrent control

a), b), c) as above

3) Studies with a no-treatment concurrent control

a), b), c) as above

4) Studies using an active concurrent control

a), b), c) as above

5) Studies using explicit historical control that are considered by the sponsor to represent well-controlled studies, including those with a baseline observation period (patient as own control) and those using a distinct group of patients treated at another time, in another location, by another investigator, and/or in a separate study

a), b), c) as above

Additional logical groupings within the above groups may be made by the sponsor, such as grouping by other study design feature (parallel, crossover, placebo withdrawal), by regimen (dose, dose interval), by duration, or by patient population (but if the population is so different that a separate claim results, the studies supporting each claim should be separated).

c. Reports of individual studies - content

For each study, there should be provided:

1) A brief synopsis, one to two pages in length, describing the study population, critical design features, and effectiveness and safety results, including critical numerical data.

A narrative description of the outcome without numerical data or a statement of the "statistical significance" of an effect is not useful. The use of tables is crucial to an efficient presentation.

2) The protocol (a plan for the study prepared prior to its conduct), including a sample of the case report form(s) used to carry out the study, and any protocol amendments made during the study. (The protocol should be placed as an appendix following the full report.) If several studies used an identical or nearly identical protocol, it need be included only once, with a reference to its location, and a description of any minor differences from the reference protocol appended to the report of each study.

3) Any publication that reports on or analyzes all, or any portion of, the data in the study. (The publication should be placed as an appendix following the report of each study.) If there are significant discrepancies between the data or analyses in the application and those in the published report, they should be explained.

4) A list of all investigators and other persons whose participation materially affected the conduct of the study and a brief description of their training (physician, psychologist, etc.) and of the role of each in the study, such as the particular observations or decisions for which each was responsible, should be provided as an appendix to the report. If there was an external (to the applicant) data monitoring group, its members should be included. A curriculum vitae or equivalent description of training and experience (e.g., biographical sketch format in PHS Form 398, Application for Public Health Service Grant) should be provided for each investigator as an appendix to the study report. This listing should include:

a) Investigators

b) Any person carrying out important study observations on a regular basis, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. Do not include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for a regular study participant.

c) The author(s) of the report, including the responsible statistician(s).

d) A statement [314.50 (d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

5) A report of the study. Except as noted below, the description and analysis of the study should be the full report described in Section III of this guideline, for (a) all completed studies and (b) any ongoing studies with interim results that are intended to support effectiveness. Ordinarily, for completed studies or ongoing studies with interim analyses that on their face do not support effectiveness, for favorable studies that the sponsor considers flawed or unreliable, and for incomplete studies no longer active (see paragraph b.1).c) above), a briefer description of the results related to effectiveness (but sufficient to convey the outcome of the study quantitatively, even if no statistical analysis was performed) should be provided in addition to a brief summary of the study design and conduct. The reason for providing only the brief report should be given, if not apparent (e.g., the flaws that prevent the study from being relied upon). Any study with a statistically significant negative result (i.e., favoring placebo or other control therapy) or a strong negative trend should be reported in detail. For an ongoing study without interim analysis, of course, no effectiveness report is possible, and, except for serious adverse effects, there may also be little safety data available as well. Safety-related data should be presented thoroughly, as described below in Section III, for all these studies, even where a full analysis of effectiveness is not included. For any ongoing study subjected to either a full report or a briefer description and analysis, a projected completion date for the study should be given. For discontinued studies, the reason(s) for discontinuation should be given.

Non-supportive studies must not be simply ignored, even if their effectiveness results are not presented in complete detail. They should be discussed and

analyzed in Section II G, Integrated Summary of Effectiveness Data. In addition, there should be exploration of the reasons for such "negative" or non-supportive studies, as they may suggest influences of study populations, dosages, study designs or other features that need to be understood. The brief description of these studies should provide information on these factors. Nonetheless, these studies in general will not benefit from the detailed description of study design and statistical methods, and analysis of effectiveness variables described in Section III.

The report should refer to the volume and page number where additional tabulations and case report forms for the study are located.

In some cases, particularly involving drugs that are being developed simultaneously in many countries, there will be a redundancy of controlled trials beyond what is reasonably needed to serve as a basis for evaluation of the drug, and preparation of the full reports described in Section III may be needlessly burdensome and unnecessary. It may also be difficult to obtain complete data when studies are conducted by a subsidiary of the U.S. applicant not familiar with the preparation of applications for submission to United States or European regulatory authorities. When such a situation is thought to exist, the applicant should initiate a discussion with the reviewing division to' reach agreement on which controlled studies can be presented briefly, rather than in full report. Even the brief report, however, should provide a short description of the reported outcome of the trial regarding effectiveness and safety results and a complete evaluation and report of deaths, adverse dropouts, and other serious adverse events [see 111. B.10.b.6)]. The report of the study should make clear the limitations of the analysis.

d. Overall summary of data from controlled studies

The applicant may provide an overall summary and evaluation of the data from controlled trials supporting each claimed indication, integrating the effectiveness and safety results of all trials. Preferably, however, this summary may be omitted and effectiveness data from controlled trials included only in the Integrated Summary of Effectiveness Data (Section II.G below). Similarly, the safety data from controlled trials should be included with other data in the section on Integrated Summary of Safety Information (Section II.H below).

E. Uncontrolled Clinical Studies [21 CFR 314.50(d)(5)(iii)]

1. Overview

Uncontrolled studies will not, in general, be useful in contributing to substantial evidence of the effectiveness of a drug, but they can provide support for the controlled studies and provide critical safety information for several reasons:

a. If the uncontrolled studies are relatively large compared to the controlled trials, uncontrolled studies may provide information on relatively rare events not likely to be seen in smaller studies.

b. In the absence of a control group it is difficult to determine whether adverse events common in the treated population even in the absence of drug exposure (e.g. , those related to the underlying disease) are related to the test drug; uncontrolled studies can, however, identify uncommon events (liver injury, renal failure, hematologic events), events that reoccur on rechallenge, and events that bear a close temporal relationship to drug use and resolve on discontinuation of treatment.

c. The less strict entry criteria and control over concomitant treatment usual in such trials may sometimes allow identification of drug-drug or drug-disease interactions not evaluable in the controlled trials.

The section on uncontrolled studies should include all uncontrolled studies involving each claimed use of the drug, including incomplete or terminated studies, and studies from the clinical literature.

2. Format/content

The following information should be presented:

a. A table of all studies included in the section, grouped as described below. The table should list investigators, provide study identifiers (including protocol number and publication citation, if available), give the starting date of the study in the application, give the location of the full report of each study and its tabulations and case report forms, if any, and give the number, age range, and sex distribution of subjects, study design, the specific formulation and dosage size used, the dose range, and the duration of dosing. See Table 1 in Appendix A for an illustration of such a table.

b. Reports of individual studies - order of presentation

For each indication, studies should be grouped according to completeness and availability of case reports and within these groups by duration (shortest to longest), patient population, or other pertinent characteristics, as follows:

1) Completed Studies

a) Full case reports available

i. Domestic
ii. Foreign

b) Case reports not available, including published reports

2) Incomplete studies

a) and b) as above

c. Reports of individual studies - content

For each study there should be provided:

1) A brief synopsis, one to two pages in length, describing the study population, study design, and important results. Safety-related data should be emphasized and tabular presentations used where appropriate.

2) The protocol, including a sample of the case report form(s) used to carry out the study, and any protocol amendments made during the study. (This should be placed as an appendix following the full report.) If several studies used an identical protocol it need be included only once, with a reference to its location appended to the report of each study.

3) Any publication that reports on or analyzes all, or any portion of, the data in the study. (The publication should be placed as an appendix following the report of each study.) If there are significant discrepancies between the data or analyses in the application and those in the published report, they should be explained.

4) A list of all investigators and other persons whose participation materially affected the conduct of the study and a brief description of their training (physician, psychologist, etc.) and of the role of each in the study, such as the particular observations or decisions for which each was responsible should be provided as an appendix to the report. A curriculum vitae or equivalent description of training and experience (e.g., biographical sketch format in PHS Form 398, Application for Public Health Service Grant) should be provided for each investigator. This listing should include:

a) Investigators.

b) Any person carrying out important study observations on a regular basis, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. Do not include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for a regular study participant.

c) The author(s) of the report, including the responsible statistician(s).

d) A statement [314.50(d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

5) A report of the study. For uncontrolled studies, the description of effectiveness results can be brief, generally omitting a statistical analysis entirely. It may be appropriate to expand the report if there is an important observation to be made or if the data are intended to support a claim or other section of labeling. If the uncontrolled study is an open extension of a controlled trial this should be noted and the results of the open study compared briefly with the controlled trial results. Except as noted below, analysis of safety-related information should be thorough, as described below in Section III. If it is not apparent why the study is considered uncontrolled (e.g., if the design seems to indicate a controlled trial), an explanation should be provided.

As was the case for controlled trials (see II.D.2.c.5), in some cases, particularly where a drug is being evaluated in many countries simultaneously, there may be a redundancy of information on the more common adverse events. With the agreement of the reviewing divisions, the less accessible studies may be reported more briefly. There should, however, be a complete evaluation and report of deaths, adverse dropouts, and other serious events for all uncontrolled studies [see 111. B.10. b.6)]. The report of such studies should make clear the limitations of the analysis.

d. Overall summary of data from uncontrolled studies

The overall summary and evaluation of these studies should be incorporated into the integrated summaries of effectiveness and safety data (see Sections II.G and H below).

F. Other Studies and Information [21 CFR 314.50 (d)(5) (iv)]

1. Overview

This section includes a description and analysis of any additional information obtained by the applicant from any source, foreign or domestic, that is relevant to the evaluation of the safety and effectiveness of the product. This information will, in general, be pertinent principally to the safety evaluation, as it includes results of controlled or uncontrolled clinical trials of uses of the drug other than those claimed in the application, commercial marketing experience, and reports in the literature or otherwise obtained, other than those cited in the Controlled Trials or Uncontrolled Trials sections above.

2. Format/content

The following information should be presented in this section:

a. A table of all studies and other information included in this section, grouped as described below. The table should, as applicable, list investigators, provide study identifiers (including protocol number and publication citation, if available), give the location in the application of the full report of each study and its tabulations and case report forms, if any, and give the number, age range, and sex distribution of subjects, study design, the specific formulation and dosage size used, the dose range, and the duration of dosing. See Table 1 in Appendix A for an illustration.

b. Reports of individual studies - order of presentation

Studies should be grouped according to design and availability of case reports, and within these groups by other pertinent characteristics in accordance with sponsor preferences, as follows:

1) Controlled studies of uses other than those claimed in the application, both complete and incomplete.

   a) Studies with case reports available.

   b) Published reports and other reports for which full case reports are not available.

2) Uncontrolled studies of uses other than those claimed in the application.

   a) Studies with case reports available.

   b) Published reports and other reports for which full case reports are not available.

3) Commercial marketing experience and foreign regulatory actions.

   a) List of countries in which drug has been approved, with dates of approval and a list of countries in which approval has been applied for with dates of application.

   b) All reports obtained from foreign regulatory authorities or foreign affiliates, licensers, or licensees of the applicant, including reports of, or analyses of, adverse effects, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other experience. A description should be provided of how information from each of these authorities and companies was sought.

      A copy should be provided of any letter from a foreign regulatory body that refuses drug approval on safety grounds. Copies of approved labeling from European countries, Canada, Australia, New Zealand, and Japan should be provided, with translation. Important differences from proposed U.S. labeling with respect to contraindications, warnings, precautions, adverse reactions, or dosing instructions should be identified and explained.

c) Epidemiologic studies.

d) Spontaneous reports from foreign marketing experience of serious adverse experiences [see 21 CFR 314.80(a)].

4) Reports from literature or elsewhere not otherwise reported, with a description of the search strategy used to assess the world literature.

a) Published case reports, letters, etc.

b) Other information.

c. Reports of individual studies - groups 1), 2) - content:

1) A brief synopsis, one to two pages in length, describing the study population, study design, and important results. Safety related data should be emphasized and tabular presentation used where appropriate.

2) The protocol, including a sample of the case report form(s) used to carry out the study, and including any protocol amendments made during the conduct of the study. (This should be placed as an appendix following the full report.)

3) Any publication that reports on, or analyzes all, or any portion of, the data in the study. (The publication should be placed as an appendix following the report of each study.) If there are significant discrepancies between the data or analyses in the application and those in the published report, they should be explained.

4) A list of all investigators and other persons whose participation materially affected the conduct of the study and a brief description of their training (physician, psychologist, etc.) and of the role of each in the study, such as the particular observations or decisions for which each was responsible, should be provided as an apprendix to the report. A curriculum vitae or equivalent description of training and experience (e.g., biographical sketch format in PHS Form 398, Application for Public Health Service Grant) for each investigator should be provided as an appendix to the study report. This listing should include:

a) Investigators.

b) Any person carrying out important study observations on a regular basis, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. Do not include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for a regular study participant.

c) The author(s) of the report, including the responsible biostatistician(s).

d) A statement [314.50(d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

5) A report of the study. The description and analysis of effectiveness results can be brief, generally omitting a statistical analysis entirely, although it may be expanded if the applicant has reason to do so. Analysis of safety-related information should be thorough, as described in Section H below, except in cases where, with the agreement of the reviewing division, a more limited analysis is considered acceptable [see II.D.2.c.5) and II.E.2.c.5)].

d. For commercial marketing experience (group 3) reports should explain the nature of the reported observations, the reporting system, the number of patients who received the drug or amount of drug distributed, etc., as appropriate.

e. Overall summary of other studies and information

The overall summary and evaluation of these studies and other information should be incorporated into the integrated summaries of effectiveness and safety data (see Sections G. and H. below).

G. Integrated Summary of Effectiveness Data [21 CFR 314.50 (d)(5)(v)]

The content of this section should be included in both the clinical and statistical technical sections.

1. Overview

This section should provide an integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication. It should also include a summary of evidence supporting the dosage and administration section of the labeling, including the dosage and dose interval recommended, and evidence pertinent to individualization of dosing and need for modifications of dosing for specific subgroups (e.g., pediatric or geriatric patients, or patients with renal failure). If certain subgroups that are candidates for treatment with the drug have not been included (e.g., older patients), so that the effectiveness of the drug has not been assessed in them, this should be noted and the implications considered.

The individual controlled studies to a great extent speak for themselves with respect to their ability to provide the evidence of effectiveness required by law. This section should provide an overview of the results, showing that they do satisfy the regulatory requirements for approval, i.e., represent adequate and well-controlled studies demonstrating the claimed effect, particularly if results are inconsistent or marginal. For example, the sponsor would explain here his basis for seeking to rely on a single study. Equally important, this section should include an examination of study-to-study differences in results, effects in subsets of the treated population, dose-response information from all sources, any available comparisons with alternative drugs, and any other information, so that the nature of the drug's effectiveness can be as fully defined as possible, and the user of the drug can be given the best possible information on how to use the drug and what results to expect.

2. Format/Content

Format for this section cannot be rigidly described. The applicant should take note of the suggestions for content below but should choose the format that best suits the data.

a. Identification of studies fulfilling the statutory requirements for adequate and well-controlled studies showing that the drug has its intended effect.

If the intended or claimed effect is on a "surrogate" endpoint, i.e., not the ultimate reason for treatment, e.g., to reduce mortality or morbidity, but an endpoint more readily measured and thought to be related to, and likely to predict, a favorable effect on the ultimate endpoint, the basis for choice of the endpoint should be discussed and its validity supported. In some cases,

established Agency policy may decrease the need for this discussion and it may be sufficient to refer to past Agency decisions (e. g., antihypertensive, oral hypoglycemic, and lipid-lowering agents have generally been approved on the basis of demonstrated effects on blood pressure, blood sugar, and blood lipids, respectively without evidence, at the time of approval, of an effect of the particular drug on survival or morbidity.)

b. Comparison and analysis of results of all controlled trials

The objective of this section is to define the effect of the drug in the studies that were carried out.

Generally with the help of tables showing major study design features, numbers of patients, number of dropouts, and major outcomes, and consistent with the report of individual study results described above, the results from all controlled trials, including those well-controlled studies that did not favor the study treatment and including controlled trials (e.g., single dose studies) that were included under clinical pharmacology, should be summarized, examined, and compared. In comparing study results, if many variables or time points were analyzed, representative ones, usually those that were identified as the primary endpoints in the individual studies, should be selected for display and evaluation. Ordinarily, studies with similar controls (placebo control, active control) should be discussed together. A variety of methods have been used to compare study results, including study-by-study display of results (and confidence intervals) such as mean differences from placebo (illustrated by Figure 1 in Appendix A), relative risk, or odds ratio [see Figures 1, 2, page 185 in Yusuf et al: Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. European Heart J. (1985) 6, 556-585] or "scattergrams" showing treatment on one axis and placebo on the other, the 450 line representing a no-effect line,

It is generally not helpful to pool results from individual studies not designed for analysis in that fashion, but if the applicant wishes to offer such an analysis, it should be presented in full in this section. If such pooling is attempted, particular attention should be paid to statistical considerations, selection bias in choosing studies, etc.

