Health Canada Santé Canada

THERAPEUTIC PRODUCTS PROGRAMME GUIDELINE

PREPARATION OF HUMAN NEW DRUG SUBMISSIONS

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For more information, please contact:

Therapeutic Products Programme
Health Protection Branch
Health Canada
Health Protection Building
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

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Préparation d'une présentation de drogue nouvelle à usage humain

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TABLE OF CONTENTS

1 INTRODUCTION

This guideline is to be used in the preparation of Human New Drug Submissions for presentation to the Drugs Directorate in compliance with the requirements of Division 8 of Part C of the *Food and Drug Regulations*. These regulations are intended to ensure that the content of all Human New Drug Submissions is factual, relevant, and complete, and that the manner of presentation is uniform and logical, and facilitates effective and speedy evaluation.

This guideline is not intended to be exhaustive or inflexible. Within the framework provided, appropriate adaptation may be made according to the type of drug product and the data available.

When preparing Human New Drug Submissions, it may also be helpful to consult other guidelines, such as those for *Product Monographs* or *Toxicologic Evaluation*.

2 REGULATORY REQUIREMENTS

Observance of the guidelines contained herein should ensure compliance with Sections C.08.002, C.08.003, and C.08.005.1 of the *Food and Drug Regulations*.

Deviation from these guidelines may be acceptable following prior discussion with the specific Division of the reviewing Bureau. Deviations, additions, or omissions-authorized or not-must be explained, either by introductory remarks or within each relevant section of the submission, whichever is more appropriate.

3 PRESENTATION OF THE SUBMISSION

The subsections that follow describe the requirements for the presentation of a Human New Drug Submission for review by the Health Protection Branch (HPB-Bureau of Biologics, Bureau of Human Prescription Drugs, Bureau of Pharmaceutical Surveillance, and Bureau of Nonprescription Drugs).

3.1 Format

Human New Drug Submissions should be organized into five parts as outlined in Table 1 (page 4). Details regarding the content and manner of presentation of each part are given in Section 4 of this guideline. The structure of a Human New Drug Submission, listing subsections within each part, is presented in Appendix A.

In certain instances, it may be necessary to follow a special or unique format. In such cases, the concurrence of the Bureau and the Division in charge of evaluating the particular drug should be obtained in advance.

3.2 Language

Information in the submission should be recorded in either English or French. Material in a foreign language should be accompanied by an English or French translation-with the possible exception of case-report forms (consult the appropriate Bureau first).

TABLE 1

Presentation of Submission

Part	Content	Cross-Referenced to Parts	Suggested Colour for Binder	No. of Copies*
1	MASTER VOLUME Submission Certification Application Form Table of Contents Brief Summary Product Monograph A Draft of Every Label to be used in Conjunction with the New Drug List of Prior Related Submissions Non-Canadian Package Inserts	3, 4	Red	2
2	CHEMISTRY AND MANUFACTURING		Blue	2
3	COMPREHENSIVE SUMMARY	4	Brown or yellow	2
4	SECTIONAL REPORTS	5	Green	1
5	RAW DATA Raw Data (Investigational) Individual ClInical Case Reports	4	Black or microfiche	1

* Drugs with devices require an additional copy of Parts 1, 2, and 3.

3.3 Legibility and Size

All documents should be legible. The page size, including tables, should be uniform.

3.4 Binding

The submission should be bound for easy access to its information. Three-ring binders meet this criterion and should be used for Parts 1, 2, 3, and 4 of the submission. If these binders cannot be colour-coded as suggested in Table 1, then the labels on the spines of the binders must be so colour-coded.
(Part 5 would use white labels.)

3.5 Labelling

Each volume should be identified with the name of the drug, including, where applicable, the trade, generic, and code names. The name of the manufacturer, and the sequence of subsections within each Part (e.g., 2.1, 3.1, 4.1-4.12) should also appear. The necessary information should appear both on the spine of the ring binder and on its front cover.

Each volume should be sequentially numbered on the spine and front cover, starting at 1. This numbering is to be used solely to facilitate the reception, handling, transmission, and storage of the submission by HPB.

3.6 Pagination

The pagination may be sequential for the entire submission or by volume. In the comprehensive summary and sectional reports, individual sections of text should be identified both by the assigned decimal number and by the correct title, as suggested in this guideline. Cross-references should include both volume and page number.

3.7 Study Results

Study results for different dosage forms of the drug, with different routes of administration, should be submitted or listed separately under pertinent headings in the various parts of the submission.

4 THE STRUCTURE OF A HUMAN NEW DRUG SUBMISSION

4.1 Part 1: Master Volume

1.1 Submission Certification

The Submission Certification must be presented according to Section C.08.005.1 of the *Food and Drug Regulations*. It is preferred, but not required, that manufacturers use their letterhead for the submission certification.

The submission certification is to be signed by the senior executive officer of the manufacturer in Canada and the medical or scientific director of the manufacturer. If the submission certification or any significant part of the certification was prepared by an agent authorized by the manufacturer, the submission certification must also be signed by that agent.

1.2 Application Form

The appropriate HPB application form for Human New Drug Submissions should be completed, signed, and presented in this section.

1.3 Table of Contents

List the contents of the submission, using the form and decimal classification shown in Appendix A. Any section not included in the submission should have its omission explained. Each Part (1 to 5) of the submission should be clearly identified. The full title of each study within a part should be listed, and a specific, descriptive subtitle should be added where necessary to make recognizable the nature of the information. Specify the volume and page number of each item. Each volume of the submission should have its own table of contents.

1.4 Brief Summary

This section is a summary of approximately 300 to 500 words (or more, if necessary) providing the following information:

1.4.1 Name of the Applicant

1.4.2 Structural Formula (where known) of the New Drug with Chemical Name, Molecular Formula, and Weight

1.4.3 Other Names or Designations for the New Drug

1.4.4 Pharmacologic and Chemical Relationship to Other Drugs

1.4.5 Historical Reference to the Discovery and Development of the Drug (optional)

1.4.6 Therapeutic Classification

1.4.7 Route of Administration

1.4.8 Indications and Contraindications

1.4.9 Dosage and Administration

1.4.10 Brief Description of Important Positive and Negative Features of the New Drug

1.5 Product Monograph

The *Drugs Directorate Guidelines: Product Monographs*, available from the Drugs Directorate, Health Protection Branch, describes the content of an acceptable product monograph. To facilitate discussion of this document with the applicant, the text should be typed double-spaced, with a 6-cm right-hand margin. If a Patient Package Insert (PPI) is envisaged, a full copy of the proposed text should also be included.

The text of the working copy of the product monograph should be cross-referenced to supporting data in the Comprehensive Summary (Part 3) and to the Sectional Reports (Part 4). An additional, non-annotated copy is required.

