

**GUIDELINE FOR THE FORMAT AND
CONTENT OF THE SUMMARY FOR NEW
DRUG AND ANTIBIOTIC APPLICATIONS**

February, 1987

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U.S. FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

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GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS

I. INTRODUCTION

This guideline is intended to assist drug firms in preparing the summary to a new drug application required under 21 CFR 314.50(c). The summary section is to be included in the archival copy and in each technical section of the review copy of the application. The guideline is issued under 21 CFR 10.90. A person may, but is not required to, rely upon the guideline in preparing the summary section of an application. When a different approach is chosen, a person is encouraged to discuss the matter in advance with FDA to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

Each full application is required under 21 CFR 314.50(c) to contain a summary, ordinarily 50 to 200 pages in length, that integrates all of the information in the application and provides reviewers in each review area, and other agency officials, with a good general understanding of the drug product and of the application. The summary should discuss all aspects of the application and should be written in approximately the same level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel who will use the summary in the context of their review of an application, advisory committee members may be furnished the summary. To the extent possible, data in the summary should be presented in tabular and graphic forms. After purging the summary of nondisclosable data and information and modifying it as necessary to reflect the agency's views and conclusions, the agency may use the summary to prepare the Summary Basis for Approval document for public disclosure under 21 CFR 314.430(e)(2)(ii).

This guideline discusses an acceptable format for preparing a well-structured and unified summary for submission in an application.

II. SUMMARY FORMAT AND CONTENT

The summary should comprehensively present the most important informatics about the drug product and the conclusions to be drawn from this information. The summary should avoid any editorial promotion of the drug product, i.e., it should be a factual summary of safety and effectiveness data and a neutral analysis of these data. The summary should contain an annotated copy of the proposed labeling, a discussion of the product's benefits and risks, a description of the foreign marketing history of the drug (if any), and a summary of each technical section. Each section of the summary should be appropriately identified with headings. Information in the summary should be presented in the order listed below.

A. Proposed Text of the Labeling for the Drug Annotated (21 CFR 314.50(c)(2)(1))

1. Provide the proposed text of the labeling.
2. For each statement, or related groups of statements in the labeling, provide references (volume(s) and page number(s)) to information in the summary and in the technical sections of the application that support the statements. For general statements, e.g., the statement of indications, the references will be to large segments of the application. More specific statements can be referenced more precisely.

3. For any serious adverse experience that is described in the summary and technical sections but is not reflected in a contraindication, warning, or precaution in the labeling, explain the omission. Similarly, explain the omission of any contraindications, warnings, or precautions present in the labeling of drugs that are pharmacologically closely related to the new drug. (Some judgment must be used here; the intent is to elicit an explanation of why a member of a class (benzodiazepines, beta-blockers, thiazide, diuretics, etc.) lacks important warning information included in labeling of other members, not to explain every difference in labeling.)
4. Prescription drug product labeling is required to conform to the content and format provisions of 21 CFR 201.57. If the application is for a prescription drug product; state the reason for omitting any section or subsection of the labeling format described in 21 CFR 201.57.

B. Pharmacologic Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits (21 CFR 314.50(c)(2)(ii))

Identify the pharmacologic class of the drug and briefly discuss the drug product's scientific rationale, its intended use, and its potential clinical benefit(s).

C. Foreign Marketing History (21 CFR 314.50(c)(2)(iii))

Briefly describe the foreign marketing history of fine drug and any different salt, ester, dosage form, or complex of the drug. Include (1) a list of the countries where marketed, with dates of marketing, if known, and (2) a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness. Specific reasons for withdrawal should be given.

D. Chemistry, Manufacturing, and Controls Summary (21 CFR 314.50(c)(2)(iv))

Provide a general overview of the chemistry, manufacturing, and controls information for the drug substance and drug product. The following information should be included:

1. Drug Substance

a. Description including physical and chemical characteristics and stability

- (1) Names--Indicate, where appropriate and available, the established name (generic name), synonym(s), code designation(s), the proprietary name (brand name, trademark), identification number (e.g., Chemical Abstracts Service (CAS) registry number), and chemical name.
- (2) Physical and chemical characteristics---Describe the physical and chemical properties of the drug substance, such as appearance, physical form, solubility, melting point, boiling point, molecular weight, and structural and molecular formulas (include Wiswesser Line Notation (WLN) if utilized). Where applicable, provide information on isomers, polymorphs, pKa values, and pH.
- (3) Stability-Provide a narrative summary of results of studies on the stability of the drug substance. State whether additional stability studies are ongoing or planned.