If there are important differences in outcome between studies of generally similar design, an attempt (admittedly often difficult) should be made to explain why results were

different. Factors such as differences in patients (disease definition, disease stage, severity, prior treatment), in drug dose or regimen, in methods of observation, in adherence to protocol, or inadequate power (high beta error rate) may offer such an explanation and should be considered and any important differences displayed. Often such analyses will raise questions for future exploration rather than provide definitive answers.

c. Results of uncontrolled studies

Uncontrolled studies should be discussed to the extent they contribute supportive evidence of effectiveness. If controlled trials are plentiful and strongly supportive, it should not be necessary to provide more than a tabular display of the results of the uncontrolled studies.

d. Analysis of dose-response or blood level-response information

There should be an integrated summary and analysis of all data, from animal, pharmacokinetic, pharmacodynamic and other clinical pharmacology studies, and from controlled and uncontrolled clinical studies, that bear on the dose-response or blood level-response relationship of effectiveness, the dose-blood level relationship, the method of dose selection, and the choice of dose-interval , and that support the dosing recommendations proposed in labeling, including the recommended starting and maximal doses, the method of closet titration, and any other instructions regarding individualization of dosage. Any identified deviations from relatively simple dose-response or blood-level response relationships due to non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be described and their implications for clinical usage discussed. Limitations of the data, e.g., because the study design did not permit evaluation of effects at each dose, should be candidly exposed and any plans for further studies disclosed. If dosing recommendations are different from those in other countries, the differences should be explained. The analysis of effectiveness dose-response can be separated from and referred to in, or integrated with, a similar section of the Integrated Summary of Safety Data.

Any evidence of different dose-response relationships in age, size, sex, disease, or other subpopulations should be described, including evidence of different pharmacokinetic or pharmacodynamic responses. The ways in which such differences were looked for, even if none were found, should be described (e.g., specific studies in subpopulations, analysis of effectiveness results by subgroup, or blood level determinations of test drug).

e. Analysis of responses in subsets of the overall population: drug-demographic, drug-drug, and drug-disease interactions

Although analysis of responses in subsets of the population, particularly when they are devised and carried out after the study is complete, cannot carry the same statistical or clinical weight as a study designed to test a prior hypothesis, available data should be examined for consistent differences in response among reasonable subsets of the overall population, at least with respect to the effectiveness seen in trials, to the dose needed, and to pharmacokinetic responses (as assessed by blood level measurements during clinical trials or by formal pharmacokinetic studies). Subsets of interest will vary with the drug and condition studied but would usually include: sex, race, age, and size, and might include disease severity, concomitant illness, concomitant drug, smoking and ethanol usage history, and prior therapy. The numbers of exposed patients in the major subsets (age, sex, race) should be displayed or referred to if such a tabulation appears in the Integrated Summary of Safety Information. The examination of subsets need not routinely involve formal statistical analysis. Of interest are differences of clinically meaningful size. If these are not observed, minor differences, likely to reflect the fact that multiple subsets have been analyzed rather than true differences, should be described, but need not be analyzed further.

f. Evidence of long-term effectiveness, tolerance, and withdrawal effects

Drugs for chronic use are not usually studied for the full intended period of use, but are generally studied for periods of 6 months to a year. Available information on persistence of effectiveness over time should be summarized and evidence of tolerance or withdrawal effects noted.

H. Integrated Summary of Safety Information [21 CFR 314.50 (d)(5)(vi)1

The content of this section should be included in both the clinical and statistical technical sections.

1. Overview

This section should integrate safety information from all sources, including pertinent animal data, clinical pharmacology studies, controlled and uncontrolled clinical trials (including controlled trials for indications not claimed in the application), and foreign marketing experience or epidemiologic studies related to any use of the drug. Dose-response and blood level-response relationships for adverse effects should be identified, as should drug-drug

or drug-disease interactions, and any demographic or clinical features that predispose to adverse effects, such as age, renal or hepatic impairment, etc. A description of any statistical analyses not included under the individual study report should be provided.

While other parts of the application present safety results of each study, the integrated summary is an overall analysis, examining all studies together. This allows examination of differences among population subsets not possible with the relatively small numbers of patients in individual studies and, especially important, allows evaluation of more serious adverse effects too rare to be detected with assurance in single studies. Thus, the integrated summary is, in part, simply a summation of data from individual studies and, in part, a new analysis that goes beyond what can be done with individual studies.

In every analysis and display it is critical that the data base used (all studies, certain studies, certain patients in certain studies such as those exposed for a particular period, etc.) and the numbers of patients involved in the analysis (the denominator) be given. The denominator is critically important and must be chosen with care. In calculating adverse event rates not all exposed patients are at risk of certain events; e.g., most drug-related liver injury requires exposure of several weeks, so that short-term studies should probably not be part of the denominator for rate of liver injury. The rates should be based on the relevant exposed population.

If the relevant population is uncertain, more than one denominator (all patients, all patients exposed for one month or more, etc.) can be used.

If a potentially important adverse reaction is expected (e.g., because of an animal finding or because it is thought to be an effect associated with the pharmacologic class) but is not seen, or is seen no more often than in a placebo group, it is important to discuss how the effect was sought and the ability of the studies to have found such an effect had one been present.

Updates of safety information are required under the regulations to include “new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling,” in essentially the same format as the integrated summary. Because the content of the update will depend on the nature of the additional data, it

will generally be useful to consult with the reviewing division before preparing the update. It is possible to provide the safety update information as a report that refers only to the new data obtained since the last update or since the original submission, but it is preferable to provide a document incorporating the new data with the data and analyses in the initial integrated summary of safety information, as well as showing the new data. If the additional data are relatively few and come principally from foreign sources or other studies that have not been incorporated into overall analyses in the initial submission, it may be sufficient to concentrate on the serious or potentially serious adverse events, or an unusually high frequency of a less serious event, providing a narrative description of these events. The regulations require that case report fores be provided for all patients who died in a clinical study or, unless the requirement is waived, who failed to complete a study because of an adverse experience.

2. Format/content

a. A table of all investigations pertinent to safety, identified by protocol number and principal investigator, grouped by type (clinical pharmacology, adequate and well-controlled studies, uncontrolled studies, and other studies), and including studies of indications other than those sought in the application giving:

1) Type of study (controlled, double blind, randomized, etc.)
2) Status (continuing, discontinued)
3) Location of full report
4) CRF's, available or not
5) Number of patients on each treatment
6) Indication studied
7) Age range of patients in each study and sex/race distribution
8) Duration of drug exposure in the study
9) Dose range in the study
10) Frequency of dosing

(The tables prepared for earlier sections, 11. C-F, may be reproduced here.)

b. Overall extent of exposure

The extent of exposure to active drugs (number of patients exposed in all studies, duration of exposure, and dose) should be described in tables, including:

1) Number of patients exposed altogether and for specified periods of time, e. g., one day or less, more than one day to one week, more than one week to one month or more than one month.

The numbers should be given for sex and for other particularly relevant demographic subgroups, such as the geriatric age group. A life-table presentation may be an efficient way of displaying duration of exposure. Patients included in more than one study (e.g., a controlled trial followed by a long-term extension) should be counted only once. If it cannot be determined whether the same patient appears in more than one study, this should be indicated. If certain subgroups that are candidates for treatment with the drug have not been included (e.g., older patients), so that the safety of the drug has not been assessed in them, this should be noted and the implications discussed.

2) Number of patients exposed to various doses for defined periods.

This can be difficult to display. One simple way to do this is to attribute to each patient the dose he was on for the longest time, providing a crude, but reasonable, picture of exposure. This, however, underestimates the total exposure to a particular dose. Alternatively, it is possible to count each dose duration segment for each patient exposed to several doses. Thus, a patient given 3 different doses for 3 different months would be counted 3 times, as an exposure at each of 3 doses. It may simplify the display to group a range of doses as low, medium, and high. There are no doubt many other reasonable ways to display exposure; the applicant should consult with the reviewing division if in doubt.

c. Demographic and other characteristics of study population

The relevant demographic, baseline, and other characteristics of the study population will depend on the drug, but will usually include:

1) Age, both mean and numbers within defined ranges, such as decades
2) Sex
3) Race
4) Body weight
5) Primary diagnosis
6) Secondary diagnoses
7) Concomitant therapy taken during the study
8) Smoking status and history
9) Ethanol use

10) Relevant prognostic variables (e. g., the frequency of such adverse events as arrhythmias, sudden death, or heart failure is affected by such prognostic factors as previous acute myocardial infarction)

These should be presented for the entire drug-exposed population and for logical groups of studies, such as all controlled trials, short-term trials, longer term trials, etc. , preferably the same groupings used in displaying adverse experiences (see next section).

The groups should be defined clearly and the studies included specified. For the controlled trials, a similar display should be provided for control agents.

d. Adverse experiences in clinical trials

1) The overall adverse event experience in all studies should be described in a brief narrative, supported by the following more detailed tabulations and analyses.

2) Display of adverse events and occurrence rates

All new adverse events (i.e., those not seen at baseline or that worsened during treatment), which are sometimes called treatment emergent signs and symptoms (TESS), should be summarized in tables listing each event, the number of patients in whom the event occurred, and the rate of occurrence in treated patients (patients exposed in more than one trial should be counted in a denominator only once).

a) Grouping of studies

The rate for all studies pooled (i.e., the number of patients with an event divided by all exposed patients), but excluding short-term studies, may be calculated, but it is usually not the best measure of true event rates; grouping studies in some fashion, however, can often give a better estimate of the usual response than analysis of single studies can.

Ordinarily, separate analyses should be made of studies with available case report forms and those studies that lack them. Any studies not subjected to a full safety analysis, per agreement with the reviewing division [see II.D.2.c.5), II.E.2.c.5), and II.F.2.c.5)], should not be included in the denominators of the adverse event rates for which they were not analyzed in full.

Among the studies with CRF's, various groupings should be considered, including:

i. All controlled trials, or subsets of controlled trials, such as all placebo-controlled trials, trials with any positive control, trials with a particular positive control, or trials of particular indications (and thus carried out in different populations)

   These studies are the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. For such trials, of course, rates in control and treatment groups should be compared.

ii. All trials, excluding short-term studies in normals

   Short-term studies in patients also would usually be excluded and presented separately. Note, however, that this analysis should not exclude patients in longer studies who left the study early because of intolerance; only planned short-term studies would be omitted.

iii. All trials of roughly similar duration

iv. Trials in which adverse event reports are elicited by checklist or direct questioning and those in which events are volunteered

v. Foreign trials; domestic trials

It is almost always useful to carry out the groupings suggested in i and ii; the others chosen will vary from drug to drug and will be influenced by inspection of individual study results. Whatever methods are used, it must be recognized that, as for single trial results, any specific numerical rate is a rough approximation at best, and represents a result in a specific population, with specific observers, and with specific observation techniques. The range of adverse event rates in various studies may thus be as important as any arbitrarily constructed mean.

b) Grouping of events

Adverse events should be grouped by body system, as shown in the individual study report (see Section III.B.10.b.). In combining data from many different studies it is important to use standardized terms to describe events and collect synonymous terms under a single primary term. This can be done with a standard dictionary (e.g. , COSTART, which is used to classify post-marketing terms) or another method. Rates should be presented for primary terms (defined or referenced to a dictionary) or as a single value for a defined group of terms (e.g., heartburn, indigestion , or dyspepsia might be considered a single adverse event).

The primary terms should be grouped by body system and arranged in decreasing frequency, and should be divided into severity categories. They may be further divided into those considered related to drug use and those not considered so related, with an explanation of how such determinations were made.

3) Analysis of adverse event rates

Once rates of adverse events are calculated for the various study groupings, they can be analyzed in various ways. For controlled trials, rates should be compared in treatment and control groups and events that appear unrelated to treatment should be identified (e. g., those that appear at approximately equal rates and severity in both groups in a placebo-controlled study state). In these comparisons, as in any analysis of controlled trials, attention should be paid to comparability of groups for pertinent variables.

In uncontrolled studies, comparisons with a concurrent control are not possible; it may be useful to compare treatment with baseline periods and to compare rates in controlled and uncontrolled studies, especially where patient populations are similar.

The more common adverse events, especially if serious or very troublesome to patients, that appear to be related to drug use should be analyzed for relationship to dosage, to mg/kg dose, if weight data are available,

to dose-interval, to duration of treatment, to cumulative dose or dose-exposure time product in some cases, to demographic characteristics such as age, or to other baseline features, such as renal function, and to blood level, if blood level data are available. As in the case of similar analyses of effectiveness, minor differences should be described but need not be analyzed with rigorous statistical methods. It is substantial differences, potentially useful to the prescribing physician, that are sought in such analyses. If a finding of "no difference," e.g., no evidence of an increasing rate of an important adverse event with age, is considered important or a potential labeling claim, there should be an analysis of the statistical power or confidence limits of the finding.

A final display of adverse reaction rates should be developed for use in labeling. Many ways of displaying the data in labeling have been utilized and discussions with the reviewing division will be useful.

4) Display and analysis of deaths, dropouts due to adverse events (adverse dropouts), and other serious or potentially serious adverse events

The lists of patients who died or who left a study prematurely due to adverse events, and patients with other serious or potentially serious adverse events from individual studies should be combined for this section to make overall lists of deaths, adverse dropouts, including laboratory abnormalities leading to termination, and other serious adverse events. As in the individual studies, the listing should include a patient identifier and the information called for in Section III.B.10.b.5), the study identifier, the location of the report, and the location of the narrative description of the event. Alternatively, it may be convenient to reproduce these narrative descriptions in this section. For these overall lists, the adverse events should be grouped by body system and within systems by reactions of the same general type.

In addition to the individual patient listings, if there are many deaths and adverse dropouts, it will be helpful to give rates of such events in a table similar to that for all adverse reactions (see Table 2 in Appendix A for an example of such a table for controlled trials; a similar table could be made for uncontrolled studies or for all patients in trials of more than a certain duration, such as one day).

The significance of these serious and potentially serious adverse events should then be evaluated from at least two points of view.

a) The recognized and clearly drug-related events that lead to dropping out or death, even if they are expected effects of the drug, represent the most important safety concerns associated with use of the drug, as indicated by the outcome and investigator behavior. They deserve particular attention in labeling with respect to warning information and to specification of any steps that can be taken to avoid, mitigate, or treat them. In addition, the data base should be searched for any feature that seems to increase the risk of these events, such as a patient demographic characteristic (age, sex, race), a concomitant illness (such as renal failure), dosage above a certain level, or particular concomitant treatment.

b) The serious, potentially life-threatening events that are not known to be drug-related should be searched for clues to an unexpected drug relationship. It has historically been tempting to consider as intercurrent illness, or as related to the underlying disease, adverse events that in retrospect were drug-related. It should be appreciated that in most treatment populations of 1000-2000, screened at baseline for major abnormalities and basically well except for a specific illness, such events as acute hepatitis, acute renal failure, aplastic anemia, agranulocytosis, thrombocytopenia, seizures, ventricular tachyarrhythmias, gastrointestinal hemorrhage, stroke, pulmonary embolism, acute myocardial infarction, peripheral arterial obstruction, or sudden death are unusual and will usually not occur in the course of a several-month period of observation. Any such events deserve close scrutiny, comparison between treatment groups, and, if possible, comparison with historical series of the same patients.

   Obviously, certain populations will be pre-disposed to some of these kinds of events, but the extent of such predisposition should be evaluated with available data, not assumed.

It may not, indeed often will not, be possible to decide whether a particular serious event is drug-induced, but such events should be noted for future review and consideration in the post-marketing period and perhaps identified in labeling as a possible adverse effect of uncertain relationship to the drug. Steps planned to evaluate adverse events further should be noted.

Either of the above analyses may be facilitated by use of life table approaches (or cumulative occurrence tables) to define risk in relation to time on drug. This may be done by grouping all patients from all studies (see Appendix A, Table 3) or by examining studies individually (see Appendix A, Table 4).

e. Clinical laboratory evaluation in clinical trials

This section should combine data from individual studies, using analyses similar to those in individual study reports, such as changes in mean or median, analysis of shifts in individuals, and analysis of individual marked abnormalities, to provide an overall analysis. The number of patients included in any analysis (number who had a particular test) should be clear. It will generally be appropriate to include separate analyses of studies that include a control, where the control can assist in the interpretation of changes seen, and those that do not, where the only comparison available is with the patient's own baseline.