The section under the heading References should be referenced in the text by number and presented according to the Vancouver style, which can be summarized as follows:

For articles:

Name and initials of all authors; full title of the article; name of the journal, abbreviated according to the *Index Medicus;* year; volume; first and last page number. For example:

McCormack W.M., Brown P., Lee Y-H., Kass E.H, The Genital Mycoplasmas, New England Journal Med 1973; 288:78-9.

For books:

Name and initials of authors; full title of the chapter; name and initials of editor(s) preceded by "In:"; full title of the book; city; name of publisher; year of publication; first and last page. For example:

> Taylor-Robinson D.,
> McCormack W.M.; Mycoplasmas in human genitourinary infections, in: Tully J.C., Whitcomb R.F., eds. The mycoplasmas. Vol. 2. Human and animal mycoplasmas. New York Academic Press, 1979; 307-66.

Apart from the first letter, titles of articles are not capitalized.

1.6 A Draft of Every Label to be used in Conjunction with the New Drug

Typewritten or other draft label copy is acceptable for review purposes. Labels (i.e., inner and outer labels) and inserts should be prepared in accordance with the appropriate regulations (see the guideline entitled *Labelling of Drugs for Human Use)*.

1.7 List of Prior Related Submissions

List any prior submissions that relate to the submitted drug and under which investigations reported in this submission were conducted, cited, or incorporated by reference. Indicate where the prior submissions are mentioned in the present submission (volume and page number):

1.7.1 Investigational New Drug Submissions (IND)

1.7.2 New Drug Submissions (NDS)

1.7.3 Supplements to New Drug Submissions (S/NDS)

1.7.4 Master Files

1.8 Non-Canadian Package Inserts

If a drug has been marketed outside Canada, the applicant is encouraged to supply the following information: names of countries; date of approvals; and monographs or package inserts used in major countries.

4.2 Part 2: Chemistry and Manufacturing

This part of the submission should include information under the following headings, as suggested in the guideline entitled Chemistry and Manufacturing: New Drugs, available from the Drugs Directorate.

2.1 Drug Substance

- 2.1.1 Names
- 2.1.2 Source
- 2.1.3 Method of Manufacture
- 2.1.4 Structure Elucidation and Confirmation
- 2.1.5 Physicochemical Properties
- 2.1.6 Impurities
- 2.1.7 Reference Standard
- 2.1.8 Specifications and Test Methods
- 2.1.9 Batch Analyses
- 2.1.10 Stability

2.2 Dosage Forms

- 2.2.1 Names
- 2.2.2 Source
- 2.2.3 Developmental Pharmaceutics
- 2.2.4 Formulation and Method of Manufacture
- 2.2.5 Specifications for Excipients
- 2.2.6 Specifications and Test Methods
- 2.2.7 Packaging
- 2.2.8 Stability

2.3 Addendum for Biologics

2.3.1 Description of Manufacturing Facilities

2.3.2 Work Flow

2.3.3 Other Drugs Prepared in the Same and in Adjacent Areas

2.3.4 Evidence Establishing Ability to Produce a Consistent Product (over Several Consecutive Lots of the Drug)*****

2.3.5 Proposed Format of a Protocol for Lot Release of Product*****

2.3.6 Characteristics of the Product

- Safety
- Potency
- Pyrogenicity
- Identity
- Sterility
- Protein content
- Moisture content
- Particulate matter
- Freedom from extraneous blood proteins and blood group substances*****

2.3.7 Active and Passive Immunization Studies

***** May or may not be imperative; check with the Bureau of Biologics, Drugs Directorate before filing submission.

4.3 Part 3: Comprehensive Summary

This section is pivotal in the review process. It comprises factual, concise descriptions of the methodology, results, conclusions, and evaluation of each relevant investigational and clinical study. It should be presented in sufficient detail to allow an independent evaluation of

the properties, safety, efficacy, dosage, and conditions of use of the drug. It is imperative that the Comprehensive Summary state, clearly and unambiguously the chemical and pharmaceutical formulation used in each study of the new drug.

The summary should contain separate discussions and evaluations of the significance of each area of study. An integrated appraisal of the overall content of available information as it pertains to the safety and effectiveness of the product under the proposed conditions of use should also be included.

Information in the Comprehensive Summary should be extensively cross-referenced to the Sectional Reports (Part 4).

The Summary should be typed single-spaced, on one side of the page. It should be bound at the left edge of the page and have a 6-cm margin on the right. Methodology and results should be presented in tabular or point form.

Depending on the type of submission and the quantity of data submitted, it is expected that most summaries will occupy between 20 and 200 pages. Summaries slightly in excess of 200 pages will occasionally be accepted, after prior discussion with the appropriate Division Chief.

3.1 Investigational Studies

3.1.1 Pharmacology

When standard tests are used, each pharmacologic study can be summarized by giving

- the name and nature of the test;
- the species, number, sex, age, weight, and strain of animals;
- information on dosage form or formulation, or both;
- routes of administration;
- treatment regimen and duration of treatment;
- parameters evaluated;
- significant observations and conclusions; and
- results, with their degree of statistical significance.

The dates of the studies and names of the laboratories conducting the studies should be mentioned. Names and addresses of contract laboratories conducting studies should be listed. Dosage units should be consistent in all the studies.

Alternatively, the same information could be presented in tabular form.

More extensive information should be provided when studies are conducted using new

methods. Studies should be grouped under the headings that follow (3.1.1.1 through 3.1.1.4).

3.1.1.1 Primary Therapeutic Activity

These studies provide the primary basis for clinical trials of the drug.

3.1.1.2 Secondary Therapeutic Activity

These studies show secondary pharmacologic actions that are relevant to the expected use or to adverse effects of the new drug.

3.1.1.3 Metabolism

These studies concern the absorption, distribution, metabolism, and elimination of the drug.

3.1.1.4 Others Studies

Other studies considered pertinent to the efficacy or safety of the new drug are presented here.

3.1.2 Toxicology

Consult the guideline entitled *Toxicologic Evaluation* for the extent and type of information required for submission of, and evaluation by, HPB.

The summary of toxicologic studies should preferably be presented in tables that indicate:

a) the species, number, sex, age, weight, and strain of animals;

b) information about dosage form or formulation, or both;

c) the routes of administration;

d) the treatment regimen and duration of treatment;

e) the parameters evaluated;

f) significant observations and conclusions; and

g) results, with their degree of statistical significance.

The dates of the studies and the names of the laboratories conducting the studies should be mentioned. Names and addresses of contract laboratories conducting studies should be listed. Information should be provided under the headings that follow (3.1.2.1 through 3.1.2.7).

3.1.2.1 Acute Toxicity

3.1.2.2 Long-Term Toxicity (subchronic and chronic)

3.1.2.3 Carcinogenicity

3.1.2.4 Mutagenicity

3.1.2.5 Reproduction and Teratology

3.1.2.6 Dependence Liability (when applicable)

3.1.2.7 Other Studies

3.1.3 Microbiology

Summaries of all pertinent microbiologic studies should be presented, including methods used, together with a discussion and evaluation of the results. Cumulative minimal inhibitory concentration (MIC) tables are highly desirable. The studies should be grouped under the headings that follow (3.1.3.1 through 3.1.3.3).