- b. Manufacturer-State the name and address of the manufacturer of the drug substance. If more than one firm is involved in the manufacturing, processing, packaging, labeling, and control operations, briefly describe the responsibilities of each.
- c. Method of manufacture Provide a brief description of the method of synthesis or isolation (e.g., synthetic process, fermentation, extraction, recombinant M procedure) of the drug substance.
- d. Specifications and analytical methods--Where test methods and specifications are those in an official compendium or other public standard (e.g., United States Pharmacopeia (U.S.P.), National Formulary (N.F.), Code of Federal Regulations (CFR)), cite the appropriate standard used. If not in an official compendium or other public standard, no further information need be submitted.

2. Drug Product

- a. Composition and dosage form-State the composition of the drug product, setting forth the name and amount of each active and inactive ingredient contained in the drug product in the form in which it is to be distributed (e.g., amount of ingredient per tablet, capsule, milliliter).

Provide a description of the dosage form in sufficient detail to characterize the drug product fully. For example, indicate the type of dosage form (tablet, capsule, suspension) and whether it is a controlled release formulation, and describe the physical characteristics, such as the shape, color, type of coating, scoring, and identification marks.

- b. Manufacturer-State the name and address of the manufacturer of the drug product. If more than one firm is involved in the manufacturing, processing, packaging, labeling, and control operations of the drug product, briefly describe the responsibilities of each.
- c. Specifications and analytical methods--Where test methods and specifications are those in an official compendium or other public standard (e.g., U.S.P., N.F., CFR), cite the appropriate standard used. If not in an official compendium or other public standard, no further information need be submitted.
- d. Container/closure system--Provide a brief description of the proposed container/closure system in which the drug product is to be marketed.
- e. Stability-State the proposed expiration dating period and storage conditions and provide a narrative summary of the stability studies justifying the expiration dating period.
- f. Investigational formulations-Provide the quantitative composition and lot number of each dosage form used in each important clinical study including bioavailability and pharmacokinetic studies, clinical pharmacology studies, controlled clinical trials, and

large uncontrolled studies. Identify the studies (protocol number and location of report) using each dosage form.

E. Nonclinical Pharmacology and Toxicology Summary (21 CFR 314.50(c)(2)(v))

Provide a brief overview of all applicable studies, with order of presentation as consistent a possible with the outline below and with the sequence for study type, species, dose, etc., recommended for the corresponding technical section.

Where appropriate, present the data in tabular or graphic summaries that permit identification and comparison of the type, incidence, and dose relationships of the pertinent observations. Summarize the conclusions derived from these studies, noting the Pharmacologic profile and emphasizing notable toxicologic effects, species similarities and/or differences, and identified mechanisms. Discuss the appropriateness and adequacy of these data for supporting the drug's proposed therapeutic use.

Typical information to be included:

1. Pharmacology

a. Tabulate test models employed, route of administration, dose range or median effective dose, activity comparison with other drugs, etc., for:

- (1) Primary pharmacological action related to the proposed therapeutic indication.
- (2) Secondary ecological actions in order of clinical importance as possible adverse effects or as ancillary therapeutic effects.

b. Pharmacological interaction with other drugs as appropriate to the drug class.

2. Acute toxicity studies

Tabulate species, sex, age, dose range, routes of administration, vehicle, toxic signs, lethal doses, time of death, etc.

3. Subchronic/chronic/carcinogenicity and related toxicity studies

Provide a table showing the studies that were carried out, including species and strain, number of animals, sex, age, dose, dose schedule, route of administration, and vehicle (formulations).

For each species, summarize notable treatment and dose-related changes in survival, percent weight gain, toxic signs, hematology, clinical chemistries, organ weights, and pathology.

Pathology data should be presented in tabular summaries to show group differences (or similarities) in incidence and, where appropriate, relative severity of identified lesions in the particular organs or tissues.

For each carcinogenicity study:

- a. Provide, for each treatment group, the number of animals entered and the number surviving 12, 15, 18, 21, and 24 months.
- b. Provide a summary table of tumor occurrences with deaths and sacrifices combined, organized by body system, organ, tumor type, and dose level (including historical and positive controls, if any). The body of the table should contain the total number of animals with tumors of the stated type, disregarding time of discovery. The table should facilitate comparisons across dose groups.
- c. Indicate in the above table each tumor found to show a statistically significant dose response (positive or negative) at the $p=0.05$ level (one-sided) using a mortality-adjusted statistical test of dose-response over the entire study time unadjusted for multiple comparisons or multiple testing. In the above table provide the calculated p-value for the significant dose-response test for each of these tumors.

4. Special toxicity studies

Report results of studies appropriate to particular formulations or routes of administration, e.g., irritation studies for topical or parenteral products or hemolysis studies for parenteral products.

Tabulate data as appropriate.

5. Reproduction studies

Report results of segment I, II, III reproduction studies and results of reproductive function evaluation and any other studies related to reproduction, fertility, and fetal toxicity.