Any clinically significant abnormality found in one or more patients should be discussed, unless it has been considered earlier under adverse dropouts, and it is usually useful to examine smaller deviations of the same parameter in other patients, and closely related measu rements.

It may be useful to display relationships between laboratory tests (e. g., to identify the numbers of patients with both elevated transaminase and elevated' bilirubin), to look at clinically relevant subsets of patients (e.g., those with a specified abnormality on more than one measurement), or to examine relationships between particular adverse events and particular laboratory abnormalities. The patients identified as having both events (both lab abnormalities or the ADR and the abnormality) or being in the clinically relevant subset of lab abnormalities can then be examined more closely.

As for the analysis of adverse events, relationship of drug-related abnormalities to dose, to mg/kg dose to duration of treatment, to cumulative dose, or to particular patient characteristics (age, renal or hepatic function abnormalities, concomitant illness, etc.) should be explored. The particular results seen with any drug will often suggest further analyses.

The fact that different laboratories utilize different normal values can pose a problem. However, data based on the same test method may be grouped. The method for doing this should be described. It may be necessary to "normalize" some lab parameters, such as transaminases, so they can be combined across studies (i.e., record percent above upper limit of normal rather than actual value).

f. Adverse events, including laboratory abnormalities, from sources other than clinical trials

All sources of adverse events, other than trials, including foreign marketing experience (information from regulatory authorities, foreign subsidiaries, journal articles, letters to the editor), formal epidemiologic studies, etc., should be summarized. The procedures used to examine these sources, including the method used to search the world literature, should be described.

g. Animal data

Animal data pertinent to human safety should be summarized (reference to the overall summary may be sufficient), particularly including results of carcinogenicity testing and reproductive testing. The implications of comparative ADME studies should be discussed. Planned additional studies or repetitions of studies should be described and the implications of any important findings for labeling, use restrictions, etc., discussed.

h. Analysis of adverse effect dose-response information

There should be an integrated analysis of all data, from animal , clinical pharmacology, controlled and uncontrolled studies, that bear on the dose-response and blood level-response relationships of adverse effects, the method of dose selection, and the choice of dose-interval, and that support the dosing recommendations proposed. Particular attention should be paid to the comparison of effectiveness and adverse effect dose-responses (the "therapeutic ratio"). The implications of this analysis for individualization of therapy to minimize adverse effects while maintaining effectiveness should be discussed.

Any evidence of different dose-response relationships in age, sex, disease, or other subpopulations should be described. The ways in which such differences were looked for, even if none were found, should be described (e.g. , specific studies in age or sex subpopulations, or in patients with renal or hepatic impairment or specific concomitant illness; analyses of adverse event rates by subgroup; use of trough and/or other blood level determinations of drug, etc.).

i. Drug-drug interactions

Formal study of all possible interactions is impossible, but the application should include a frank discussion of available data:

1) Potential interactions

Theoretically likely interactions, such as those predictable from the known pharmacologic properties of the drug (e.g., effects on protein binding, on renal or hepatic blood flow, or on hepatic enzymes, or interactions known to occur with other members of the pharmacologic class) should be identified.

2) Drugs likely to be co-administered with the new drug in clinical use should be identified.

3) All data bearing on drug-drug interactions should be summarized, including:

a) Formal pharmacokinetic and pharmacodynamic studies

b) Experience from clinical trials

The concomitant therapies used in all studies should be listed and the number of patients using each concomitant drug while exposed to the test drug given. These concomitant therapy subgroups should be examined for any unusual adverse event profile. Such an evaluation is not nearly so rigorous as a formal trial intended to study potential interactions but as it is impossible to study all potential interactions, this analysis provides some assurance that major effects are not present.

It may also be useful to examine trough or other blood levels of critical concomitant therapy (e.g. , digoxin, theophylline, antiarrhythmics) before and during use of the test drug, looking for changes in relation to test drug use (a "drug interaction screen").

j. Drug-demographic and drug-disease interactions

Data bearing on drug-demographic and drug-disease interactions should be summarized, including:

1) Formal pharmacokinetic and pharmacodynamic studies

2) Experience from clinical trials should be analyzed as for drug-drug interactions, above, with emphasis on diseases or demographic features that could alter metabolism or distribution of drug, to look for features that are associated with more frequent or more severe adverse effects.

k. Pharmacologic properties other than the property of principal interest

For almost any drug in any pharmacologic class, it is important to have a reasonably complete pharmacologic profile. We know, for example, that CNS drugs can have profound cardiac effects, and cardiac drugs profound CNS effects. Certain kinds of data seem relevant to almost any drug and the availability of such information is relevant to any reviewer.

The application therefore should describe the available data from human and animal studies about other pharmacologic properties of the drug, especially those that have proved often to be pertinent to the use of drugs, particularly to their unwanted effects and drug-drug interactions, including:

effects on liver blood flow or liver metabolizing enzymes,
effects on renal blood flow, GFR, or renal concentrating mechanisms,
effects on the electrophysiologic properties of the heart,
effects on hemodynamic measurements,
effects on the sympathetic or parasympathetic nervous systems,
effects on CNS function,
effects on endocrine function, and
effects on immunologic functions

Evaluation of these properties does not necessarily require formal human pharmacologic study. It might, for example, be reasonable to conclude from controlled trials that show no sedation or dry mouth that a drug does not have sedative or anticholinergic properties. Sometimes results of clinical trials will suggest more formal study; any planned further study should be described.

l. Long-term adverse effects

Available long-term (6 months or more) data should be summarized and delayed adverse effects identified.

m. Withdrawal effects

Specific studies of withdrawal effects and evidence from withdrawal events that occurred in the course of clinical trials should be summarized.

3. Update of Safety Information [21 CFR 314.50 (d)(5) (vi)(b)]

(As noted above, not all of the following sections may be necessary, especially if additional data are few, or represent principally marketing and other open experience, and would not alter the data and conclusions in the original integrated summary of safety information materially.)

a. Table of new investigations (or added data in previously reported investigations), as in Section II.H.2.a above.

b. Additional extent of exposure and, if total exposure has been substantially changed (as a rule of thumb, increased by 25% or more), reanalysis of total exposure as in Section II.H.2.b above.

c. Demographics of additional exposure and reanalysis of total exposure as in Section II.H.2.c, if exposure has substantially changed.

d. Adverse experiences in new investigations, analyzed and displayed as in Section II.H.2.d above. If the new exposure is substantial, i.e., a 25% increase or more, an overall analysis examining both the new and old data together should ordinarily b carried out, using the same displays and analyses as in the original submission, as described in Section II.H.2.d. If the new data overall lead to conclusions that are substantially different from conclusions based on earlier data, it will be necessary to examine possible causes of the differences, and it may be necessary to provide complete reports of the safety aspects of individual studies, as described in Section III.

As indicated earlier, the reviewing division may decide that some of these analyses will not be useful; e.g., if the data base is already very large, further analysis of the more common adverse events may not be helpful. In that event, detailed analysis might be restricted to deaths, adverse dropouts, and other serious or potentially serious adverse events (see Section II.H.2.d.4) above), to less serious events of particular interest based on the analysis in the initial submission, and to events in particular subpopulations not well represented in the initial submission (e.g., elderly patients or patients with impaired renal or hepatic function).

e. Clinical laboratory evaluation

New data should be presented as described above for adverse experiences in the new investigations (II.H.3.d).

f. Adverse events from sources other than clinical trials

New data in these categories, including an update of the search of the world literature, should be provided as described in Sections II.H.2.f,II.F.2.b.3) and 4), and II.F.2.d.

g* Other analyses

Ordinarily, it will not be necessary to provide the additional analyses of dose-response, drug-drug interaction, or drug-demographic or drug-disease interaction (Sections II.H.2.h-j) unless the new data are very extensive and substantially improve the ability to carry out such analyses. Relevant animal data and information on other pharmacologic properties, long-term adverse effects, or withdrawal effects should be provided (see Sections 11. H.2. g and 11. H.2.k-m).

1. Drug Abuse and Overdosage Information [21 CFR 314.50 (d)(5)(vii)]

If a drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act, should be provided. If the drug is pharmacologically or structurally related to another drug known to have abuse potential, and studies of its abuse potential have not been performed, the reasons these studies are considered unnecessary should be discussed.

Studies related to overdosage and any observed instances of overdosage should also be provided, including information on dialyzability, antidotes, or other treatments. Animal data may be useful.

J. Integrated Summary of Benefits and Risks of the Drug
[21 CFR 314.50(d)(5)(viii)]

Ordinarily the integrated summary of benefits and risks can be a brief recapitulation of the main evidence of effectiveness and the main adverse effects, showing that under the conditions of use defined in labeling, the expected benefits of use exceed the risks. In some cases, however, more detailed discussion is needed to deal with difficult risk/benefit decisions. When to provide such discussion must be left to the applicant, but the following situations suggest a need for special attention:

1. Presence of a particularly severe known or potential human toxicity (such as hepatotoxicity, induction of seizures, severe hematologic toxicity, induction of severe birth defects, abortifacient properties), especially if frequent. In that case, use of the drug may need to be directed, through labeling or other means, to particular subsets of patients, and special precautions may be needed. It will generally be necessary to consider the risks and benefits of alternative therapies and to consider a possible role for the new drug only as a "not for initial use" or as a "last resort" agent.

2. A positive or possibly positive carcinogenicity finding requires detailed discussion, including whether or not use of the drug needs to b? limited because of it and whether there is need for repeat studies.

3. Marginal effectiveness or inconsistent evidence of effectiveness bears discussion, especially in relation to other drugs for the same purpose. The poor results could, among other reasons, reflect poor study design in some of the studies, lack of available patients for study due to the presence of effective marketed drugs, or a truly marginal effect.

4. A particularly limited data base, often all that is obtainable for drugs intended for relatively rare diseases, calls for some discussion, e.g., of plans to obtain additional data after marketing or why the data base should be considered sufficient.

5* When the claimed effect is on a "surrogate" endpoint, i.e., not the ultimate reason for treatment, such as to reduce mortality or morbidity, but on an endpoint more readily measured, and thought to be related to, and likely to predict, a favorable effect on the true endpoint, discussion of the risks and benefits of the drug should reflect this. (Note also need for discussion in Integrated Summary of Effectiveness data, G.2.a.)

The applicant should address in this section any important risk/benefit questions that remain unanswered, particularly potential safety problems whose evaluation awaits further data, and should detail plans for further study or evaluation to resolve the unanswered questions.

III. THE FORMAT AND CONTENT OF THE FULL INTEGRATED CLINICAL AND STATISTICAL REPORT OF A CONTROLLED CLINICAL STUDY

A. Introduction

The study report described in this section is an "integrated" full report in which the clinical and statistical descriptions, presentations, and analyses are integrated into a single report, incorporating tables and figures into the main text of the report, or at the end of the text, and with appendices containing the protocol, investigator information, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output, etc. The integrated full report should not be derived by simply attaching a separate statistical report to the clinical report. The format and content of the full integrated report of a controlled clinical study described in this section is based on previous separate clinical and statistical draft guidelines and describes a report that will satisfy the needs of both disciplines. Specific statistical issues, including discussions of dropouts and missing data, multiple investigator studies, interim analysis, adjustments for covariates, multiple endpoints, use of an "efficacy subset," and active control studies, now appear in Section III.B.9.c.2). A discussion of machine-readable data bases is presented under Section III.B.9.d.2). and Appendix B. Finally, the discussion on protocol and protocol cover sheet now appears in Appendix t.

The following description of the data that should be provided in a complete description and analysis of a study reflects what is needed for a controlled clinical trial in which there is equal interest in both the effectiveness and safety information. For uncontrolled studies or studies of conditions for which no claim is made in the application (Sections II.E and F above), or controlled studies that plainly do not show effectiveness or that are flawed in design or conducted such that they should not be considered as contributing to evidence of effectiveness [see Section 11. D.2. c.5)], the effectiveness results and details of design (Sections III.B.6-9) may be presented more briefly. Safety aspects of these studies, however, should be treated as described in this section.

Clinical pharmacology studies vary greatly in design and need for detailed analysis, but, in general, the detailed presentations should be similar to those for a well-controlled study, adapted as appropriate to the specific situation.

The guidance provided below is more detailed than guidance provided in the past and is intended to notify the applicant of virtually all of the information that need routinely be provided so that post-submission requests for further data and analyses can be reduced as much as possible. Nonetheless, specific requirements for data presentation and analysis, especially related to demonstration of effectiveness, vary from drug class to drug class and cannot be described in general terms; it is therefore important to refer to specific clinical guidelines and to discuss data presentation and analyses with the reviewing division.

The report should provide enough information on the methods and conduct of the study so that there is no ambiguity in how the study was carried out and should provide enough individual data, including the demographic and baseline data used to assess group comparability, and details of analytic methods, to allow replication of the critical analyses. It is also particularly important that all analyses, tables, and figures carry, in text or as part of the table, clear identification of the patient population base from which they were generated.

Analysis of safety-related data can be considered at three levels. First, the amount of exposure (dose, duration) should be examined to determine the extent to which safety can be assessed from the study. Second, the more common adverse events, including laboratory test changes, should be identified, classified in some reasonable way, compared for treatment groups, and analyzed, as appropriate, for factors that may affect the frequency of adverse reactions, such as time dependence, relation to demographic characteristics, relation to dose, cumulative dose or blood level, etc. Finally, potentially serious, but less common, adverse events should be identified, usually by close examination of patients who left the study prematurely because of an adverse event or who died,

The full integrated report of the individual study will include the most detailed discussion of individual adverse events or laboratory abnormalities, but it is usually essential to reexamine these as part of an overall safety analysis of all available data (Section 11. H).

In presenting the detailed description of how the study was carried out, it may be possible simply to restate the description in the initial protocol. Often, however, it is possible to present the methodology of the study more concisely in a separate document. In each section describing the design and conduct of the study (Sections II.B.6-9), it is particularly important to clarify features of the study that are not well-described in the protocol and identify ways in which the study as conducted differed from the protocol.

At several points, detailed patient data listings are requested (demographic and baseline data, effectiveness data, certain safety data). The full data extracted from case report forms are provided in the case report tabulations (Section IV), but these, being entirely comprehensive, serve as an archival or reference document, not as listings suitable for ordinary review. The data listings requested as part of the report (in an appendix to it) are focused on the particular variables critical to the analyses carried out, allowing the reviewer to examine the individual patient data underlying critical group measurements. While in general it is desirable to include as many variables as possible in a single listing, this should not be at the expense of clarity. An excess of data should not be allowed to lead to overuse of symbols instead of words or easily understood abbreviations, too small displays, etc. It is preferable to divide the tables.

In any data listing, imputed values, if used, should be identified in a conspicuous fashion. Detailed explanations should be provided as to how such imputations were done and what underlying assumptions were made. Imputations should, however, be avoided as much as possible, as they are potentially biased and likely to lead to disagreement or controversy.

In general, a study planned as a **multicenter** study, in which all centers are analyzed, can be presented as a single study with the investigator as a **covariate** or blocking factor. Any critical differences between clinics in the conduct of the study should be noted and the impact of such differences assessed. Key efficacy measures should be displayed by investigator and the larger studies should be analyzed separately. See Section **III.B.9.c.2)d)** for additional comments on **multicenter** studies.

It cannot be emphasized too strongly that in the following outline the specific **sequence** is not critical, but the topics listed should be considered and omitted only if clearly not pertinent. Additional topics might be added at appropriate places if necessary.

B. The Full Integrated Clinical and Statistical Report of a Controlled Clinical Study

The report of an individual study should generally include the following:

1. Title page

   The title page should contain the protocol number (or other identifier), the title of the report, the name and affiliation of the investigator(s), the names and telephone numbers of

the sponsor's staff members who should be contacted for clinical and statistical questions, the dates of initiation (first patient enrollment) and completion (last patient's last observation), date of any early termination, and the date of the report.

2. Table of contents for the study

   The table of contents for the study should include volume and page number of each major part, including tabulations and case report forms. It should provide a list of appendices, if any, and of any tables separated from the text of the report.

3. Identity of the test materials, lot numbers, etc.

   For long-duration trials of test materials with limited shelf-lives, the logistics of resupply of the materials should be described. Any use of test materials past their expiration date should be noted, and patients receiving them identified. Any modifications of active control drugs from their usual commercial state should be noted (e.g., grinding a tablet and placing it in a capsule to facilitate blinding) and steps taken to assure that its clinical performance is unaltered noted.

4. Introduction

   The introduction should contain a brief statement of general intent and design of the trial. It should provide brief background information to place the study in proper context within the drug's clinical development and to indicate any special features or aims of the study.

5. Study objectives

   A statement of the specific objectives of the study should be provided. In addition to the primary objective, any secondary questions and subgroup hypotheses should be stated explicitly. It should be noted whether the objectives were pre-planned or formulated during or after completion of the study.