3.1.3.1 <u>In vitro</u> Studies

3.1.3.2 Sensitivity Disc Interpretation and validation Studies

3.1.3.3 In Vivo Studies
(Including animal model efficacy studies)

3.1.4 Published or Unpublished Investigational Articles

A list of all published and unpublished reviews, papers, reports, and "Letters to the Editor" about any investigational aspect of the drug should be included in the form of a bibliography. This bibliography should indicate where (volume and page) in "Sectional Reports" (Part 4) the full text can be found. A summary of each salient document should accompany the list.

3.1.5 Discussion and Evaluation of Investigational Studies

This section should provide an overall evaluation of the potential hazards, the potential efficacy, and the pharmacological and pharmacokinetic properties of the drug, based on findings in laboratory animals or in *in vitro* systems.

Unusual or important pharmalogical or toxicological observations and their potential clinical implications should be well discussed. It would also be useful to give the rationale for the design of certain animal studies and for the selection of animal species, treatment regimen, and parameters evaluated, and to discuss the conclusions.

3.2 Clinical Studies

Clinical studies should be presented in tabular or summary form. Each summary should provide information about methods, results, side effects, serious or unexpected adverse experiences, and interpretation of the results. Enough information should be given to permit an independent scientific evaluation of the study. Each summary should be cross-referenced to Sectional Reports (Part 4).

When the investigators have contributed an analysis and a discussion of the results of their study, the summary of the study should indicate this fact and should note the volume and the page numbers where the full text of the contribution can be found.

3.2.1 Clinical Pharmacology

3.2.1.1 Pharmacodynamics

"Pharmacodynamics" should include summaries of single- and multiple-dose studies in volunteers, dose-range studies, studies of drug effects on various organic functions (these can be organized by individual study or by major phenomena or activity), drug interaction studies, and so on.

3.2.1.2 Pharmacokinetics

"Pharmacokinetics" includes metabolic studies. Correlations with, and differences from, similar data from animal studies should be discussed in this section, including comparative blood levels and relevance of results.

3.2.1.3 Bioavailability

Human New Drug Submissions for "generic" drug products should contain appropriate, adequate, and validated data from comparative bioavailability studies.

The comparative studies should use the corresponding Canadian innovator drug product as the reference standard.

3.2.2 Clinical Trials

The clinical trials for each claim or indication proposed for the drug should be summarized separately. Each summary should present both the favourable and the unfavourable evidence.

Each summary should include information about:

- the investigator,
- the site of the study,
- the number of patients enrolled and completing the study,
- the duration of the study,
- the diagnoses (criteria), including severity and stage of disease,
- patient demographic data,
- drug dosages and schedules,
- criteria of effectiveness,
- clinical and laboratory monitoring of safety,
- results,
- statistical conclusions, and
- interpretation.

Key data on individual patients respecting efficacy and safety should be incorporated into each summary.

3.2.2.1 Pivotal Trials

Pivotal trials are defined as trials of high scientific quality, which provide the basic evidence to determine the efficacy, properties, and conditions of use of the drug. The term implies well-planned, well-designed, and, usually, controlled studies where results are properly collected, recorded, and analysed by using appropriate statistical tests. Pivotal trials are conducted by qualified investigators, using the recommended doses of the drug with the proposed formulation and for indications that are being claimed. Pivotal trials may provide favourable and unfavourable evidence.

Controlled trials are trials in which potential variation has been appropriately stratified and randomized to allow a direct, meaningful comparison between two or more treatments.

Efficacy studies that can be performed and interpreted only on the basis of a non-concurrent (historical) control should contain a predetermined, clear, and justified account of the basis for, and the applicability of, the chosen control values.

3.2.2.2 Non-Pivotal Trials

If, in the view of the sponsor, some of these trials add useful information about the efficacy and safety of the new drug, they should be summarized under this heading.

3.2.2.3 Special clinical Trials

Special trials that are not summarized elsewhere should be included under this heading (e.g., clinical studies to assess the drug's dependence liability).

3.2.2.4 Other Clinical Trials

List under this heading all clinical trials included in the submission but not summarized under Section 3.2 of the submission, including those trials that have been prematurely terminated for reasons unrelated to drug effects, or those that were considered irrelevant for evaluating the effectiveness of the drug. The reasons for discounting any study or for declaring a study irrelevant should be stated.

3.2.3 Published or Unpublished Clinical Articles

The sponsor of the drug (i.e., drug manufacturer, university) should provide a commentary on the content of the references listed in Sectional Reports (Part 4). The relation and relevance of the references to the current submission should also be discussed.

3.2.4 Discussion and Evaluation of Clinical Results

The discussion and evaluation of clinical data should be divided into two parts: effectiveness and safety.

3.2.4.1 Effectiveness

When the number of studies for each claim or indication is considerable, it is advisable to display all the results in tabular form or in lists. The tables or lists should include essential information concerning each study, such as:

a) clinical investigator,

b) design of study,

c) number of patients,

d) diagnosis,

e) dosage,

f) duration,

g) number of patients completing the study, and

h) results, with their degree of statistical significance and their clinical significance.

In some instances, the overall evaluation of effectiveness can be assisted by the preparation of a variety of summary tables. Favourable and unfavourable results should be compared and discussed.

Studies of anti-infective drugs should be summarized by groups of organisms and by site of infection, as well as by disease severity, dosage, or route of administration, where applicable.

3.2.4.2 Safety

This section should include tabulations of all side effects or adverse experiences, including drug interactions and abnormal laboratory findings, regardless of whether they are considered to be drug-related. The side effects or adverse experiences, expected or unexpected, should be tabulated according to sex, age, dosage form, dose administered, formulation, or other relevant factors, as appropriate. As much information as possible should be taken into consideration when adverse experiences are being classified as drug-related, possibly drug-related, or not drug-related.

Severity and incidence of adverse experiences should also be classified by organ system. The more important adverse experiences should be discussed individually in terms of their incidence, severity, dose relationship, and other factors related to the occurrence, prevention, and management of the effect in question. An attempt should be made to correlate the findings in animal and clinical studies.

3.2.5 Overall Conclusions from Clinical Studies

This section should provide a discussion of the benefits and risks of the drug under the conditions of use recommended, based on an evaluation of the research data available.

3.2.5.1 Risk Acceptability

Weigh the expected clinical benefits of the drug against the possibility of adverse experiences. Determine risk acceptability.

3.2.5.2 Benefit/risk ratio

Assess and compare the benefit/risk ratio of the drug in relation to related drugs or others drugs used as standards in controlled clinical trials.

3.2.5.3 Relationship of dose to adverse experiences

Indicate dosage levels (mg/kg) at which adverse experiences occurred in animals, and compare with the levels at which adverse experiences were observed in clinical studies.