Tabulate teratology study data (segment II) showing group differences and similarities in gross visceral and skeletal abnormalities.

Tabulate data from fertility and reproductive performance studies (Segment I) and perinatal-postnatal studies (Segment III) if differences are observed from controls (or if controls have unusually high incidence of abnormalities).

6. Mutagenicity studies

If mutagenicity tests were performed, tabulate available data in the order recommended in the technical section. In vitro non-mammalian cell system, in vitro mammalian cell system, in vivo mammalian system, in vivo non-mammalian system.

7. Absorption, distribution, metabolism, excretion (ADME)

Tabulate available data by species, strain, and doses in the order recommended in the technical section.

Compare absorption, distribution, metabolism, and excretion (ADME) in the species used in the toxicology studies. Identify qualitative, or notable quantitative, ADME differences among

the various animal species and humans and discuss their possible relevance to observed species differences in toxicity and to extrapolation of findings to humans.

F. Human Pharmacokinetic and Bioavailability Summary (21 CFR 314.50(c)(2)(vi))

The summary should include the following:

1. A brief description of each bioavailability and pharmacokinetic study of the drug in humans performed by or for the applicant, including the type of study, the study objective, the study design, the analytical and statistical methods used, and the study results. If any of the clinical trials provide pertinent kinetic information, these data should also be summarized.
2. A brief description of the pharmacokinetic characteristics of the active ingredients) and the performance of the dosage form, integrating conclusions from the bioavailability and pharmacokinetic studies, and, if appropriate, from clinical trials, including volume of distribution, half-life, route and rates of excretion and/or metabolism, the rate and extent of absorption from each dosage form studied, and the proportionality of absorption over the therapeutic dosage range (dose proportionality). If pertinent, comparison with the bioavailability of other dosage forms should be described. Any identified differences in pharmacokinetics among patient subgroups (e.g., age, renal status) should be identified.
3. A brief discussion of the dissolution profile of the drug.

G. Microbiology Summary (21 CFR 314.50(c) (2) (vii))

For anti-infective drugs, provide a summary of the results of the microbiological studies of the drug. The summary should include:

1. A brief description of the known mechanisms of action and structural or other similarities to known families of antimicrobial drugs.
2. A brief description of the antimicrobial spectrum of the drug and a summary of the results of in vitro susceptibility testing demonstrating concentrations of the drug required for effective use.
3. A brief discussion of known mechanisms of resistance to the drug and the results of any in vitro studies that demonstrate the development of resistance to the drug or any known epidemiologic studies that demonstrate prevalence of resistance factors.
4. A brief description of the clinical microbiology laboratory test method needed for effective use of the drug.

H. Clinical Data Summary and Results of Statistical Analysis (21 CFR 314.50(c)(2)(viii))

1. Clinical Pharmacology

Give a description and the results of the phase I absorption, distribution, metabolism, excretion, tolerance, dose-ranging, drug interaction, dependence, and other pharmacologic studies, including a comparison with the animal data. The following format should be used:

- a. A tabular presentation of studies by protocol, investigator, study design (randomized, double-blind, open, parallel, crossover, etc.), drug or other treatment used for comparison (if any), number of subjects, age, sex, dose, duration of dosing.
- b. A short narrative description of the design and results of each study with any tables or figures needed to convey results effectively.
- c. Conclusions drawn from this group of studies. This section should summarize the critical pharmacologic findings, especially those relevant to clinical use of the drug, such as dose response or blood-level response data, duration of action data, and any potential problems associated with metabolism or excretion (e.g., high first pass effect, dependence on renal function, etc.). This section, while emphasizing the main (intended) pharmacologic effects, should describe available data (citing also relevant animal data) pertinent to other common, important pharmacologic properties, including cardiac electrophysiologic effects, hemodynamic effects, anticholinergic effects, and central nervous system effects. Documented age-related effects, if any, should be highlighted.

2. Overview of Clinical Studies

There should be a brief overview of the clinical trials carried out, including reference to any specific FDA guideline used and any FDA/sponsor discussions of major issues, such as an end of phase 2 conference. Critical features of the trials should be explained, such as duration, choice of study design (kind of control), and particular advantages or potential toxicities or adverse effects looked for, as well as the size and exposure duration of the data base used to evaluate safety. A brief review of pertinent clinical literature may be helpful, including literature on closely related drugs that provide insight into potential problems or areas of special interest.

3. Controlled Clinical Studies

List all controlled studies related to each proposed indication, whether they provide positive, equivocal, or negative evidence, for each specific claim of effectiveness.