6. The investigational plan

   a. Overall design and plan of the study

      The overall study plan and design, and the organization of the study should be described briefly but clearly, using charts and diagrams as needed. The descriptions should include the treatments (specific drugs and doses) being

compared; the patient population; the level and method of blinding (e. g., open, double-blind, single-blind, some blinded observers with other participants unblinded, etc.); the method of assignment of patients to treatment groups (e.g., randomization, stratification); the study configuration (parallel, crossover, etc.); and the sequence and duration of all study periods, including, as appropriate, a previous therapy withdrawal period, a baseline open or single-blind placebo period, the drug treatment period (sometimes including a titration and fixed dose period), a therapy withdrawal or post-treatment observation period, and any other defined period. It is usually helpful to display the design graphically (Appendix A, Figure 2, provides an example of a study flow chart showing doses, timing of clinic visits, and measurements at each visit). The actual protocol should be included as an appendix to the study report (Section III.B.13.c). Essential features of a protocol are discussed in Appendix C of the guideline and an example of a protocol cover sheet, which would enable the reviewer to quickly ascertain the principal features of the study design, is provided. If the study had an organizational structure in addition to the investigator (safety committee, data-monitoring committee, ECG committee, etc.), it should be described.

If other submitted studies used an essentially identical protocol, this should be noted and any differences described. It may be possible in that case to eliminate most of the description of the investigational plan.

If there was no written protocol for the study, there should be a detailed description of how the details of study design and conduct were determined.

Any important change in the protocol or conduct of the study made after the study was initiated should be described and its implications considered. Such changes could include dropping a treatment on the basis of intolerance or an interim analysis showing lack of effectiveness, altering the dose or dosing regimen, altering entry criteria, etc. These changes should be described briefly in this section and more fully in other sections where appropriate.

b. Description and discussion of the design and choice of control group(s)

The specific control chosen and the study design used should be discussed, as necessary. Generally, the control (comparison) groups that are identified in regulations are placebo concurrent control , no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. These controls are described further in 21 CFR 314.126. In addition to the type of control, other critical design features that may need discussion are use of a crossover design and selection of patients with particular prior history, such as response or non response to a particular drug.

Known or potential problems associated with the design chosen, and its suitability for the specific claims under study, should be discussed. For example, for a crossover design, there should be consideration of the likelihood of spontaneous changes in the disease during the study, and the need (or lack of need) for reestablishment of baseline between treatment periods, or a plan to estimate residual effects to show that they are inconsequential. For a positive (active) control study, there should be evaluation of the appropriateness of the control and of the dose employed (e.g., regulatory approval of the treatment for the condition studied, literature support for effectiveness), and of whether the study was intended to show a difference between treatments or show similarity between them; if intended to show the latter, the present study design and patient population should be compared with previous studies of the control agent that were successful in showing effectiveness compared to placebo. Problems associated with the use of positive control study designs to demonstrate equivalence of a new drug to a standard agent have been considered in detail in recent publications: Temple R: "Government Viewpoint of Clinical Trials," DIA Journal: January/June 1982; Temple, R: "Difficulties in Evaluating Positive Control Trials," American Statistical Association: August 1983, pp. 1-7. The limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, etc.) and deserve particular attention.

Other specific features of the design may also deserve discussion, including presence or absence of washout periods and the duration of the treatment period, especially for a chronic illness. The rationale for dose and dose-interval selection should be explained, if it is not obvious. For example, once daily dosing with a short half-life drug whose effect is closely related in time to blood level is not usually effective; if the study design uses such dosing, this should be explained, e.g., by pointing to pharmacodynamic evidence that effect is prolonged compared to blood levels, and the procedures used to seek "escape" from drug effect at the end of the dose-interval, such as measurements of effect just prior to dosing, should be described. Similarly, in a parallel design dose-response study, the choice of doses should be explained.

c. Study population

The patient population and the selection and exclusion criteria used to enter the patients into the study should be described, and the suitability of the population for the purposes of the study discussed. Specific diagnostic criteria used, as well as specific disease requirements (e.g. , disease of a particular severity or duration, results of a particular test or physical examination, or particular features of clinical history, such as failure or success on prior therapy), should be presented.

If there are both screening criteria and new criteria for randomization or entry into the drug treatment part of the trial, these should be described.

The planned sample size and the reasons for choosing it should be provided, including statistical considerations, practical limitations, etc.

d. Method of assigning patients to treatment

The specific means of assigning patients to treatment groups should be explicitly described, including any stratification or blocking procedures. A detailed description of the randomization scheme, including how it was executed, should be given in an appendix with references cited if necessary. A table exhibiting the randomization codes, patient identifier, and treatment assigned should be presented in the appendix. For a multicenter study, the table should be given by center. If the random numbers were generated by a computer, the seed number used should be indicated.

If randomization is not used, it is important to explain how other techniques, if any, guarded against systematic selection bias.

For a historically controlled trial, it is important to explain how the particular control was selected and what other historical experiences were examined, if any, and how their results compared to the control used.

e. Dose selection

Describe procedures for assigning the dose of test drug and control agent. These procedures can vary from simple random assignment to a selected fixed drug/dose regimen, to some specified titration procedure, to more elaborate response-determined selection procedures, e.g., where dose is titrated upward at intervals until intolerance or some specified endpoint is achieved. Procedures for back-titration, if any, should also be described.

The precise treatment (drug, control) used during study periods of the study (placebo baseline, randomized treatment, withdrawal, etc.) should be completely clear.

The timing of dosing in relation to meals should be described, if specified, and, if it was not specified, this should be noted.

f. Blinding

A description of the specific procedures used to carry out blinding should be provided (e.g., how bottles were labeled, double dummy techniques), including the circumstances in which the blind would be broken for individual or all patients, and who had access to patient codes. If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Measures taken to assure that drug and placebo are indistinguishable should be described, and the appearance, shape, smell, and taste of the test materials should be described.

If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained; e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Helter tapes are often read by automated systems that are presumably immune to observer bias. If blinding is considered desirable but not feasible, the reasons and implications should be discussed. Sometimes blinding is attempted but is known to be imperfect because of obvious

drug effects in at least some patients (dry mouth, bradycardia). Such problems or potential problems should be identified and if there were any attempts to assess the magnitude of the problem or manage it (e.g., by having some measurements carried out by people unfamiliar with the clinical status of the patient), they should be described.

9" Effectiveness and safety variables recorded and data quality assurance

The specific effectiveness and safety variables recorded and laboratory tests conducted, their schedule (days of study, time of day, relation to meals, and the timing of critical measurements in relation to test drug administration, e.g., just prior to dosing), and the methods for measuring them should be provided. It is usually helpful to display graphically the frequency and timing of effectiveness and safety measurements; visit numbers and times should be shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret). See Appendix A, Figure 2. Any important instructions to the patient should be noted.

The means of obtaining adverse event data should be described (volunteered, checklist, questioning), as should any specifically planned follow-up procedures for adverse events or any planned rechallenge procedure. Any rating of adverse effects by the investigator or sponsor (e.g., severity rating, likelihood of drug causation) should be described and criteria for such ratings, if any, given.

If effectiveness or safety is to be assessed in terms of categorical ratings, numerical scores, etc., the criteria used for point assignment (e.g., definitions of point scores) should be provided. Similarly, any definitions used to characterize outcome (e.g., criteria for determining occurrence of acute myocardial infarction, designation of the location of the infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between TIA and stroke, assignment of cause of death) should be explained in full.

Any steps taken at the investigation site or centrally to assure accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain

tests, centralized ECG reading, or audits based on probability sampling methods, should be described. For multicenter trials, it should be noted whether investigator meetings or other steps were taken to prepare investigators and standardize performance.

If anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g., a committee to review x-rays or ECG's or to determine whether the patient had a stroke, acute infarction, or sudden death) the person or group should be identified and procedures, including means of maintaining blindness, described fully.

h. Compliance with dosing regimens

Steps to document patient compliance (pill counts, blood or urine levels, etc.) should be described.

i. Appropriateness and consistency of measurements

If any of the effectiveness or safety assessments is not standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), its reliability, accuracy and relevance should be documented. It may be helpful to describe alternatives considered but rejected.

j. Criteria for effectiveness

The primary measurements and endpoints used to determine effectiveness should be clearly specified. Although the critical effectiveness measurements are often obvious, when there are multiple variables, or when variables are measured repeatedly, the protocol should identify the primary ones, with an explanation of why they were chosen, or designate the pattern of significant findings that would be interpreted as supporting effectiveness. If the protocol did not identify the primary variables, the study report should explain how these critical variables were selected (e.g., by reference to publications or past FDA action) and when they were identified (i.e., before or after the study was completed), and discuss the need, or lack of need, for statistical adjustments of type I error criteria for multiple comparisons.

k. Concomitant therapy

Describe which drugs were allowed during the study, how their use was recorded, any other specific rules and procedures related to concomitant therapy, and why allowed concomitant therapy would not be expected to confound treatment effect due to drug-drug interaction or how their independent effects could be ascertained.

l. Removal of patients from the study or analysis

The predetermined reasons for removing patients from therapy, if any, should be described, as should the nature and duration of follow-up procedures. In addition, any pre-set rules regarding which patients are "evaluable" should be described. Indecisions about evaluability are made after blinding is broken, this should be noted specifically, and the potential bias introduced thereby discussed.

7. Statistical methods planned in the protocol

a. Statistical and analytical plans

Describe the planned statistical analyses and any changes made during or after the conduct of the study. In this section emphasis should be on which analyses and comparisons were planned, not on the specific statistical techniques used. If critical measurements were made more than once, the particular measurements (e.g., average measurements over the entire study, values at particular times, values only from study completers, or last on-therapy value) planned as the basis for comparison of drug and control should be specified. If there were any planned reasons for excluding from analyses patients for whom data are available, or any subgroups whose results were to be examined separately, these should be identified. If categorical responses (globals, severity scores, responses of a certain size) are to be used in analyzing responses, they should be clearly defined.

Planned monitoring of the results of the study should be described. If there is a data monitoring committee, either within or outside the sponsor's control, its composition and operating procedures should be described and procedures to maintain study blinding should be given. The frequency and nature of any planned interim analyses, any specified circumstances in which the study would be terminated, and any statistical adjustments to be employed because of interim analyses should be described.

b. Statistical determination of sample size

The planned sample size and the basis for it, such as statistical considerations or practical limitations, should be provided. Formulae for sample size and power calculation should be given together with their derivations or source of reference. Estimates used in the formulae should be given and explanations provided as to how they were obtained.

For a positive control study intended to show that a new therapy is at least as effective as the standard therapy, the sample size determination should specify a "delta value," a difference between treatments that would be considered clinically meaningful. A difference smaller than this delta would therefore indicate that the new therapy was clinically equivalent to the standard therapy. The power to detect a treatment difference of magnitude delta or greater (see Tables 5 and 6 in Appendix A for illustrations) should be given.

8. Disposition of patients entered

There should be a clear accounting of all patients who entered the study. The numbers of patients who entered and completed each phase of the study, or each week/month of the study (a flow chart is often helpful; see Table 7 in Appendix A), should be provided, as well as the reasons for all post-randomization discontinuations, grouped by treatment assignment and by major reason (lost to follow up, adverse experience, poor compliance, etc.). There should also be a patient-by-patient listing, by treatment group, giving a patient identifier, the reason for leaving, the treatment (drug and dose), and the duration of treatment before participation ended (see Table 8 in Appendix A for illustration). Whether or not the blind for the patient was broken at the time he left the study should be noted. It may also be useful to include other information, such as critical demographic data (age, sex), concomitant medication, and the major response variable(s) at termination.

For a multicenter study, these data should be displayed by center.

9. Efficacy results

a. Data sets analyzed

Exactly which patients are included in the effectiveness analysis should be precisely defined, e.g., all patients with any effectiveness observation or with a certain minimum number of observations,, only patients completing the trial, all patients with an observation during a particular time window, only patients with a specified degree of compliance, etc. It should be clear, if not defined in the study protocol, when, relative to study completion, and how, inclusion/exclusion criteria were developed. As a general rule, even if the applicant's preferred analysis is based on a reduced subset of the patients with data, there should be an additional "intent-to-treat" analysis using all randomized patients.

There should be a tabular listing of all visits excluded from the effectiveness analysis (see Table 9 in Appendix A for an illustration). The reasons for exclusions should also be analyzed for the whole treatment group over time (see Table 10 in Appendix A).

b. Demographic and baseline features of individual patients and comparability of treatment groups

The critical demographic and baseline characteristics of the patients, as well as other factors arising during the study that could affect response, should h presented, and comparability of the treatment groups for each relevant characteristic should be documented by use of tables or graphs. If the data sets in the "intent-to-treat" analysis and the applicant's preferred analysis are substantially different, comparability of treatment groups in both sets should be examined and any other reasons for such differences should be discussed. The critical variables will depend on the specific nature of the disease, but will usually include demographic variables like age, sex, race, and weight; disease factors such as specific entry criteria (if not uniform), the duration and severity of the disease, and the baseline values for the critical clinical measurements carried out during the study; concomitant illnesses such as renal disease, diabetes, or heart failure; and concomitant treatment maintained, varied, or added during the study. In a multicenter study comparability should be assessed by center and the centers should also be compared.

In addition to tables and graphs representing group data for these baseline variables, individual patient demographic and baseline data and all concomitant medications taken should be presented in tabular listings. The applicant must decide which demographic and baseline information belongs in the full report of the study (as an appendix to the study report) and which can be included in the case report tabulations (21 CFR 314.50(f)); if in doubt, the applicant should discuss the matter with the reviewing FDA division, but ordinarily the full report should include at least the critical variables mentioned above, with specific baseline laboratory values where appropriate, listed by patient, within treatment group, and by investigator, if more than one, and including all patients randomized. An illustration of such a table is given in Appendix A, Table 11.

c. Analysis of each effectiveness measure and tabulation of individual patient data

1) Analysis of measures of effectiveness

Treatment groups should be compared for critical measurements of effectiveness. In general, results of all analyses contemplated in the protocol should be presented using tables and graphs to facilitate presentation. ,,

Analyses based on continuous variables (e.g., mean blood pressure or depression scale score) and categorical responses (e.g., proportion of patients achieving cure of an infection) can be equally valid; ordinarily both should be presented if both were planned and are available. Even if one variable (e. g., in a blood pressure study, supine blood pressure at week x) receives major attention, other reasonable measures (e.g., standing blood pressure and blood pressures at other particular times) should be assessed, at least briefly. In addition, the time course of response should be analyzed, if possible. For a multicenter study, data display and analysis of individual centers should be included to give a clear picture of the results at each site, especially the larger ones. If any critical measurements or assessments have been made by more than one group (e. g., both the investigator and an expert committee may offer an opinion on whether a patient had an acute infarction), overall differences between the ratings should be shown, and each patient having disparate assessments should be identified The assessments utlized should be clear in all analyses.

2) Statistical/analytical issues

The statistical analysis used should be described, with detailed documentation of statistical methods presented in an appendix (see Section III.B.9.d). Important features of the analysis, such as the particular tests used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of drop-outs and missing data, adjustments for multiple comparisons, special analyses of multicenter studies, and adjustments for interim analyses, should be discussed.

a) Adjustments for covariates

Selection of, and adjustments for, demographic or baseline measurements, concomitant therapy, or any other covariate or prognostic factor should be explained in the report, and methods of adjustment, results of analyses, and supportive information (e.g., ANCOVA or Cox regression output) should be included in the detailed documentation of statistical methods. Information for individual studies presented in Tables 12 and 13 would be useful for documenting these types of adjustments in the individual study reports; in addition, comparisons of effects of various prognostic variables as illustrated in these tables would be useful in the Integrated Summary of Effectiveness Data for Controlled Studies (see Section II.G.2.b of this Guideline).

b) Handling of dropouts or missing data

There are several factors that may affect dropout rates. These include the duration of the study, the nature of the disease, the effectiveness and toxicity of the drug under study, and other factors that are not therapy related. Ignoring the patients who dropped out of the study and drawing conclusions based only on patients who completed the study can be misleading, but a large number of dropouts, even if included in an analysis, may introduce bias, particularly if there are more early dropouts in one treatment group. While the effects of early dropouts, and sometimes even the direction of bias, can be difficult to determine, possible effects should be explored as fully as possible. It may be helpful

to examine the observed cases at various time points or, if dropouts are very frequent, to concentrate on analyses at time points when most of the patients are still under observation and when the full effect of the drug has been realized.

The results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population randomized (the intent-to-treat analysis). Several factors need to be considered and compared for the treatment groups in analyzing the effects of dropouts: the reasons for the dropouts, the time to dropout, and the proportion of dropouts among treatment groups at various time points.