3.2.5.4 Effective/recommended clinical dose

Based on the basis of the results of the clinical studies, state the effective and recommended clinical dosage range in the most appropriate manner. The range will usually be expressed in mg/kg[1,2] and will include frequency and manner of administration, based on clinical considerations.

[1] In radiatIon units (millicuries) for radiopharmaceuticals; in mL or mL/kg for parenteral contrast media.
[2] Or mg/m^2 surface area.

3.3 Status of Research and Development of the Drug

3.3.1 Cut-Off Dates

Indicate the cut-off date for inclusion of research and development data in the submission. If different cut-off dates were used for different sets of data, please specify (e.g., manufacturing, investigational, clinical).

3.3.2 Canadian Investigational Studies

List on-going Canadian investigational studies of the new drug and provide a brief annotation about the nature of the studies and the expected dates of completion.

3.3.3 Canadian Clinical Studies

List all Canadian clinical studies of the new drug and briefly note the nature of the studies, regardless of whether they have been completed or of their expected dates of completion.

4.4 Part 4: Sectional Reports

This part of the submission should include a detailed description of each available, completed preclinical or clinical study.

The sectional reports should be based on raw quantitative and qualitative data, necessitating compilation of, and reference to, summary tables and graphs that illustrate the various steps in the process of data reduction and analysis. The collection of individual data points in tabular form and the subsequent intermediate summary tables and graphs should be included as an addendum.

Every effort should be made to quantify results and to represent data in readable tables and graphs that illustrate appropriate control and treatment statistics (e.g., number of observations, defined average, degree of variability, and level of statistical significance). The reason for choosing the particular statistical approach should be explained. When applicable, the range of normal values for the laboratory carrying out the analysis should also be indicated.

Detailed accounts of, and reasons for, all protocol modifications, deviations, or violations should be highlighted and explained. Show comparisons of treatment groups (assessed for each relevant baseline variable or combination of variables), and consistency of drug effects across relevant subgroups.

For national or international collaborative studies or multiple investigators/clinics, display the efficacy and safety variables for each investigator/clinic, and analyse the studies separately for each, where possible.

If the data from some or all investigators/clinics are to be combined in a composite analysis, statistical methods that can separate the investigator/clinic effect from the treatment and other effects should be used. Justification should be given for the pooling of any data.

The statistical model underlying the analysis should be precisely and completely presented. Summary statistics should be presented to enable the reviewer to verify the results of the analysis quickly and easily (i.e., all data sets on which statistical analyses are based should be accessible). When relevant, the statistical power against specific alternatives should be presented, particularly for those tests that failed to reject the null hypothesis. These requirements are not meant to exclude relevant narrative material.

Each sectional report should include:

a) the name of the investigators/clinics,

b) the study design and methodology,

c) the results (with appropriate analyses), and

d) a discussion and interpretation of results.

The protocol and the biostatistical report should be added as appendixes.

The investigator's *curriculum vitae* (or the appropriate HPB application forms) should appear as appendixes to each sectional report; alternatively, they can be assembled in a separate volume at the end of Part 4.

4.1 Investigational Studies

4.1.1 Pharmacology

Include reports of all animal and *in vitro* studies under the headings that follow (4.1.1.1 through 4.1.1.4).

4.1.1.1 Primary Actions

This section includes studies related to the pharmacologic actions that provide the primary basis for proposed trials of the drug. The studies may also show the minimum effective dose (where relevant) but should emphasize adequate description of the dose-effect relationships that produce pharmacologic responses in each species of animal investigated.

4.1.1.2 Secondary Actions

This section includes studies related to the secondary pharmacologic actions that may be relevant to expected use or to adverse effects of the new drug.

4.1.1.3 Absorption, Distribution, Metabolism, and Elimination

Studies of the metabolism (or detoxification), absorption, distribution, enzyme induction, excretion, and pharmacokinetics of the drug should be presented here.

4.1.1.4 Other Studies

Information on the pharmacologic activities of the drug that may be pertinent to safety and relevant to proposed clinical trials should be presented here. These studies may include other actions demonstrated in the screening program and on the central nervous system (CNS), cardiovascular system, respiratory system, gastrointestinal system, and so on.

4.1.2 Toxicology

Consult the guideline entitled *Toxicologic Evaluation*.

4.1.2.1 Acute Toxicity

Acute toxicity studies should be reported (tabulated) according to species and route of administration. For each study, the dose levels and the number of animals per dose level should be given, together with the weight, sex, age, and strain of animals. A brief description of the method used should be given only if the study was unusual in some important aspect.

LD_{50} values, where submitted, should include a description of the method of calculation and should be given with confidence limits at a stated probability level ($1-\alpha$), usually 0.95. Signs of toxicity, times of death, and other pertinent information should be reported. Where available, the ratio of LD_{50} to the proposed maximal human dose (assuming a human weight of 50 kg) should be stated.

4.1.2.2 Long-Term Toxicity

All chronic and subchronic toxicity studies should be comprehensively reported by species and by route of administration.

For each study, the dose levels, treatment periodicity (e.g., seven-day dosing week) and duration, and the strain, number, and age of animals per dose level should be provided. The sex of the animals used; the initial, intermediate, and final weights of the animals; and the method and frequency of administration of the new drug should be documented. Where the drug is administered mixed in the diet, daily intake should be stated in milligrams per kilogram. All parameters studied, including laboratory investigations and pathological examinations, should be listed, and all the data collected should be analysed. The results should be stated together with the degree of statistical significance. All other significant aspects of study design and methodology should be included.

Where possible, those changes associated with the pharmacological action of the drug should be distinguished from those considered to be related to toxicity. If possible, estimate maximum tolerated doses for specific toxic effects and the toxic relationship to the proposed maximum human dose.

4.1.2.3 Carcinogenicity

The summary of the carcinogenicity studies should include a brief outline of the toxicity and metabolic studies that support the selection of the species, strains, and dosage regimens used. The proposed maximum human dose should also be stated, as should maximal possible treatment times in humans.

Describe the number of animals per sex and per treatment group, the dosage regimens and routes, and the duration of administration.

Include differences in the times of onset, the sizes and growth, and the characteristics of any palpable masses, as well as other clinical signs.

The results of macroscopic and microscopic examination of tissues should be summarized in a comprehensive manner, including, if necessary, presentation of data in tabular form. Histopathology should be tabulated as interim-scheduled sacrifice and neoplastic and related non-neoplastic lesions. The results of statistical tests (with degrees of statistical significance and possible clinical significance), together with the description of the methods used, should be included and, where necessary, incorporated into the tables.

When laboratory analyses have been performed, the results and their interpretation should be included in the report and, where necessary, tabulated.

The conclusions of the investigators should be included, and the data presented should contain sufficient information to permit an independent evaluation.