For each proposed indication provide the following information:

- a. A table of all controlled studies sponsored by the applicant as well as those from published or unpublished papers or other sources. The table should include the protocol number, or other identifier, reference to any published report of the study, the condition studied, investigator(s), study design (double-blind, open, parallel, cross-over, etc.), specific formulation and dosage, drug or other treatment used for comparison, number of patients, age and sex of patients, dose, duration of therapy, location of the full report in the clinical section, and any other information deemed appropriate.
- b. A short narrative summary of each study, including enough information about study design, conduct, and analysis to allow the reader to understand what was done and what data were collected and analyzed, giving effectiveness results and adverse

events. Quantitative results (not merely p-values reflecting the significance of results) should be provided. Tabular presentations are generally most efficient. The statistical analysis of each study, including statistical techniques (specific methods), the specific endpoints used, and any patient exclusions, should be described.

- c. An analysis of, and conclusions from, each study as well as all studies as a whole related to each claim of effectiveness. If some studies are considered most important, the reasons should be explained. Any pooled analyses should be explained and presented. In this section the sponsor should identify major inconsistencies or areas needing further exploration and should specifically consider dose-response and dose-duration/dosing-frequency information, and any evidence of differences in response (effectiveness or adverse events) in specific subgroups, e.g., the elderly, persons with other diseases, etc.

4. Uncontrolled Clinical Studies Provide

- a. A table of uncontrolled studies including the protocol number or other identifier, condition studied, investigator(s), specific formulation and dosage, number of patients, age and sex of patients, duration of therapy, and location of the full report in the clinical section. Published reports need not be listed or discussed unless they are of substantial size or include an important observation.
- b. A short narrative description of the design and results of each study, including both effectiveness results and adverse experiences, with any tables or figures needed to convey results effectively.
- c. An overall analysis of these studies, and conclusions reached from them, usually consisting principally of evaluation of the safety information obtained, but also including any suggestions for further study.

5. Other Studies and Information

Provide a brief description of the remaining data not described above. This section should include summaries of studies, including controlled and uncontrolled studies, and published and unpublished papers that are not directed at the claims sought in the application but that provide pertinent safety information, as well as analysis of foreign marketing experience, if any, epidemiologic data, if any, etc.

6. Safety Summary-General Safety Conclusions

a. Extent of exposure

This section should describe the extent of drug exposure, the numbers of patients exposed to drugs for various periods of time and at various doses.

b. Adverse reactions

This section should integrate data from the controlled and uncontrolled studies and should provide estimated rates of adverse reactions. The tables of adverse reaction

rates would include the more important (serious and/or frequent) reactions, grouping, insofar as possible, terms that probably represent the same event, but would not include the complete tabulations provided in the technical (clinical) section. It is usually useful to analyze results from controlled and open studies separately and it is important also to distinguish short-term (single dose to a few days) from longer-term studies. Any differences in rates related to dose, duration of use, or patient characteristics such as age or sex, should be identified, as should evidence of, and data pertinent to, drug-drug interactions.

There should be an analysis of patients who left any study prematurely because of an adverse event or who died, in order to examine the possibility of an unexpected adverse reaction and to determine which adverse reactions seem to have the greatest clinical consequences.

For those potentially serious adverse reactions, such as hepatotoxicity or leukopenia/agranulocytosis, that have not been definitely established as drug related, the available data should be discussed as well as the additional steps contemplated in the premarketing or postmarketing stages to determine whether the drug is associated with these effects.

c. Clinical laboratory data

Provide a short summary of these data, noting clinically significant mean trends and statistically significant changes, as well as any patients with markedly abnormal values. The summary should compare the test drug with placebo or active control drug, as appropriate, and should show the numbers of patients receiving each test. Patients leaving a trial because of clinical laboratory abnormalities should be identified and evaluated.

d. Summary of other safety assessments

The results of special safety examinations carried out, such as audiometric, ECG and ophthalmologic examinations, should be summarized, including comparisons with active control drugs and placebo, if available, and the numbers of patients receiving each test.

e. Overdosage

Any information available on the treatment of overdosage should be included here.

f. Drug abuse

If the drug is subject to abuse, provide a summary of the studies or other relevant information. If the drug is not considered abusable but is a member of a class of drugs 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.

I. Discussion of Benefit/Risk Relationship and Proposed Postmarketing Studies (21, CFR 314.50 50(c)(2))

The applicant should formulate a brief benefit/risk assessment of the drug based on the results of human effectiveness studies and the toxicity of the drug in human and animal studies. The benefit/risk assessment should consider the risks and benefits of alternative treatment for the treatment population identified in labeling.

The applicant should also describe any postmarketing clinical studies that are proposed and the reasons for doing the studies, e.g., postmarketing surveillance to study, further a suspected adverse reaction; studies in children to obtain a claim for use in children; and studies to determine whether the drug is dialyzable by peritoneal dialysis.