Procedures for dealing with missing data, e.g., use of imputed data, should be described. Detailed explanation should be provided as to how such imputations were done and what underlying assumptions were made.

c) Interim analyses and data monitoring

The process of examining and analyzing data accumulating in a clinical trial, either formally or informally, can introduce bias. Therefore, all interim analyses, formal or informal, by any study participant, sponsor staff member, or data monitoring group should be described in full, even if the treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed. Minutes of meetings of a data monitoring group may be useful (and may be requested by the review division).

d) Multi center studies

A **multicenter** study is a single study involving several centers (or investigators) where the data collected from these centers are intended to be analyzed as a whole (as opposed to a post-hoc decision to combine data or results from separate studies). Individual center results should be presented, however, and statistical tests for homogeneity across centers, i.e., for detecting treatment-by-center interaction, should be provided. The significance level used to declare the significance of a given test for treatment by center interaction should be considered in light of the sample sizes involved. Any extreme or opposite results among centers should be noted and discussed. As mentioned in previous sections, "demographic, baseline, and., post-baseline data, as well as efficacy data, should be presented by center, even though the combined analysis is the primary one. Figure 1 in Appendix A with study # replaced by center on the X-axis is a display of individual center results with associated **95%-confidence** intervals.

e) **Multiple** endpoints

False positive findings increase in frequency as the number of significance tests (number of comparisons) performed increases. If there is more than one primary endpoint (outcome variable), or if there are multiple treatment groups, or subsets of the patient population being examined, statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why they are considered unnecessary.

f) Use of an "efficacy subset" of patients

Particular attention should be devoted to the effects of dropping patients with available data from analyses because of poor compliance, missed visits, or any other reason, and, as noted above, an analysis using all available data should be carried out, even if it is not the analysis preferred by the applicant.

g) Active-control studies

If the trial is an active-control study intended to show equivalence between the test drug and active control, there should be assessments of (1) the response of the standard agent in the present trial compared to previous studies of similar design that included comparison with placebo and (2) the ability of the study to have detected differences between the treatments of a defined size, e.g., by providing confidence limits for the difference between the drug and active control and/or the power to detect a difference between the treatments of specified size.

3) Examination of subgroups

If the size of the study permits, relevant demographic or baseline value-defined subgroups should be examined for unusually large or small responses and the results presented, e.g., comparison of effects by severity groups, by age, sex, or race, or by history of prior treatment with a drug of the same class. These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labeling information, patient selection, dose selection, etc.

4) Tabulation of individual response data

In addition to tables and graphs representing group data, individual response data and other relevant study information should be presented in tables. What needs to be included in the report will vary from study to study and from one drug class to another and the applicant must decide, preferably after consultation with the relevant review division, what to include in the full report (as an appendix to the study report) and what to leave for case report tabulations (21 CFR 314.50(f)). (The full report should indicate what material is included as an appendix and what is in case report tabulations.)

For a controlled study in which critical effectiveness measurements or assessments (e. g., blood or urine cultures, pulmonary function tests, angina frequency, or global evaluations) are repeated at intervals , the case report tabulations should include, for each patient, a patient identifier, all measured or observed values of critical measurements, including baseline measurements, with notation of the time during the study (e. g., days on therapy and time of day, if relevant) when the measurements were made, the drug/dose at the time (it is useful to give as mg/kg), and any concomitant medications at the time of, or close to the time of, measurement or assessment. If, aside from repeated assessments, the study included some overall evaluation(s) (responder vs. non-responder, bacteriologic cure or failure), it shqulc also be included. In addition to critical measurements, the tabulation should note whether the patient is included in the effectiveness evaluation (and which evaluation, if more than one), provide patient compliance information, if collected, and a reference to the location of the case report form, if included. Critical baseline information such as age, sex, weight, disease being treated (if more than one in study), disease stage or severity, and causative pathogen is also helpful. The baseline values for critical measurements would ordinarily b included as zero time values for each effectiveness measurement.

The tabulation described usually should be included in the full report of the study, rather than in the case report tabulations, because it represents the basic effectiveness data supporting summary tables. Such a thorough tabulation can be unwieldy for review purposes, however, and it is expected that more targeted displays will be developed as well. If there are many measurements reported, tabulations of the most critical measurements for each patient (e.g., the blood pressure value at certain visits might be more important than others) will be useful in providing a rapid overview of each individual ‘s results in a study, with each patient’s response summarized on a single line or small number of lines.

d. Documentation of statistical methods

1) Statistical considerations

Details of the statistical analysis performed on each primary efficacy measure should be presented in the appendix [Section III.B.13.f, expanding on the description provided in Section 111. B.9. c.2)]. Details reported should include at least the following information:

a) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary.

b) A statement of the clinical claim tested in precise statistical terms, e.g., in terms of null and alternative hypotheses.

c) When statistically reasonable and appropriate, the power against specific clinically meaningful alternatives for those tests that fail to reject the null hypothesis to indicate whether the study size was adequate. In addition, in an active control study if a substantial number of patients were not included in a given analysis for reasons such as dropout or non-evaluability, then a post-study calculation of the power of the test to detect a meaningful treatment difference, usually called the "delta value" (this "delta value" should have been specified in the protocol), should be provided.

d) The statistical methods applied to estimate effects, construct confidence intervals, etc. Literature references should be included (Section III.B.12), where appropriate.

e) The assumptions underlying the statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. When extensive statistical analyses have been performed by the applicant, it is essential to consider the extent to which the analyses were planned prior to the

availability of data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions. This is particularly important in the case of any subgroup analyses, because if such analyses are not pre-planned they will ordinarily not provide an adequate basis for definitive conclusions.

(1) Unnecessary data transformation should be avoided. In the event data transformation was performed, a rationale for the choice of data transformation along with the interpretation of the estimates of treatment effects based on transformed data should be provided.

(2) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the FDA statistical reviewer in determining whether reanalysis of data is needed.

(3) Only appropriate statistical methods should be used; using many methods for the same data is not appropriate. For similar protocols the method applied should be the same.

f) The ten statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e. , p-value), and intermediate summary data, in a format that enables the FDA statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one- or two-tailed. The rationale for using a one-tailed test should be provided.

For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples, and the pooled estimate of variance. The documentation of multi-investigator studies analyzed by analysis of variance techniques should include, at a minimum, an analysis of variance table with terms for investigators, treatments, their interaction, error, and total. For crossover designs, the documentation should include information regarding sequences, patients within sequences, baselines at the start of each period washouts and length of

washouts, dropouts during each period, treatments, periods, treatment by period interaction error, and total . For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value, and the expected mean square. Generally, it is recommended that SAS Type III or equivalent analyses be provided in addition to any other analyses.

Intermediate summary data should display the demographic data and response data, averaged or otherwise summarized, for each investigator-by-treatment combination (or other design characteristic such as sequence) at each observation time.

2) Format and specifications for submission of data requested by FDA's statistical reviewers

In the report of each controlled clinical study, there is a requirement for data listings (tabulations) of patient data utilized by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the FDA statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form, preferably on floppy diskettes or on magnetic tapes. In addition, patient data so submitted should be in a format readily acceptable for use on the FDA computers. Guidance on how to provide these data is provided in Appendix B.

e. Analysis of doses administered and, if possible, dose-response and blood level-response relationships

Unless the study involved fixed doses, the actual doses received by patients should be shown and individual patient's doses should be tabulated. While many studies cannot provide dose-response information because time effects cannot be distinguished from dose effects as patients are titrated, or because only poorly responsive patients are given the larger doses, the available data should be examined for whatever information they can yield. In examining the dose-response, it is helpful to calculate dose as mg/kg body weight. Blood level information, if available, should also be related to response.

f. Analysis of drug-drug and drug-disease interactions

Any relation of response to concomitant therapy or concomitant illness should be noted-.

g* By-patient displays

While individual patient data ordinarily can be displayed in tabular listings, with patients and each measurement date in columns and the collected data in rows, it has on occasion been helpful to construct individual patient profiles in other formats, such as graphic displays. These might, for example, show the value of a particular parameter(s) over time, the drug dose over the same period, and the times of particular events (e.g., an adverse reaction or change in concomitant therapy). Where group mean data represent the principal analyses, this kind of 'case report extract" may offer little advantage; it may be helpful, however, if overall evaluation of individual responses is a critical part of the analysis.

10. Safety results

a. Extent of exposure

The extent of exposure to study drugs (and placebo, if any) (number of patients exposed, duration of exposure, and dose) should be described. While mean exposure may be helpful, it is also valuable to describe exposure in reasonable categories, e.g., one day or less, two days to one week, more than one week to one month, as appropriate to the drug class. In some cases it may be useful to display dose exposure as mg/kg dose. The duration of post-treatment follow-up should also be described. It is assumed that all patients entered into treatment who received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

b. Adverse experiences

1) The overall adverse event experience in the study should be described in a brief narrative, supported by the following more detailed tabulations and analyses. In all tabulations and analyses events associated with both test drug and control drug should be displayed.

2) Display and analysis of all adverse events and occurrence rates

All new adverse events (i.e., those not seen at baseline or worsened even if present at baseline), which are sometimes called treatment emergent signs and symptoms (TESS), should be displayed in tables listing each reported adverse event, the number of patients in each treatment group in whom the event

occurred, and the rate of occurrence in each treatment group. Adverse events should be grouped by body system and each event should be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables can also divide the adverse events into those considered related to drug use and those considered not related, or use some other causality scheme (e.g., remote, possible, probable, definite). For any such categorization, the categories should be defined. Even when such a causality assessment is used, the tables should include all adverse events, whether or not considered drug related, including events thought to represent intercurrent illnesses. Subsequent analyses may distinguish between adverse events that are, or are not, considered drug related.

So that it is possible to analyze and evaluate the data in these tables, it is useful to identify each patient having each adverse event, as grouped in the table, by individual patient number, for some or all of the controlled trials (which studies to display in this fashion should be discussed with the reviewing division). An example of such a tabular presentation is shown below:

Adverse Reaction: Number Observed and Rate, with Patient Identifications

Treatment Group X N=50

	Mild*		Moderate		Severe		Total	
	Related	NR	Related	NR	Related	NR	Related	NR
Body System A								
Event 1	6(12%)	2(4%)	3(6%)	1 (2%)	3(6%)	1 (2%)	12(24%)	4(8%)
	N11**	N21	N31	N41	N51	N61		
	N12	N22	N32		N52			
	N13		N33		N53			
	N14							
	N15							
	N16							
Event 2								

*NR · not related; this could be expanded, e.g., as definite, probable, possible

**Patient identification number

If this presentation is utilized, it may be useful also to provide the table without the patient identifying numbers for quicker reference; treatment and control groups could be shown on the same page. If both tables are used, the latter should be included in the main report, the former in an appendix.

In some cases it is useful to give the number of patients who had an adverse event or no adverse event. Patient identification numbers need not be listed for these categories.

3) Grouping adverse event terms that probably represent the same event

It is important, in presenting adverse events, both to display the original terms used by the investigator and to attempt to group related reactions (i.e., events that probably represent the same phenomena) so that the true occurrence rate is not obscured. One way to do this is with a standard adverse reaction dictionary, but experience at this time is too limited to recommend a particular one for this purpose. In general, the individual study report should emphasize the reported terminology, leaving use of a standard dictionary for the integrated summary of safety data. Nonetheless, probably synonymous reactions should be grouped (e.g., heartburn, indigestion, or dyspepsia).

4) Analysis of adverse events

The basic display of adverse event rates described above should be used to compare rates in treatment and control groups. In addition, if study size permits, the more common adverse events that seem to be drug related should be examined for relationship to dosage and to mg/kg dose, to dose regimen, to duration of treatment, to total dose, to demographic characteristics, such as age, or to other baseline features, such as renal status, and to blood level, if data are available. A variety of additional analyses may be suggested by the study results or by the pharmacology of the drug.

It is not intended that every adverse event be subjected to rigorous statistical evaluation. It may be apparent from initial display and inspection that a significant relation to demographic or other baseline features is not present. Adverse events that are relatively important (those that lead to

discontinuation or dose changes or are characterized as severe) deserve closest attention. Consultation with the reviewing division is encouraged if questions arise about the kind of analysis needed.

If the individual studies are small, it may be more useful to reserve analyses other than the comparison of treatment and control for the integrated summary of safety data.

Under certain circumstances, the standard life table method analysis may be more informative than reporting of crude adverse event rates.

5) Listing of each patient's adverse event(s)

All adverse events for each patient, including the same event on several occasions, should be listed using the terminology supplied by the investigator. Laboratory findings that constitute an adverse event (ECG abnormality suggesting infarction, serious arrhythmia, etc.) should be included. Ordinarily, this listing should be included in the case report tabulations section [21 CFR 314.50(f)], but it could be included instead as an appendix to the study report. The listing should be by investigator (if more than one), and by treatment group, and should include:

patient identifier
age, sex, race, weight
treatment and dose and mg/kg dose at time of adverse experience
compliance measure, if available
date of onset, if known, or clinic visit at which event was discovered
duration of treatment at time of adverse experience
the adverse experience
duration of adverse experience
intensity (e.g., mild, moderate, severe)
action taken (none, change in dose, therapy interrupted or stopped, etc.)
outcome (e.g., recovered, no residual effect; persistent but no treatment; persistent and being treated; residual effect being treated; residual effect, no treatment; death)
relationship to test drug (how this is determined should be explained in the table or elsewhere)
location of case report form, if provided

For the table to be of reasonable size it will be necessary to use some abbreviations and codes. These should be clearly explained at the beginning of the listing, or, even better, on each page. For an example of a table, see Table 14 in Appendix A.

6) Display and analysis of deaths and dropouts due to adverse events (adverse dropouts) and other adverse events that are serious or potentially serious.

There should be listed all patients who left the study prematurely because of an adverse experience, including a laboratory abnormality that led the investigator to terminate participation, but not including instances of therapeutic failure. The listing should include a patient identifier and the same information as called for in section 5) above, as well as the location of the case report, and this listing should be part of the report, not placed in the tabulations section. A similar table should be prepared for patients requiring dose reduction or institution of concomitant therapy because of an adverse event.

All deaths during, or within a short period after, the study should be similarly listed.

If there were other serious adverse events, not included among patients who died, left the study, or had a dosage adjustment, these should also be listed.

For all deaths and all potentially serious adverse experiences, there should be a brief narrative describing each event and assessing the likelihood that the drug was responsible. Whether an adverse experience is potentially serious is a matter of judgment, and the basis for the judgment should be explained.

The significance of the fatalities and adverse dropouts should be assessed, particularly with respect to whether any of these events may represent a previously unsuspected important adverse effect of the drug.

For serious events that appear of particular importance, it may be useful to utilize life table approaches to show their relation to time on drug and to assess their risk over time. Ordinarily, however, rates of such events will be so low that such an analysis should be reserved for the Integrated Summary of Safety Information Section.

C. Clinical laboratory evaluation

1) Listing of individual laboratory measurements by patient

The results of all safety-related laboratory tests carried out on every patient should be provided in tabular listings, unless the agency has agreed in advance that a particular tabulation is not pertinent to a review of the drug's safety. These tabulations should, in general, be placed in the "Case Report Tabulations" section of the NDA, unless the applicant has reason, or is asked by the agency, to place certain of them elsewhere.

In these tabulations, each row should represent a patient visit at which a laboratory test was run with patients grouped by study, and within a study by investigator (if more than one), and by treatment group. Within each treatment group, patients generally should be listed in numerical order of patient identifier number. The tabulations should then provide a few columns of critical information about each patient, such as the visit or number of days into study period at the time of examination and drug dose (total and mg/kg), if this is variable, at the time of testing. Age, sex, and weight can also be provided although this may be available readily from other near-at-hand tabulations. The remainder of the tabulation should consist of columns giving the results of each laboratory test, one column per test, as shown on the next page:

							Laboratory Tests		
Patient	Time	Age	Sex	Race	Weight	Dose	SGOT	SGPT	AP X
#1	0	70	M	W	70 kg	400 mg	VI*	V5	V9
	1						V2	V6	V10
	2						V3	V7	V11
	3						V4	V8	V12
#2		65	F	B	50 kg	300 mg	V13	V16	V19
	:						V14	V17	V20
	2						V15	V18	V21

* Vn = value of a particular test

How many tests can be displayed in a single table will be variable but as many as possible should be included consistent with legibility, so that as complete as possible a view of each patient's laboratory experience can be encompassed by a single look at the data. If several tables are needed, tests should be grouped logically, e.g., hematologic tests together, tests of liver function together, and tests of renal function, urinalysis, and electrolytes together.

Normal laboratory ranges should be readily available at the beginning of tabulations or at the head of each page and differences among laboratories should be noted.

Some means should be devised for identifying all abnormal values, such as underlining, brackets, or asterisks, etc.