4.1.2.4 Mutagenicity

Briefly describe the rationale for the selection of the tests performed, including the selection of species, strains, or cell types, and positive control.

a) In Vitro *Tests*

Include a summary of the methodology, including the manner in which the tests were performed, the number of replicates, the different concentrations employed, the use of metabolic activators, the duration of exposure to the test substance, the duration of incubation, and the method of observing results. The results should be summarized in a comprehensive manner and should include conclusions pertaining to the tests and extrapolation to humans, with consideration given to animal metabolic studies, blood levels, and concentration of the drug and metabolites in germinal tissue.

b) *Animal Studies*

Analogous considerations-as for prokaryocyte or cell culture studies (i.e., equivalent parameters) should be detailed, taking into account the fact that the studies are *in vivo* (e.g., concentration in plates, dose level in animals).

4.1.2.5 Reproduction and Teratology

Reproductive and teratologic studies should be reported by species and by route of administration. For each study, the dose levels used, the period of drug administration in relation to stage of pregnancy, the parameters of pregnancy studied, and the methods of examining the young should be specified.

The reported results should include a description of effects of the new drug on fertility, on the mother, on pregnancy, on the fetus, and on postnatal development of the young. The relationship of the doses used in the reproductive and teratologic studies to known toxic doses for the same species and to proposed doses in humans should be discussed.

4.1.2.6 Dependence Liability
(when applicable)

4.1.2.7 Other Studies

Any study not included with the toxicity, carcinogenicity, reproductive, or teratologic and mutagenicity studies are to be summarized here. "Other Studies" might include tissue irritation, skin sensitization, specific toxic effects, a comparison of properties of different formulations of the drug, or any of the other types of toxicity studies that are outlined in the guideline entitled *Toxicologic Evaluation* and that are applicable to the candidate drug. Many of these studies will involve comparative positive controls.

4.1.3 Microbiology

4.1.3.1 <u>In vitro</u> Studies

The following information should be presented:

a) antimicrobial spectrum,

b) minimal inhibitory concentrations (MIC values-estimates determined on relevant clinical isolates and standard laboratory strains,

c) experimental evidence to support bactericidal or bacteriostatic action,

d) assessment of resistance (studies designed to measure the incidence of resistance of organisms at various drug concentrations),

e) minimal bactericidal concentration (MBC),

f) effect of innoculum size on the determination of MIC and MBC,

g) protein-binding studies,

h) resistance-development studies,

i) regression studies to establish the size of inhibition zone versus MIC as a basis to determine the sensitivity for a pathogen to the specific antibiotic, and

j) studies on cross-resistance and other interactions with other antimicrobial agents.

4.1.3.2 Sensitivity Disc Interpretation and Validation Studies

Include *in vitro* MIC or zone diameter correlations and the clinical basis for the chosen breakpoints.

4.1.3.3 In Vivo Studies

The following information should be included:

a) protection test experiments, using experimentally infected animals designed to evaluate the potential for therapeutic effectiveness;

b) development of resistance *in vivo* (studies designed to show any drug-induced change in th characteristics of the infecting organism); and

c) changes in the body flora (studies involving microbiologic culture techniques of body tissues and fluids designed to evaluate the effect of the drug on the natural body flora, with special emphasis on overgrowth and superinfection).

4.1.4 Published and Unpublished Investigational Reports

Include copies of published and unpublished reports of investigational studies.

4.2 Clinical Studies

The following information, when available to the applicant, should be provided with each clinical study:

a) each investigator's name, academic title and affiliation, and address.

b) the date of initiation and completion of the study.

c) the design of the study (attach the protocol as an appendix).

d) pertinent information describing the dosage form employed in the study and the periods of therapy, expressed as a mean and as a range.

e) the reference intervention (placebo, reference compounds, or other) listing the results of previous similar therapy, if any.

f) the diagnosis (or primary and secondary diagnoses), including severity and stage of disease, duration, numbers, sex, age distribution, and method of selection of patients in each drug and control group.

g) concomitant therapy, if used, including extra medication, as well as other treatments that can vary and influence study results (e.g., surgery or debridement of infection site).

h) the objective and subjective criteria of effectiveness used for the study. (Give full description of methods, and frequency of all observations or patient examination.)

i) the periods of administration of the control and drug preparations, and the kinds and numbers of observations made for each.

j) a reconciliation of the number of patients admitted to the study and the number completing the trial (i.e., detailed description of "dropouts." including the reasons).

k) the results (positive, negative, or inconclusive) related to the pharmacologic action or possible clinical effects of the new drug, including results of all laboratory, diagnostic, and monitoring tests.

l) the results related to adverse effects of the new drug.

m) the statistical analysis of the results (including a description of the methods employed).

4.2.1 Clinical Pharmacology

4.2.1.1 Pharmacodynamic Studies

Under this heading, include reports of single- and multi-dose studies in volunteers, dose-range studies, studies of drug effects on various organic functions, drug interaction studies, and so on.

4.2.1.2 Pharmacokinetic Studies

Under this heading, include reports regarding binding sites, biological half-lives, elimination, pharmacokinetics, and so on. Also include studies concerning absorption, distribution, metabolism, enzyme induction, and excretion of the drug and, where appropriate, of its active metabolites.

4.2.1.3 Bioavailability Studies

4.2.2 Clinical Trials

Clinical trials should be grouped under the headings that follow (4.2.2.1 through 4.2.2.5).

4.2.2.1 Pivotal Trials

See 3.2.2.1 of the submission for the definition of pivotal trials.

4.2.2.2 Non-Pivotal Trials

4.2.2.3 Special Clinical Trials

4.2.2.4 Uncompleted Clinical Trials

4.2.2.5 Other Clinical Trials

"Other clinical trials" includes the use of the drug in different formulations for indications and at doses not being claimed. Trials with poor methodology could be incorporated into this section.

4.2.3 Published and Unpublished Clinical Reports

Copies of all published and all available unpublished reviews, papers, reports, or "Letters to the Editor" regarding the clinical use of the drug and any aspect of its efficacy and safety should be included and summarized in the form of a bibliography. The bibliography should indicate where (volume and page) in "Sectional Reports" (Part 4) the full text can be found. A summary of each salient document should accompany the list.

4.3 Curriculum Vitae
(of each Investigator and the appropriate HPB Form)

4.5 Part 5: Raw Data

This part of the submission should be divided into two main sections: preclinical studies and clinical studies.

5.1 Preclinical Studies

This section contains the raw data pertaining to investigational studies, if not incorporated into the sectional reports (4.1 of the submission).

5.2 Clinical Studies

Where a participant enrolled in a study included in the submission died or did not complete the study because of a serious or unexpected adverse experience, provide a copy of every clinical case report pertaining to that participant, regardless of the reason for the death or adverse experience.

The clinical case reports should be collated by investigation and by study, and the studies grouped by claim.

All other available clinical case reports not falling into the above-mentioned category should be retained for submission on request within regulatory or administrative time frames.

Individual clinical case reports should be signed and dated by the responsible clinical investigator.

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STRUCTURE OF A HUMAN NEW DRUG SUBMISSION

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THERAPEUTIC PRODUCTS PROGRAMME GUIDELINES

PREPARATION OF HUMAN NEW DRUG SUBMISSIONS

Supplement

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Catalogue No. H42-2-38-1998E

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INTRODUCTION

The present document is a supplement to the Drugs Directorate Guidelines on the 'Preparation of Human New Drug Submissions' (1991). The document provides the applicant with recommendations as to the presentation of some of the preclinical and clinical data in an organized fashion and with a tabular format to accompany the narrative. The sample tables are a recommended format but alternative data presentation would be acceptable provided the tables concisely express the same information.

The recommended data presentation should facilitate the review of the submission. The supplement should be viewed as an addition to the guideline; it does not replace any of the requirements outlined in the latter.

PART 3: COMPREHENSIVE SUMMARY

3.1.1. Pharmacology

In order to obtain information regarding the extent of the pharmacological evaluation, the profile of the new drug, the dose range in which it is effective, oral vs parenteral efficacy, the standard(s) used, etc., available data should be tabulated (for an example see **Table 1)**. Effective doses should be listed in increasing order, starting with the experimental condition and species in which the minimal effective dose (MED) was established. Secondary pharmacological effects should be divided into tests that were carried out to determine the safety features of the drug and tests which indicated potential ancillary action(s). Results of in vitro binding studies should also be tabulated. The table should include the standard(s) used and indicate whether or not they exerted pharmacological activity in a given experimental model. The references should provide easy access to the sectional reports which describe the methodology and provide detailed data.

3.1.2. Toxicology

In order to assess the scope of toxicity testing, all studies should be listed and briefly described. Examples are provided in **Tables 2 and 3**. The studies should be grouped by species, and in order of increasing duration and/or route of administration. Table headings should include animal species and strain, initial group size per sex, route and mode of administration (e.g., gavage, diet), designated doses, duration of study in weeks, week of any interim sacrifices, the name of the laboratory performing the study, and the report number with reference to the location of the study (both in the Summary and Sectional volumes). Any procedural differences from those recommended in the Drugs Directorate Guidelines on 'Toxicologic Evaluation', should be identified.

The results of toxicity studies should be summarized in tabular format. Tables should be grouped by study type, e.g., acute, subchronic, chronic toxicity, carcinogenicity, reproductive, etc. studies. The title of the table should identify the type of study, while the body of the table should contain the species, strain, number, sex and age of the animals, dosage, route of administration, duration of treatment, parameters evaluated and significant observations.

The latter include behavioral and weight changes, clinical pathology, and gross/histopathology for toxicity studies; maternal effects (paternal effects in Segment I studies), and drug effect in fetuses and neonates to weaning in the reproductive studies. **Table 4** is an example of such a tabular presentation.

Table 5 provides an example of appropriate safety-related mean laboratory data presentation. To facilitate the review of such data, all values obtained in the course of the study for a given parameter should be listed on one page. Normal laboratory ranges should be readily available at the beginning of tabulations or at the head of each page. Statistically significant differences between groups should be indicated by an asterisk, while all abnormal values should be clearly identified by underlining, brackets, etc.

To facilitate the review of the carcinogenicity data, separate tables presenting tumor data for male and female animals of each species tested should be presented as follows:

(a)The period (e.g., week) in which each tumor was discovered should be listed chronologically per dose group (control, low, medium, high). The animal number, whether the animal was sacrificed or died, the site of the tumor, the tumor type, and an assessment of the malignancy of the tumor should also be identified (**Table 6**);

(b)A summary table of tumor occurrences, with deaths and sacrifices combined, should be organized by body system, organ, tumor type, and dose level (including historical and positive controls, if any) (**Table 7**). The body of the table should contain the total number of animals with tumors of the stated type, disregarding time of discovery. The number of animals treated and the number examined should be identified for each group.

Such tables would facilitate comparisons across dose groups.

For all long-term toxicity and carcinogenicity studies,animal deaths and sacrifices should be presented in summary tables, showing for each period (e.g., week) and for each dose group, the number of animals entering the period, the number dying, the number sacrificed, the number of these animals necropsied completely, and the number necropsied to any extent (**Table 8**).

3.1.1.3. & 3.2.1.2. Pharmacokinetics

All bioavailability and pharmacokinetic studies that have been completed, including those in animals, should be listed (see **Table 9**). As noted in the column headings, each study is to be identified by report number and a reference to the location of the full report within the submission. Information on subjects, dosage, route of administration, design, formulation and other core information should also be provided.

The key pharmacokinetic parameters that characterize the new drug should be summarized. The information provided in **Table 10** should facilitate the identification of those factors (sex, age, disease state, dosage schedules, drug or food interaction, etc.) that may alter the time course and/or the concentration of the drug in the blood. Furthermore, similarities and differences between animals and man can be detected easily. Pharmacokinetic parameters, both in adults and special patient populations, should be determined over the entire recommended clinical dose range.

Table 11 enables the reviewer to compare blood levels in animals that were associated with abnormalities/toxic manifestations, with those in man that were associated with adverse drug reactions. The table emphasizes the importance of (a) incorporating pharmacokinetic studies into toxicologic evaluations to ensure the availability of pharmacokinetic information in the same species and at the same doses as those used in the toxicity studies and (b) correlating the adverse drug reaction profile of the new drug with blood levels observed at clinically recommended doses.

3.2.1. Clinical Pharmacology & 3.2.2. Clinical Trials

All clinical studies, including clinical pharmacology, pivotal trials, non-pivotal trials, and special clinical studies, should be listed in separate tables with the title clearly identifying the type of studies that are summarized in the table (an example is given in **Table 12**). The table should list investigators and provide study identifiers (including protocol number and publication citation, if any), and the starting date and completion status of the study. Reference columns should identify the location of the report. Also, the study design (randomized, double-blind, parallel, cross-over, etc.), the control treatment, the specific formulation and dosage strength used, the dose range, dose regimen, and duration of dosing should be mentioned. Lastly, the number of patients who enrolled and

the number of patients who were subsequently evaluable for efficacy analysis should be reported, followed by their age range and sex distribution.

At present, this supplemental documentation to the Drugs Directorate Guidelines on the 'Preparation of Human New Drug Submissions' does not contain tables for data presentation regarding efficacy evaluations, due to the complexity of the numerous classes of drugs that the Bureaus deal with. However, an example is provided for anti-infective agents (see **Table 13**).

There should be a clear accounting of all patients who entered the study. The number of patients who entered and completed each phase of the study, or each week/month of the study should be provided, as well as the reasons for all post-randomization discontinuations (an illustration is provided in **Figure 1**).