2) Listing of each abnormal laboratory value

While the complete record of laboratory tests should be included in the Case Report Tabulations, a by-patient listing of all abnormal values should be included with the full report of the study, generally as an appended table. Format is generally as above, with patients' visits representing rows and laboratory tests the columns.

It may be desirable to exclude certain abnormal values from this listing. For example, single, non-replicated, small abnormalities of some tests (e.g. , uric acid or electrolytes) or occasional low values of some tests (e.g., transaminase, alkaline phosphatase, BUN, etc.) can probably be defined as insignificant clinically and excluded. Any such decisions should be clearly explained, however, and the complete list of values provided in 1) above should identify every abnormal value.

Normal values for the laboratory carrying out each test should be provided.

3) Evaluation of each laboratory parameter

The necessary evaluation of lab values must in part be determined by the results seen, but, in general, the following analyses should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study size. In addition, normal laboratory ranges should be given for each analysis.

a) Mean (median) values over time

Mean (or median if more appropriate) values of each parameter over the course of the study (e.g., at each visit), as well as the range of values and the number of patients with abnormal values, or with abnormal values that are of a certain size, e.g., twice the upper limit of normal, 5 times the upper limit, etc. Graphs may be used.

b) Individual patient changes

Analysis of individual patient changes by group. A variety of approaches have been used, including:

i. "Shift tables" - These tables show the number of patients who are low, normal, or high at baseline and then at selected time intervals.

ii. Tables showing the number or fraction of patients who show a change in parameter of a predetermined size at selected time intervals. E.g., for BUN, it might be decided that a change of more than 10 mg/dL should be noted. For this parameter, the number of

patients having a change less than this or greater than this would be shown for one or more visits, usually grouping patients separately depending on baseline BUN (normal or elevated). The possible advantage of this display, compared to the usual shift table, is that changes of a certain size are noted, even if the final value is not abnormal.

iii. A graph plotting the initial value for each patient on the abscissa and a subsequent value on the ordinate. If no change occurs, the patient will be located on the 45° line. A general shift to higher values will show a clustering of patients above the line. As this display can show only a single time point for a single treatment, interpretation requires a time series of these plots for treatment and control groups. This kind of display identifies outliers readily.

c) Individual marked abnormalities

Although minor transient changes may not warrant detailed discussion, marked changes (defined by the applicant) require separate discussion. While a narrative of each patient whose abnormality led to discontinuation of treatment should be provided under section III.10.b.6) above, marked changes that do not lead to discontinuation should also be discussed in narrative form. An analysis of these marked changes, together with a recapitulation of the discontinuations, should be provided for each parameter. The significance of the marked changes and likely relation to the treatment should be assessed, e.g., by analysis of such features as disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy.

11. Summary and conclusions

The effectiveness and safety results of the study should be briefly summarized, referring as needed to tables, figures, and sections above as needed; particular attention should be paid to unusual findings, such as inconsistencies among related measures or failure of the expected response or a particularly serious adverse experience that may, or may not be drug related. Limitations of the study, e.g., non-applicability to particular subgroups or subpopulations, if any, should be identified. .

12. References

A list of articles from the literature pertinent to evaluation of the study should be provided, and, if necessary, copies of important publications should be attached.

13. Appendices

a. Cross-references of all pertinent materials

A table cross-referencing all summary tables, figures, and graphs to relevant supporting data, including patient data listings, ANOVA tables, and other pertinent information, should be provided (see Table 15 in Appendix A for an illustration). Alternatively, and preferably, the sponsor may provide such information with each table.

b. Protocol, sample case report form, and amendments [see Section 11. D.2. c.2)]

c. Publications based on part or all of the results of the study [see Section II.D.2.c.3)]

d. List of investigators [see Section 11. D.2. c.4)]

e. Randomization scheme and codes (see Section III.B.6.d)

f. Documentation of statistical methods (see Section 111. B.9.d)

g. Patient data listings (or reference to their location in the Case Report Tabulations)

i. Demographic data

ii. Individual effectiveness response data

iii. Adverse reaction listings [see Section 111. B.10.b.5)] and table of adverse event rates including patient numbers [see Section III.B.10.b.2)]

iv. Listing of each abnormal laboratory value [see Section III. B.10. c.2)]

IV. CASE REPORT TABULATIONS [21 CFR 314.50(f) (1)1

The requirements for tabulations are described in the regulations [21 CFR 314050 (f)(1)1.

A. Data to Be Tabulated

1. Effectiveness data from adequate and well-controlled trials, including all measurements made

2. Data from clinical pharmacology (phase 1) studies

3. Safety data (adverse events, laboratory data) from all studies

Essentially all data of these types are to be tabulated except that the applicant and agency may agree to the deletion of particular tabulations not pertinent to the evaluation of safety or effectiveness. These tabulations are distinct from, and more extensive than, the tabulations of individual patient data called for as parts of the full reports of controlled clinical studies and the safety portions of reports of all studies. These case report tabulations contain, in an organized fashion, essentially" all data (of the above three types) collected in the case report. Generally, the tabulations in study reports will be subsets of relevant effectiveness and safety variables used in analyses and tables. As in the tabulations in study reports, any unreported value should be clearly identified as such.

B. Format of Tabulations

1. General requirements

As with all tables and graphs, headings should be clear and well-defined and the study they refer to specifically identified. As many columns as possible, consistent with legibility, should be included to allow comparison across variables. The usual presentation is by patient and, for each patient, by visit, with patients- grouped by study, by investigator, and by treatment.

2. Specific requirements:

a. Demographic and baseline information

There should be tabular listings of each patient's baseline demographic features (age, sex, race, weight), the basis for including him in the study (entry criteria met), recorded features of the disease (duration, severity, prior treatment, etc.), concomitant illness, any drugs to be continued during the study, and any drugs added during the study. (Admission history forms may have many items not needed for evaluation; what to include should be discussed with the reviewing division.)

b. Measures of effectiveness

For controlled studies, tabulations should include all recorded measures, including questionnaire items, physical or electrical measurements (BP, EKG, Helter, electrocardiogram, x-ray, etc.), global ratings, and diary records, and should be presented with enough other information about the patient to allow measures to be interpreted, such as time of measurement and drug dose. [See 111.5 .9. c.4)]

c. Measures of safety

All adverse experiences and all laboratory measurements should be recorded as described in III.B.10.b.5) and c.1).

v. CASE REPORT FORMS [21 CFR 314.50(f)(2)]

As stated clearly in the regulations, 21 CFR 314.50(f)(2) and (3), only certain case report forms (CRF) will routinely be requested: those for any patient who died during a clinical study or who did not complete the study because of an adverse event, whether or not that event was believed to be drug related, including patients receiving reference drugs or placebo.

While not all CRF's will be required routinely, reviewers will usually need access to CRF's on the critical well-controlled studies. In order to choose these appropriately, and at a time when they can be provided without causing delay in review of the application, FDA reviewers will designate, approximately 30 days after receipt of an application, the critical studies for which case reports will be requested.

A description of an adequate case report form is beyond the scope of this document, except to observe that, in general, it should record clearly all demographic and diagnostic information, all dosing information with the study drug and other therapies, and all observations made. It should be possible to distinguish observations not made from those that are made but are "negative." One caveat seems in order. Efforts to make the forms as easy to analyze as possible have led to a substitution of checklists for narrative in many situations. Case report forms should retain room for spontaneous comments by the investigator, especially with respect to unusual responses and adverse experiences. The investigator should be free to use adverse experience terms he finds suitable and room on the form should be left for this. Common adverse experience terms can, of course, be listed, as well as any modifying statements that can help evaluate causality, severity, etc.

VI. THE ARCHIVAL COPY AND GENERAL CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS

A. The Archival Copy

Under the current regulations, the drug sponsor is required to submit a complete archival copy of the new drug application and a review copy to each one of six reviewing disciplines [21 CFR 314.50(h)]:

1. Chemistry, Manufacturing, and Control
2. Nonclinical Pharmacology and Toxicology
3. Human Pharmacokinetics and Biovailability
4. Microbiology
5. Clinical
6. Statistics

The purpose of the archival copy is to permit the individual reviewers to refer to information that is not contained in the review copies of their technical sections, to give 'other agency personnel access to the application for official business, and to maintain in one place a complete copy of the entire application. The organization and content of the archival copy of an NDA is as outlined below [21 CFR 314.50(h)(1)]:

ARCHIVAL COPY OF A NEW DRUG APPLICATION

COVER LETTER

a. APPLICATION FORM (356H)
b. INDEX
c. SUMMARY
d. TECHNICAL SECTIONS

1. CHEMISTRY, MANUFACTURING, AND CONTROL SECTION
2. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION
   HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION
;: MICROBIOLOGY SECTION
5. CLINICAL DATA SECTION
6. STATISTICAL SECTION

e. SAMPLES AND LABELING
f. CASE REPORT FORMS AND TABULATIONS

B. Clinical and Statistical Sections

The review copies for the clinical and statistical reviewing disciplines should be separately bound, each containing a copy of the COVER LETTER, a copy of the INDEX, a copy of the SUMMARY, and a copy of their respective technical sections as outlined below:

Review Copy for the Clinical Reviewing Division

COVER LETTER
a. APPLICATION FORM (356H)
b. INDEX
c. SUMMARY
d.5 CLINICAL SECTION

Review Copy for the Statistical Reviewing Division

COVER LETTER
a. APPLICATION FORM (356H)
b. INDEX
c. SUMMARY
d.6 STATISTICAL SECTION

c. The COVER LETTER of an NDA

The review copies of an application for the clinical and statistical disciplines should include a copy of the COVER LETTER contained in the archival copy of the application. This cover letter: (i) confirms any agreements or understandings between FDA and the applicant; (ii) identifies one or more persons the agency may contact regarding the application; and (iii) conveys any other important information about the application.

This cover letter should identify the reviewing division including the HFD number to which the application is being submitted. If the letter is addressed to the director of a reviewing division, then an appropriate place for the HFD-number would be after the name of the director of that division. In addition to the cover letter, other relevant correspondence should also be included here. Letters of authorization may also be included here, if applicable.

D. The APPLICATION FORM (356h) of an NDA [21 CFR 314.50 (a)]

For a detailed description of the information needed for this form, the sponsor should refer to the Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications (pages 16-18).

E. The INDEX of an NDA [21 CFR 314.50(b)]

The archival copy of the application is required to contain a comprehensive index by submission number, volume number, and page number to the SUMMARY, the TECHNICAL SECTIONS, and all supporting information including SAMPLES AND LABELING [21 CFR 314.50(e)] and CASE REPORT FORMS AND TABULATIONS [21 CFR 314.50(f)]. If microfiche is used for portions of an application, the fiche number should also be given.

The index should identify the location of the major sections and subsections of the various technical sections and the location of each study report and summaries by submission number, volume number, and page number. It is most helpful if, where a section is omitted (e.g., if there are no uncontrolled studies), the listing is included anyway, labeled "not appl icable." This index should be included in the clinical and statistical sections.

If the volume of the material permits it, the COVER LETTER, APPLICATION FORM, INDEX, and SUMMARY, should all be bound in a single volume. It is not necessary to include a copy of the INDEX at the beginning of every volume. It suffices to include a copy of the INDEX in the first (summary) volume.

F. The SUMMARY of an NDA [21 CFR 314.50(c)]

For a detailed discussion on the format and content of a SUMMARY, the applicant may refer to the Guideline for the Format and Content of the Summary for New Drug and Antibiotic Applications.

VII. OUTLINE OF THE CLINICAL AND STATISTICAL SECTIONS

CLINICAL SECTION

A. List of Investigators, List of IND's and NDA's (Section II.A)

B. Background/Overview of Clinical Investigations (Section II.B)

C. Clinical Pharmacology (Section II.C)

1. Table of all studies, grouped by study type

2. ADME studies (absorption, distribution, metabolism, excretion)

   a. Synopsis of each study
   b. Full report of each study
   c. Summary and evaluation of all studies

3. Early dose-tolerance studies

   a, b, c as above

4. Short-term studies of therapeutic response or of a pharmacodynamic effect thought to relate to therapeutic response, , including dose-response and blood level-response studies

   a, b, c as above

5. Studies of pharmacodynamic properties other than the property thought to be related to clinical effectiveness

   a, b, c as above

6. "Special" studies

   a, b, c as above

7. Overall Summary of Clinical Pharmacology

D. Controlled Clinical Studies (Section 11. D)

1. Table of all studies, grouped by indication, study design, completion status, location, and availability of case reports

2. Indication 1

a. Placebo concurrent control studies

1) Completed Studies

a) Domestic, full case reports available

(1) Study # 101

i. Brief synopsis
ii. Protocol
iii. Related publication
iv. List of investigators
v. Integrated clinical and statistical report

(2) Study #102, etc.

i-v as above

b) Foreign, full case reports available

(1) Study # 201

i-v as above

(2) Study # 202, etc.

i-v as above

c) Published reports and other reports lacking full case reports

(1) Study # 301

i-v as appropriate

2) Ongoing studies with interim results

a)-c) as above

3) Incomplete studies no longer active

a)-c) as above

b. Dose comparison concurrent control studies

1).-3) as above

c. No treatment concurrent control studies

1)-3) as above

d. Active treatment concurrent control studies

1)-3) as above

e. Explicit historical control studies

1)-3) as above

3. Indication 2 . . . n

a-e as above

4. Optional overall summary and evaluation of data from controlled trials

E. Uncontrolled Clinical Studies (Section 11.E)

1. Table of all studies, grouped by indication, completion status, availability of case reports and location

2. Indication 1

a. Completed studies ~

1) Domestic, full case reports available

a) Study # 401

1) Brief synopsis
2) Protocol
-,3) Related publication
4) List of investigators
5) Report of the study

b) Study # 402

1)-5) as above

2) Foreign, full case reports available

a) and b) as above

3) Published reports and other reports lacking full case reports

a) and b) as above

b. Incomplete studies

1)-3) as above

3. Indication 2 . . . n

a-b as above

F. Other Studies and Information (Section II.F)

1. Table of all studies

2. Controlled studies of uses other than those claimed in the application, any design, complete or incomplete

a. Studies with case reports available

1) Study # 501

a) Brief synopsis
b) Protocol
c) Related publication
d) List of investigators
e) Report of the study

2) Study # 502, etc.

a)-e) as above

b. Studies without case reports available

1) and 2) as above

3. Uncontrolled studies of uses other than those claimed in the application

a. Studies with case reports available

1) Study # 601
a) Brief synopsis
b) Protocol
c) Related publication
d) List of investigators
e) Report of the study

2) Study # 602, etc.

a)-e) as above

b. Published reports and other reports without case reports available

1) and 2) as above

4. Commercial marketing experience

a. List of countries in which drug has been approved
b. Reports from regulatory authorities
c. Epidemiologic studies "
d. Spontaneous reports from foreign marketing experience of serious adverse experiences

5; Reports from literature or elsewhere not otherwise reported

a. Published case reports, letters, etc.
b. Other information

G. Integrated Summary of Effectiveness Data (Section II.G)

1. Identification of studies fulfilling the statutory requirements for adequate and well-controlled studies showing that the drug has its intended effect

2. Comparison and analysis of all controlled trials

3. Results of uncontrolled studies, if pertinent

4. Analysis of dose-response or blood-level response information

5. Analysis of response in subsets of the overall population: drug-demographic, drug-drug, and drug-disease interactions

6. Evidence of long-term effectiveness, tolerance, and withdrawal effects

H. Integrated Summary of Safety Data (Section II.H)

1. Table of all investigations pertinent to safety, identified by protocol number and principal investigator, grouped by study type

2. Overall extent of exposure

3. Demographic and other characteristics of the study population

4. Adverse experiences in clinical trials

   a. Narrative summary of adverse event experience
   b. Display of adverse events and occurrence rates
   c. Analysis of adverse event rates
   d. Display and analysis of deaths, adverse dropouts, and other serious or potentially serious adverse events

5. Clinical laboratory evaluation

6. Adverse events, including laboratory abnormalities, from sources other than clinical trials

7. Animal data

8. Analysis of dose-response information

9. Drug-drug interactions

10. Drug-demographic and drug-disease interactions

11. Pharmacologic properties other than the property of principal interest

12. Long-term adverse effects

13. Withdrawal effects

I. Drug Abuse and Overdosage (Section 11.1)

J. Integrated Summary of Benefits and Risks of the Drug (Section 11.J)

STATISTICAL SECTION

A. List of Investigators, List of IND's and NDA's (Section II.A)

B. Background/Overview of Clinical Investigations (Section II.B)

D. Controlled Clinical Studies (Section II.D)

Exactly as shown in the Clinical Section

G. Integrated Summary of Effectiveness Data (Section II.G)

Exactly as reported in the Clinical Section

H. Integrated Summary of Safety Data (Section II.H).

Exactly as reported in the Clinical Section

J. Integrated Summary of Benefits and Risks (Section II.J)

Exactly as reported in the Clinical Section

Appendix A

Examples of Data Presentations

This appendix contains various examples of tabular presentations of data for illustrative purposes. Applicants are encouraged to modify and improve upon these examples or to create better tables for presentation of data.