3.2.4.2. Safety

Table 14 illustrates an example of integrated safety information from placebo and standard-controlled studies, as well as from open studies. Information obtained from pivotal and non-pivotal clinical trials should be tabulated separately; similarly, only studies with similar duration of action should be combined. Adverse reactions should be grouped by body system. In combining data from many different studies it is important to use standardized terms under a single primary term. Within body systems, the primary terms should be arranged in decreasing frequency.

In order to define the risk of a clinically serious adverse event in relation to duration of drug treatment, a cumulative occurrence table should be provided (**Table 15**). Under the column for the number of events, there should be a superscript beside each value to provide a listing of the serious adverse events. Similar tables may be provided for uncontrolled studies.

The number of deaths and adverse dropouts as well as the rate of such events should be summarized in tabular format (**Table 16**). Adverse events should be grouped by body system and within systems by reactions of the same general type.

For each clinical laboratory parameter where trends towards abnormally high or abnormally low values emerged in the course of the treatment (relative to the normal range), data may be presented as illustrated in **Table 17**. The numerical figures in the table refer to the number of patients. The

interpretation of the data in the illustrative table is as follows: of those patients who had a normal laboratory value at baseline, 70 remained normal while 20 became abnormally high during treatment; of those patients whose laboratory value was abnormally high at baseline, three normalized while four remained high.

PART 4: SECTIONAL REPORTS

4.2. Clinical Studies

- Subsequent tables and figures should be integrated into individual studies.

- The entire protocol should always be included as an appendix, however, a 'Protocol Cover Sheet' (for example see **Table 18**) would enable the reviewer to quickly ascertain the principal features of the study design. The protocol cover sheet should be followed by a flow chart (see **Figure 2**) which describes the overall study plan. 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 observer with other participants unblinded, etc.); 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.

- All patients who entered the study must be accounted for. The number of subjects who entered and completed each week/month of the study should be provided for all groups (**Table 19**). There should also be a patient-by-patient listing, by treatment group, indicating patient number, the reason for discontinuation, the treatment (drug and dose), and the duration of treatment before participation ended (**Table 20**). 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.

- 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. The number of patients excluded from the efficacy analyses at the various time points, and the reasons for exclusion should be provided (see **Table 21**).

- 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). The tables may also divide the adverse events into those considered related to drug use and those considered not related (**Table 22**). Other causality schemes (e.g., remote, possible, probable, definite) may also be used. Patients having a given adverse event may be identified by individual patient number, in some or all of the pivotal trials. For quicker reference, the table may be provided without patient identifying numbers; in this case treatment and control groups could be shown on the same page. Tables without patient identifying numbers should be included in the main report, those with the patient numbers in the appendix.

- All adverse events for each patient should be listed in tabular format and the information provided as an appendix. Laboratory findings that constitute an adverse event (ECG abnormality suggesting infarction, serious arrhythmia, etc.) should be included (see **Table 23**). The table should identify the investigator and should include the patient number, demographic variables (e.g., age, sex), treatment, dose and duration of treatment at the time of the adverse experience, duration and severity of the event (e.g., mild, moderate, severe), action(s) 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), and relationship to test drug.

- The results of safety-related laboratory tests carried out in each patient should be tabulated and the information provided as an appendix. In the suggested format (**Table 24**), each row represents 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 should be listed in numerical order of patient identifier

number. Critical information about each patient, such as the visit number or number of days into the study period at the time of the examination, dose, age, sex and weight, should be provided. The remainder of the tabulation should consist of columns giving the results of each laboratory test, one column per test. Normal laboratory values 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, etc.

Finally, demographic and baseline characteristics of all randomized patients, and any other factor(s) arising during the study which could affect response, should be presented in tabular listings and made available in the appendix. These variables should be listed by patient, within treatment group and by investigator; an example of such a table is given as **Table 25**.

Table 1. SUMMARY OF PHARMACOLOGICAL EFFECTS

	Experiment	Species	New Drug: Route of administration	New Drug: Dose mg/kg	Standard	Results/ Observations
Primary Effects	1. Antagonism of pentylenetetrazole convulsions *Reference (vol/page)*	Mice	ip	0.25[a]	+	
	2. Conflict behaviour *Reference (vol/page)*	Rats	ip po	1.25 2.5	-	
	3. . . .					
Secondary Effects	1. Cardiovascular studies	Anesthetized cats	iv	1.0		
		Spontaneously hypertensive rats	po	10.0		
	2. Analgesia	Mice	po	>20		
	3. . . .					

a= MED (minimal effective dose);
pharmacological effects are to be listed in decreasing order of effectiveness
+= active
-= inactive

Table 2. LISTING OF MULTIDOSE TOXICITY/CARCINOGENICITY STUDIES

Species	Strain	Initial group	Mode of administration	Doses mg/kg/day	Duration (wks)	Interim sacrifice (wks)	Laboratory	Report No./ reference
Mouse	C57B1/6	20M + 20F	Diet	0,10,50,100	6	-	PDQ Labs	xxx/vol. 5, p.1
	C57B1/6	50M + 50F	Diet	0,5,10,50	96	-	PDQ Labs	xxx/vol. 5, p. 85
Rat	Wistar	10M + 10F	Gavage	0,10,50,100	2	-	New Drug Co.	yyy
	Wistar	20M + 20F	Gavage	0,10,30,60	13	-	New Drug Co.	yyy
	Wistar	35M + 35F	Diet	0,10,30,60	52	-	New Drug Co.	yyy
	Fisher344	70M + 70F	Diet	0,5,20,50	104	52	PDQ Labs	yyy
Dog	Beagle	2M + 2F	Capsule	0,2,5,10	2	-	New Drug Co.	yyy
	Beagle	4M + 4F	Capsule	0,1,3,6	13	-	New Drug Co.	yyy
	Beagle	5M + 5F	Capsule	0,1,3,6	52	26	New Drug Co.	yyy
							(EZI Labs-Path)	zzz
Monkey	Rhesus	3M + 3F	Gavage	0,2,5,10	13	-	New Drug Co.	xxx

Table 3. LISTING OF REPRODUCTIVE STUDIES

Seqment	Species	Strain	Initial group	Mode of administration	Doses mg/kg/day	Duration (days or weeks)	Laboratory	Report No./ reference
II Teratology	Rats	Wistar	20F	Gavage	0,5,20,50	6 to 15 of pregnancy	New Drug Co.	xxx/vol. 6, p.1

TABLE 4. RESULTS OF TOXICITY STUDIES[a]

Report No./ Reference	Study Characteristics	Parameters Evaluated	Results/ Observations
	Species Duration of treatment Doses, mg/kg/day Route of administration No., sex, age		

a: refers to acute and long-term toxicity, carcinogenicity & reproductive studies

Table 5. LABORATORY PARAMETERS

(Study; Report number/reference)

(Example of required format)

Males

			Months				
Test	**Group**	**Baseline**	**1**	**3**	**6**	**9**	**12**
ALT (SGPT)	control low medium high						
AST (SGOT)	control low medium high						
Alkaline phosphatase	control low medium high						