TABLE 1

Types of Studies and Design Features

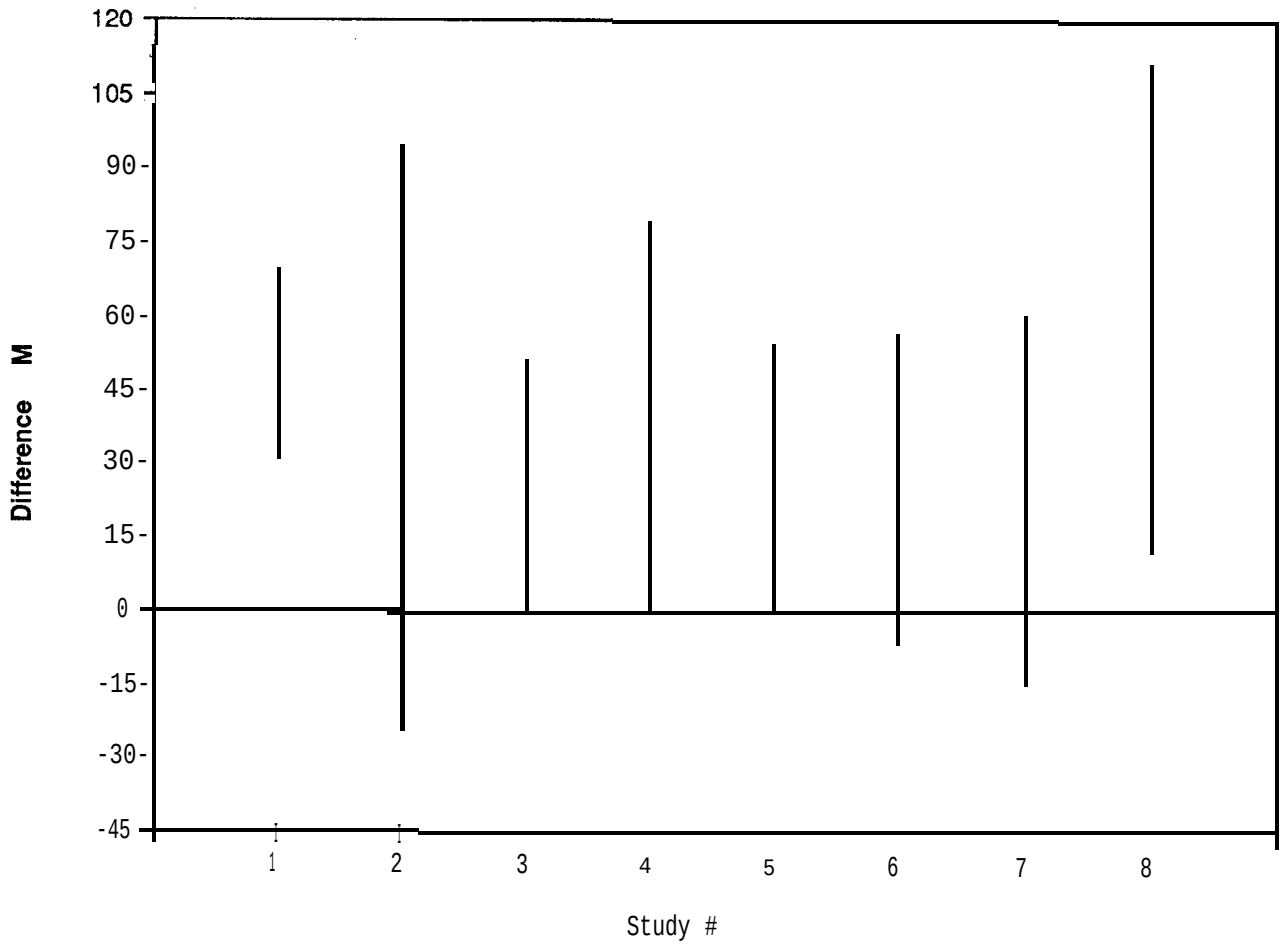
Indication 1 - Hypertension

Protocol #, Investigators, Publications	Completion status (Starting Date)	Location Product code *	Full report Data listings	CRFS	Designs (Blinding, Assignment Parallel vs. X-over (Titra vs. lst dose)	Treatment, Doses	Number entered each treatment	Age range (Mean)	% M/F B/W/O	Duration of drug treatment
001 Smith, James NEJM 365: 42-48, 1984	Complete (6/5/82)	Us. A, C	R. Vol.n.k P-l-loo 0: Vol.n.l p 200-400	Vol.n.2,p 355-400 Vol.n.3,p 1-800	DB, randomized parallel,plbo titration	Drug: 20-40mg Placebo b.i.d.	87 42	45-65 (62)	W 20/80/0	4 wk
002 Douvi er	Complete (6/12/82)	France c	Vol.n.p p 5-86	Vol.n.8, p 1-500 Vol.n.9, p 1-500	DB, randomized X-over, plbo final dose	Drug: 40mg o.d. Pl acebo Prop ranol 01: 80mg b.i. d.	57 60 55	55-75 (68)	w 5/90/5	12 wk
003 Gouo JAMA 48: 82-85, 1985	On-going	GB D, E	Vol.n.q M	NA	DB, randomized parallel plbo, titra	Drug: 40-80mg o.d. Placebo	125 130	40-60 (58)	w 12/60/28	8 wk
004 Jackson	Complete (5/8/81)	Us. A, C G	Vol.n.r p 1-300	vol. 12, 1-500 vol. 13, 1-500 vol. 14, 1-500	DB, randomized dose-resp. , plbo, first	Drug. : 20mg o.d. 40mg o.d. 80mg o.d.	38 40 39	65-75 (70)	m 30/69/1	2 wk

* A separate list should be provided giving all specific formulations and sizes used and providing a unique code for each.

Figure 1

Difference In Treatment Means* and 95% Confidence Intervals.



● Mean of Test Drug Change From Baseline Minus Mean of Placebo Change From Baseline.

TABLE 2

INTEGRATED SUMMARY OF SAFETY INFORMATION

TOTAL NUMBER (PERCENT) OF DEATHS OR ADVERSE DROPOUTS IN CONTROLLED CLINICAL STUDIES

	TREATMENT GROUP			
	TEST DRUG 162 (100)	CONTROL 163 (100)	P-VALUE	COMMENTS
DEATHS AND ADVERSE DROPOUTS	45 (28)	40 (25)		
DEATHS ACCORDING TO CAUSE				
ACUTE MI				
STROKE				
GI BLEED				
•				
•				
ADVERSE DROPOUTS ACCORDING TO BODY SYSTEM				
DIGESTIVE SYSTEM				
GI PAIN				
DYSPEPSIA				
•				
•				
•				
SKIN AND APPENDAGES				
RASH				
ALOPECIA	63 (39)	7 (4)	0.001	
ETC.				

TABLE 3

INTEGRATED SUMMARY OF SAFETY INFORMATION

FREQUENCY OF A CLINICALLY SERIOUS ADVERSE
EVENT BY TIME OF OCCURRENCE FOR ALL SUBJECTS STUDIED
(ILLuSTRATION)

TIME INTERVAL OF OCCURRENCE (MONTH)	CUMULATIVE #EXPOSED	CUMULATIVE #EVENT	RATE	CONTROL CUMULATIVE #EXPOSED	CONTROL CUMULATIVE #EVENT	CONTROL RATE
0-1						
1-2						
2-3						
3-4						
4-5						
5-6						
CRUDE RATE						

TABLE 4

INTEGRATED SUMMARY OF SAFETY INFORMATION

FREQUENCY OF A CLINICALLY SERIOUS ADVERSE
EVENT BY TIME OF OCCURRENCE FOR STUDIES OF VARIOUS TIME PERIODS
(Illustration)

DURATION OF STUDY (MONTH)	STUDY #	TIME INTERVAL OF OCCURRENCE (MONTH)	TEST			CONTROL		
			CUMULATIVE			CUMULATIVE		
			#EXPOSED	#EVENT	RATE	#EXPOSED	#EVENT	RATE
3	1	0-1						
		1-2						
		2-3						
		CRUDE RATE						
	2	0-1						
		1-2						
		2-3						
		CRUDE RATE						
	•	•						
		•						
		•						
	Combined	0-1						
		1-2						
		2-3						
		CRUDE RATE						
6	5	0-1						
		1-2						
		•						
		•						
		5:6						
		CRUDE RATE						
•								
•								
•								

FIGURE 2
FLOW CHART OF STUDY
(STUDY #)

	Single Blind							Double-Blind Treatment Period						
	Screening Period		Placebo Period					25 mg C bid / 12.5 mg C bid / 6.25 mg C bid / P bid					Standard Treatment	
Visit	(7d)	2	(7d)	3	(7d)	4	(7d)	5	(7d)	6	(7d)	7	(6a)	(6b)	8
Consent	X														
History	X														
Physical	X											X			
BP/BR	X		X		X		X	X		X		X			
body weight	X		X		X		X	X		X		X			X
Capsule count			X		X		X	X		X		X			X
Concomitant medication			X		X		X	X		X		X			X
Adverse experiences			X		X		X	X		X		X			X
EGG	X											X			
CBC	X							X				X			
Clinical chemistry	X							X				X			
Urinalysis	X							X				X			
Blood level of carvedilol								X				X			
Discharge non-qualified patients	×		×		×		×	×							
Assign patient number								×							
24-hour BP								×				×			

TABLE 5

Power for Various Sample Size Allocations

	Allocation of Patients to 2 Groups		Power to Detect Effect Size d		
1.	Total Sample Size 52	d =	.8	1.00	1.20
	Equal (26,26)		.80	,94	.99
	(17,35)		.75	.91	.98
	(13,39)		.68	.86	.95
11.	Total Sample Size 128	d=	.5	.6	.7
	Equal (64,64)		.80	.92	.98
	(43,85)		.75	.88	.96
	(32,96)		.68	.83	.92
111.	Total Sample Size 500	d=	.2	.3	.4
	Equal (250,250)		.61	.92	.99
	(170,330)		.56	.89	.98
	(125,375)		.44	.78	.97

*d = difference between treatments to be detected divided by standard deviation.

TABLE 6

Increase in Sample Size Needed to Maintain Constant Power

I. 80% Power for d = .5

	Total Sample Size Required
Equal Allocation	128
(1/3, 2/3) Al location	144
(1 /4, 3/4) Allocation	170

II. 80% Power for d = .8

Equal Allocation	52
(1 /3, 2/3) Allocation	59
(1/4, 3/4) Allocation	69

d = difference between treatments to be detected divided by standard deviation

TABLE 7

STUDY #
(Data Set Identification)

Disposition of Patients

Number of Patients Completing Each Period of Study

	Randomized	Treated	Week 1	Week 2	Week 4
Test Drug	#	# (%)			
Active Control					
PI acebo					
Tots 1					
Comparability test (p-value)					

TABLE 8

STUDY #
(Data Set Identification)

Listing of Patients Who Discontinued Study

Inv.:

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Predication	Reason
Test Drug								Adverse reaction . . . Therapy failure

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason
Active Control								

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason
Placebo								

(Repeat for other investigators)

TABLE 9

STUDY #
(Data Set Identification)

Listing of Patients and Visits Excluded from Efficacy Analysis

Inv.:

Treatment	Patient#	Sex	Age	Visit	Excluded	Reason(s)
Test Drug						

Treatment	Patient#	Sex	Age	Visit	Excluded	Reason(s)
Active Control						

Treatment	Patient#	Sex	Age	Visit	Excluded	Reason(s)
Placebo						

(Repeat for other investigators)

Reference Tables

Summary:

TABLE 10

STUDY #
(Data Set Identification)

Number of Patients Excluded from Efficacy Analysis

Test Drug N =

	Week			
Reason	1	2	4	8
Total				

Similar tables should be prepared for the other treatment groups.

TABLE 11

INDIVIDUAL PATIENT DATA LISTING

KEY DEMOGRAPHIC VARIABLES, BASELINE CHARACTERISTICS AND SCREENING VARIABLES

			DEMOGRAPHIC VARIABLES						CONCOMITANT MEDICATIONS		BASELINE CHARACTERISTICS		ALL SCREENING VARIABLES	
		PATIENT	V1	V2...	V6	DURATION OF	PRIOR	CONCURRENT			V6...	V9	V10	V11 . . .
INVEST.	TREAT .	ID	Sex	Race	HT	ILLNESS	THERAPY	ILLNESS	BASELINE	DURING STUDY	SDBP	SSBP	Smoking	Disease/State

TABLE 12

SUMMARY OF RESULTS FOR PROGNOSTIC FACTORS FOR ANALYSIS OF TIME TO TREATMENT FAILURE

PROGNOSTIC FACTOR	Study # 1 (P-value: from Final Cox Regression Model)	Study # 2 (P-value: from Final Cox Regression Model)
BASELINE PERFORMANCE STATUS	< .01	<.01
AGE	.02	.29
DISEASE FREE INTERVAL	.08	.48
ADJUVANT CHEMOTHERAPY	.53	.01
RACE	.96	.12
EST. COEFF. FOR TREATMENT, BETA*	-.12	-.27
STANDARD ERROR OF BETA	.12	.13
P-VALUE OF TREATMENT EFFECT	.30	.03
e^{BETA}=ESTIMATED RATIO OF HAZARD RATES (ACTIVE:TEST)*	.89	.76
(95% Confidence Interval)	(.70,1.12)	(.59,.99)

' Adjusted for all prognostic factors whose p-value was < .20 (significance at 0.20 level should not be taken as an FDA policy).

TABLE 13

EFFECT OF PROGNOSTIC FACTORS ON THE COMPARISON OF TREATMENTS
BY STUDY BEFORE AND AFTER ADJUSTING FOR PROGNOSTIC FACTORS
(T= Test Drug, A= Active Control)

Efficacy Variable	Study # 1	study #2
Time to Treatment Failure		
Estimated Hazard Ratio (T: A), Unadjusted	0.90	0.81
(95% Confidence Limits)	(.72,1.14)	(.63,1.04)
p-value	.39	.09
Estimated Hazard Ratio (T: A), Adjusted	0.89	0.76
(95% Confidence Limits)	(.70,1.12)	(.59,.99)
p-value	. 3 0	.03
Factors adjusted for are:	PS,AGE,INT[a]	PS,ADJ,RACE[a]

[a]PS = Baseline Performance Status, AGE=Age, INT = Disease Free Interval, ADJ = Adjuvant Chemotherapy, RACE = Race

TABLE 14

ADVERSE EVENT LISTING; STUDY #

Invest.	Patient	DEMOGRAPHIC VARIABLES Age	Sex	Race	UT	HT	TREATMENT/DOSE at Onset	DATE Onset	Time on Rx at Onset	Adverse Event	Duration of Event	Severity of Event	Actions Taken	Outcome	Relation to Rx	Location CRF
A	005	47	M	W	172	75	PI acebo									
	007	32	F	E	165	69	Drug 40mg									

TABLE 15

REFERENCE GUIDE FOR TABLES FOR STUDY #

Table #	Volume Page	Table Title	SOURCE OF REFERENCE: Statistical Support Information Description	Location Vol	Location Page	Data Listing(s) Type	Location Vol	Location Page
1	21 p. 10	Summary of Acute 24 Hour Blood Pressure	ANOVA Tables	21	p. 200	Raw	99	p. 400
			Interaction Info.	21	p. 300	Computed	21	p. 500

Appendix B

Guideline for Submission of Data Requested by FDA's Statistical Reviewers

This appendix provides guidance to drug sponsors on submission of data requested by FDA statistical reviewers for analysis.

APPENDIX B

Guideline for Submission of Data Requested by FDA's Statistical Reviewers

A. Statement of Nonendorsement

The specifications provided in this section are recommendations based on the statistical facilities currently in use within the FDA. References to commercial products herein should not be interpreted as an official FDA endorsement.

B. Requirements for Statistical Data Base in Computer Readable Forms

1 Definition and General Structure of a Statistical Data Base

- The dataset or data base requested for review of each controlled clinical trial reported in the statistical section of a submission will normally be a patient-by-variable type data file.

- This type of data file is often called a flat file which is simply a two-dimensional array or table of data elements (Table B-1). Each horizontal row in the table is referred to as a case or patient record that contains evaluative information on the patient. Each separate item of information in a patient record is called a field or variable.

- In practice, the data submitted in a statistical appendix can, and usually should, be subsumed under the following six categories: demographic, efficacy, safety (also side-effects), clinical laboratory, and other or mixed type if only a few variables are being studied.

- For each of these data categories the patient ID or number should be the first row entry value. The patient number will serve as the key field to merge data from two or more files to form a new "working" file that will consist of a new, combined set of variables. The patient number should be followed sequentially in the row by the appropriate variables in the particular category.

2 For Data on Floppy Diskettes

- In general, the submittal of these data on diskettes is encouraged if all statistically related files for a given study can be stored on fewer than 10 to 12 double or high density diskettes. The diskettes used should be IBM PC usable, 5.25 inch, and two-sided, IBM PS/2 usable, 3.5 inch, high density, 1.44 MB, or should meet other specifications agreed to by the reviewer and sponsor (e.g. , Macintosh usable).

- The diskettes submitted to the FDA should be properly labeled with the drug sponsor's name, address, and the NDA number or other appropriate reference number.

- The data can be submitted either in the ASCII, flat file format or as SAS datasets.

3 For Data on Magnetic Tapes

- As of the time of publication of this guideline, the standard recording mode for the library tapes used at the FDA Computer Center is 9 track, 6250 bpi. Other options are the 800, 1600, or 38000 (i.e., for 3480 cartridges) bpi. The character set should be either IBM-EBCDIC or ASCII.

- Foreign (non-IBM system generated) tapes should be IBM compatible with no label (i.e., with no headers, just data and tape mark); these foreign tapes should be submitted with the following information for each dataset in a cover letter: dataset name (DSN), volume number (VOL=SER), blocksize (BLKSIZE), record length (LRECL), and record format (RECFM).

- Additional information which will expedite processing of both the foreign and the IBM tapes includes: the type of computer on which data were generated; the type of program, routine, or language used to create the dataset(s); and tape label on the outside of the tape indicating the firm's name, address, and the NDA or some appropriate submittal type reference number.

- The FDA Computer Center normally uses only IBM standard labeled tapes. Although other mode or format may be acceptable, it is recommended that tapes be submitted in a manner consistent with the FDA standards.

- For submission of data on tapes, the sponsor is requested to consult the biostatistical reviewer for specifications relating to the proper submittal of tapes.

4 Specifics and Format of Data

- For all data files contained on floppy diskettes or magnetic tapes, each file should contain not more than 100 variables, and character fields should be minimized. Also, an asterisk (*) should be used for missing values if the file is in ASCII. (SAS uses a dot for missing values.)

- o If data are to be submitted in the ASCII, flat file format, the following convention shall be used. The contents of the character fields should not be in quotes. Numeric values should not be expressed as exponentials. Decimal points, if any, should be in fixed columns. Dates should be given as mm/dd/yy. The records should be of uniform length not exceeding 400 characters and/or spaces; the preferred record length is 132 columns or fewer. The fields within each record should be of fixed length with a space between each pair (Tables B-1 and B-2). The first case should be at the first line of the file, with the first allowable character of the first data field being at the first column of the patient record. In addition, there should be a separate data layout file describing each data file submitted.

- o For ASCII files the layout should include a list of the field names used, followed by a blank line or record, and then the basic information on each variable in the file: the location and type of variable used and, if appropriate, its permissible range of values (Table B-2).

- o For SAS data files, an output of the PROC CONTENTS should be submitted in lieu of the data layout.

- o For submission of data on tapes, a printed dump of the first 100 records should be provided. A printed copy of the entire file is highly desirable. In addition, there should be a hard copy of the data layout describing the cases under review.

- o In all cases, the data layout should also include the name, address, and telephone number of the contact person and, if practical, of the computer person who prepared the data.

- o Frequently the programs, routines, or procedures (including output) used by the drug sponsor on the requested or related data will be helpful and hence should also be submitted.

c. Provision of Consistent File Names

It is anticipated that, with the publication of this guideline, future data files will be submitted to FDA in a computer-readable form. For identification purposes, it is highly desirable that the name for each of the requested data files be consistent with the NDA number or similar reference number. If applicable, this file name should be provided in parentheses immediately after the table(s), figure(s), or result(s) referenced in the submission. In addition, the NDA or similar submission should contain an index table or summary list which cross-references the contents of the files used to their file names. This index table or summary list should contain at least the following basic items: file name, description of file, name of parent file (if any), and related

programs/output files (Table B-3). Such provision will not only facilitate the processing of requests for the data, but will also enable FDA's statistical review staff to archive and retrieve the data files in an efficient manner.

The (user specified) data file name should be in the form of "dcrnnnnn.xxx", where "d" denotes FDA's medical review division under which the submission is being evaluated, "c" the type of file to be submitted, and "rnnnnn" the one-character code representing the type of reference number used plus the five-digit reference number. The extension "xxx" is reserved for use by the drug sponsor to indicate sequential protocol and file numbers. These file extensions should be consistent with some chronological ordering scheme; for example, the drug sponsor may use A01 through A50 for program or data files written for, or derived from, the first clinical trial referenced in the submission, A51 through B50 for files related to the second protocol, and so forth. (Note: for files to be submitted on tapes, there are additional required fields and characters which must be specified in accordance with FDA's dataset naming standards.)

For FDA's medical review division (denoted by d above), the following coding scheme should be used:

A = anti-infective drug products
C = cardio-renal drug products
G ' gastrointestinal and coagulation drug products
14 = metabolism and endocrine drug products
N = neuropharmacol ogical drug products
O = oncology and radiopharmaceutical drug products
S = surgical-dental drug products
v ' anti-viral drug products
z = other or uncertain classification.

The codes for the type of file to be submitted (denoted by c above) are as follows:

P = programs, routines, or procedures
R = results (output) from above programs
H = data layout to be generated in hard copy
D = demographic data
E = efficacy data
S = safety data
C = clinical data in general
L = laboratory data in general
Z = other or mixed type

The one-character code for the type of reference number used (denoted by r above) should be as follows: N for NDA, I for IND, P for PLA, and Z for other. If Z is to be used, then the first five characters of the drug name may be used In case a five-digit reference number (denoted by nnnnn above) is not available; for a drug name that is shorter than five characters, fill in the space with the letter Z at the end.

If for some reason the reference number used is fewer than five digits, fill in the space with leading zero(s).

TABLE B-1

SAMPLE STRUCTURE OF A FLAT FILE CONTAINING PRIMARILY EFFICACY DATA

[beginning of file]

patient001 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient002 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient003 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient004 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient005 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient006 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient007 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient008 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient009 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient010 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient011 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient012 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient013 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient014 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient015 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient016 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient017 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient018 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient019 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient020 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .

patient998 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .
patient999 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 . . .

[end of file]

TABLE B-2

SAMPLE LAYOUT DESCRIBING VARIABLES IN DATA FILE DCRNNNNN.XXX

Column	Variable	Units	Scale	Description of Comments
1-5	CASENO	none	nominal	case numbered sequentially; key field
6-6				
7-11	ID	none	nominal	patient id (re permanent file)
12-12				
13-14	AGE	year	ratio	age at last birthday in 1987
15-15				
16-16	MDCODE	none	nominal	examining M.D. coded from 1 to 8
17-17				
18-20	SYS77	mm Hg	ratio	systolic blood pressure in 1977, recorded to nearest integer; range: 74 - 143
21-21				
22-24	DIA77	mm Hg	ratio	diastolic blood pressure in 1977, recorded to nearest integer; range: 48 - 98
25-25				
26-28	WT77	lb.	ratio	weight in 1987 to nearest pound; range: 92 - 217
29-29				
30-31	HT77	in.	ratio	height in 1987 to nearest inch; range: 57 - 76
32-32				
33-33	SES	none	ordinal	socio-economic status; 1=high, 5=low
70:71	YRDEATH	none	interval	year of death up to 1987; 00=alive, otherwise year of death recorded

Note: Above data file is of the mixed type.

TABLE B-3

SAMPLE INDEX TO TABLES, DATA, AND ANALYSIS FILES
FOR NDA STATISTICAL REPORTS

Drug: Test Drug Indication: Condition X Sponsor: Company A

NDA # : m Date of Submission: 08/15/87

Study: Protocol # 1

Review Division: Cardio-Renal (110) Code: c

REPORT						DATA FILE				PROCEDURE/PROGRAM FILE			OUTPUT FILE	
Statistical			Clinical			Location				Location			Location	
u	&	a	Vol.	Tab.	~	u	-	Type	Ext.	w	U	Description	&	~	m	~
6	1	(3123)	5	3	(2921)	7	(3241+)	E	A16	NL	(3408)	SAS (Means)	A01	8	(3561)	A02
6	2	(3124)	5	1	(2918)	7	(3249+)	S	A05	NL	(3409)	SAS (Means)	A04	8	(3578+)	A06
6	3	(3127)	5	2	(2922)	7	(3252+)	E	A43	7	(3407)	SAS (ANOVA)	A18	8	(3555+)	All
6	3	"	5	2	"	7	"	E	A43	NL	(3411)	SAS (GLM)	A34	8	(3586+)	A22
6	4	(3143)	5	4	(2927)	7	(3264+)	D	A62	7	(3422+)	GENCAT	A19	8	(3592+)	A37
6	5	(3147)	5	7	(2936)	NL	. . .	C	A97	NL	. . .	SAS (GLM)	A63	8	(3613+)	A49
		...			...		...		...		.....	...	...		.....	
		...			...		...		...		.....	...	...		.....	

Notes: "+" -- More than one page.
NL -- No listing provided in NDA submittal.
Data Files (Type): P = Programs, routines or procedures; R = Results (output); H = Data layout; D = Demographic data; E = Efficacy data; S = Safety data; C = Clinical data; L = Laboratory data; and Z = Others or mixed type.
File Names -- Review division/type/reference number type/reference number . extension; Review division, ref. no. type and reference number are common to all files for a given submittal. The extension number is assigned by the sponsor to describe each file.

Example: CENnnnnn.A16 (efficacy data on pp. 3241+ under Section A)

Appendix C

Protocol and Protocol Cover Sheet

As indicated in Section III.B.6 of this guideline, the actual protocol of an individual study should be included as an appendix to the study report, because the FDA clinical and statistical reviewers must have the protocol in order to be able to commence the review of a given study.

A sound protocol is a prerequisite to a successful and well-conducted study. In this appendix, the essential features of a good protocol are described, especially for the benefit of small drug sponsors. Furthermore, for the purpose of expediting the review of a study, it would be very useful for the sponsor to prepare a protocol cover sheet that summarizes the basic features of the given study as proposed in the protocol. An example of a protocol cover sheet is provided in this appendix. Such a protocol cover sheet should enable the reviewers to quickly grasp the principal features of a given study design in relation to the study objective.

APPENDIX C

Protocol and Protocol Cover Sheet

The study protocol for a controlled clinical study

The protocol is a critical document in the evaluation of a study, shaping both the conduct of the trial and the ultimate analyses. It sets out the objectives of the study in clinical terms and then relates these objectives to the statistical hypotheses that are tested. It describes critical features of the study's design and execution such as the experimental design (single-investigator or multi-investigator; parallel or crossover), patient selection and exclusion criteria, the choice of control group(s), the method for treatment allocation, the level and method of blinding, the sample size, the efficacy and safety variables to be measured, any planned interim analyses of the data, the procedures for early termination of the study (if any), the roles and responsibilities of any data-monitoring board, the proposed statistical methods, and the protocol cover sheet. In defining, ahead of time, specific subgroups for separate analysis, and the particular variables that are considered primary end-points, the protocol defines, and limits, the hypotheses the study is able to test.

A well-designed protocol usually will contain the following items. If, for a given study, any of these elements were not incorporated into the protocol used for the study, they should be supplied together with any available supporting data in the application showing that the study was in fact performed as stated.

1. A statement of the specific objectives. In addition to the primary objective, any secondary questions and subgroup hypotheses should be stated explicitly.

2. A clear statement of the study population and all patient selection (inclusion-exclusion) criteria. These criteria should provide assurance that the patients are suitable for the purposes of the study. Thus, the diagnostic criteria for the condition to be treated or diagnosed should be presented as well as any specific requirements for entry (e.g., disease of particular severity, results of specific laboratory tests, physical findings, or particular features of clinical history, such as failure or success on prior therapy).

3. A statement of the basic experimental design. This should describe any initial baseline periods, the treatments to be compared, the study configuration (parallel, crossover, etc.), and the duration of each treatment period. There should be an explanation of the design's suitability for the experimental drug and indication under study. For example, for a crossover design the protocol should consider the likelihood of spontaneous changes in the disease and the need for a reestablishment of baseline between treatment periods.

4. A description of the control group(s). Generally, the accepted types of comparison groups are placebo concurrent control, no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. These are described more fully in the revised NDA regulations at 21 CFR 314.126.

5. A description of the kind of blinding (double-blind, single-blind, etc.) and the specific procedures followed to carry it out (how bottles are labeled, double-dummy techniques, etc.). There should be a discussion of whether the level of blinding chosen is sufficient to minimize bias on the part of patients, observers, and analysts. The protocol should indicate under what circumstances the blinding will be broken.

6. A description of the method of assigning patients to the treatment groups. The method is usually intended to guard against systematic selection bias in the assignment of treatment and to help ensure comparability of the groups with respect to pertinent variables. Bias can be minimized from anticipated sources of variation (such as age, sex, severity of disease, duration of disease, use of drugs or therapy other than the test drug, concomitant illnesses, frequency of observation, etc.) as well as unanticipated sources by randomizing assignments or, if needed and appropriate, using stratified randomization.

7. A description of the efficacy and safety variables to be recorded, the times when they will be recorded, and the methods for measuring them. The appropriateness of the variables and methods should be considered. The methods should generally include those considered by experts to be reliable and accurate. There should be a clear statement as to when measurements are to be made in terms of particular follow-up times and, where appropriate, in relation to the timing of drug administration.

   For trials with multiple efficacy variables the protocol should discuss the planned interpretation of results including appropriate statistical adjustments for multiple testing, if applicable.

   This may involve:

   a. A designation of primary efficacy variables; or

   b. A designated pattern of significant findings among efficacy variables.

Note: If efficacy or safety is to be assessed in terms of categorical ratings, numerical scores, etc., well-defined criteria should be stated to ensure obtaining fairly consistent results among observers. Here the drug sponsor should utilize a method or rating instrument previously shown to discriminate between known effective and ineffective agents.

8. A brief but adequate description of any steps taken to ensure accurate, consistent, and reliable data (e.g., training sessions, instruction manuals, data verification, cross-checking or audits based on probability sampling methods).

9. A description of any planned interim analyses of the data, including the monitoring procedures, the variables to be analyzed, the statistical analyses to be used, including the choice of significance level for each interim analysis, and the frequency of analysis.

10. A description of the circumstances under which the study would be terminated before the planned number of patients has been entered in the study and of circumstances in which individual patients would discontinue the study medication prior to planned completion.

11. A description of the statistical methods to be applied to the data. Here specific questions that the statistical analyses will address in support of the study objectives are identified. For example, a description of the methodology that would be used to incorporate the responses of non-completers would be important. The major end-points for analysis should be identified. If there are several, the means of interpreting inconsistent results and multiple comparisons should be identified. Any subgroups of patients in the trial for whom results will be examined separately should be pre-specified in the protocol. Global efficacy criteria (e.g., sum of symptom-severity scores) or cut-points for defining response that will be used in the analysis to collapse or categorize one or more measured response variables (e.g., "marked" improvement) should be clearly defined.

12. A description of the statistical considerations which were used to determine the number of patients in the study. For example, an analysis of variance table depicting sources of variation and degrees of freedom corresponding to the chosen experimental design is often helpful in clarifying the analytical procedures to be followed and in determining adequate sample sizes for the study.

Protocol Cover Sheet

In order to expedite the review of a study it would be helpful if the drug sponsor provided basic information regarding the essential features of the study protocol in a protocol cover sheet. An example of a protocol cover sheet is given on the following page. Such a cover sheet would enable the reviewer to understand quickly the principal features of a study design in the course of preparing FDA clinical and statistical reviews of an NDA.

PROPOSED PROTOCOL COVER SHEET

Study Phase: II III

Name of Drug:

Active Ingredients:

Study Dosage: Route of Administration: _ _ _ _

Objective:

Patient Population:

Structure: Parallel Group Duration of treatment period:

Crossover: # of treatments: # of sequences:
# of periods: Duration of periods:
Washout Between Periods: Yes No

Other: Specify:

Multicenter: Yes # of centers: Common Training: Yes
No No

Blinding: None Single-Blind Double-Blind

Method of Patient Assignment: (Randomization: Yes No)
Brief Description:

Concurrent Control: None Placebo No Treatment

Active (specify)

Other dose(s) of test drug (specify)

Estimated Total Sample Size: Statistical rationale provided: Yes No

Primary Efficacy Variable(s):

Adverse Reactions: Volunteered Elicited Both

Plan for data analysis: (proposed statistical methods, interim analyses, etc.)
Yes No

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