Note: Normal laboratory values and ranges should be provided

Table 6. FORMAT FOR CARCINOGENICITY STUDY DATA

(1) Example of chronological listing of tumors

Males

Week	Dose Group	Animal Number	Death Status	Organ	Tumor Type	Malignancy
35	Control	010	D	Liver	hepatoma	N
52	Control	024	S	Pituitary	adenoma	N
23	Medium	052	D	Pituitary	adenoma	N
48	Medium	063	S	Liver	hepatoma	N
Term	Medium	058	T	Liver	hepatocarcinoma	Y
			(continue to the end of the study)			
Term	High	080	T	Mammary gland	fibroadenoma	N

D= deaths
S= sacrificed moribund
T= terminal sacrifice

Table 7. NUMBER OF TUMOR-BEARING ANIMALS

Males

Body system Organ Tumor type	Historical Controls (n_1 = 500) (n_2 = 400)	Vehicle Controls (n_1 = 50) (n_2 = 45)	Low (n_1 = 50) (n_2 = 49)	Medium (n_1 = 50) (n_2 = 38)	High (n_1 = 50) (n_2 = 35)	Positive Controls (n_1 = 50) (n_2 = 48)
Digestive						
Liver						
adenoma	71	6	8	10	8	15
fibroadenoma	32	4	9	9	13	22

n_1= number treated
n_2= number examined

Table 8. SUMMARY OF ANIMAL DEATHS AND SACRIFICES

(Name and nature of study; report number/reference)

Males

	Controls					Low Dose					Medium Dose					High Dose				
Week	**E**	**D**	**S**	**N**	**NP**	**E**	**D**	**S**	**N**	**NP**	**E**	**D**	**S**	**N**	**NP**	**E**	**D**	**S**	**N**	**NP**
34	70	--	--	--	--	70	--	--	--	--	70	--	--	--	--	70	--	--	--	--
35	70	1	1	1	1	70	--	--	--	--	70	--	--	--	--	70	--	--	--	--
36	68	--	--	--	--	70	1	--	--	1	70	--	--	--	--	70	--	--	--	--
39	68	--	--	--	--	69	--	--	--	--	70	--	--	--	--	70	1	--	1	--
41	68	--	--	--	--	69	--	--	--	--	70	1	--	--	1	69	--	--	--	--
43	68	--	--	--	--	69	--	--	--	--	69	1	--	1	--	69	8	--	8	--
49	68	--	--	--	--	69	--	--	--	--	68	--	10	10	--	61	1	--	--	--
52*	68	--	10	10	--	69	--	10	10	--	58	--	--	--	--	60	--	10	10	--

(continue to the end of the study)

Term*	41	2	39	41	--	40	--	40	40	--	36	--	36	36	--	38	1	37	36	2

Note: E= Number entering period
D= Deaths; S = Sacrificed moribund
N= Necropsied completely; NP = Necropsied to some extent
*= Scheduled and terminal sacrifices

Table 9. LISTING OF PHARMACOKINETIC STUDIES

	Duration	Species/type of subjects	Age	Sex	#	Route/mode of administration	Dose/dosage form	Study design	Batch No. plant/date manufactured	Report #/ reference
Animals										
Humans										

Table 10. SUMMARY OF PHARMACOKINETIC DATA

	Duration	Species/ type of subjects	Route/mode of adminis-tration	Dose/ Dosage form	T_{max}	C_{max}	AUC	$t_{½}$	Vd	Cl	Route of elimination	Report #/ reference
Animals												
Humans												

Table 11. RELATIONSHIP OF PLASMA LEVELS AND TOXIC MANIFESTATIONS/ADVERSE REACTIONS

Species study route/mode of administration	Dose mg/kg/day	# Animals/ subjects	Approx plasma levels[a] ng/ml	Effects observed[b]	Report No./ reference
Rat					
3-month tox po *(diet)*	5		<15		xxx/vol. 6, p. 25
	20		170		
	60		>400		
Rhesus monkey					
EKG effect po *(gavage)*	2.5				
.					
.					
.					
Man					
Single dose po[c]					
.					
.					
.					
Multiple dose po[c]					

a: C_{max} or C_{ss}
b: the list of toxic manifestations/adverse reactions should include abnormalities re: behaviour, laboratory parameters, histopathology, vital signs, etc.
c: formulation used (M=marketed, O=other)

Table 12. LISTING OF STUDIES AND DESIGN FEATURES

Protocol #, Investigators, Publications	Location, Product code[a]	Completion status[b] (starting date)	Reference vol/page	Designs (blinding, assignment, parallel vs x-over, placebo &/or standard, titration vs 1st dose)	Treatment doses	Number entered	Number completed	Age[c] (range)	% M/F[c]	Duration of drug treatment
001 Smith, James NEJM 365: 42-48, 1984	U.S. A, C	Complete (6/5/88)	Vol.1 p 200-400	DB, randomized parallel, plbo, titration	Drug: 20-40mg Placebo b.i.d.	85 85	70 72	62 (45-65)	55/45	4 wk
002 Douvier	France B	Complete (6/12/87)	Vol.7 p 5-86	DB, randomized x-over, plbo, standard final dose	Drug: 40mg o.d. Placebo Propranolol: 80mg b.i.d.	60 60 60	50 45 55	68 (55-75)	60/40	12 wk

a: a separate list should be provided giving all specific formulations and sizes used and providing a code for each
b: indicate whether completed or on-going
c: refers to subjects entered

TABLE 13. EXAMPLE OF COMPREHENSIVE EFFICACY DATA PRESENTATION FOR ANTI-INFECTIVES

Indication[1]	Dosage(s)[2]	Patients Enrolled	Patients Evaluable for Efficacy	Clinical[3] Cure and Failure Rates		Microbiological[4] Cure and Failure Rates		Pathogen Cure[5] Rates Cured/evaluable & Failed/evaluable			Report No./ Reference
				Cured / Evaluable(%)	Failed / Evaluable(%)	Cured / Evaluable(%)	Failed / Evaluable(%)	Pathogen Name	Dosage 1	Dosage 2 etc	
	1. 2. etc. . .										
	Comments[6]										

Note: For explanation see next page.

Explanation of Notations in Table 13

1. Indication: Indication by clinical syndrome studied or by tract. If by tract, a list of all clinical syndromes studied (e.g., pneumonia, acute exacerbations of chronic bronchitis for lower respiratory tract infections) and total number of patients evaluable for each syndrome.

2. Dosage(s): All dosages used including frequency and duration. Control therapies to be included as well where applicable. All routine concomitant anti-microbial therapy to be included.

3. Clinical Cure Rates: Cure rates are to be calculated from patients cured. If improved patients are included then they should be represented as follows: cured + improved / evaluable patients eg.

   i) if 75 cured and 25 improved out of 125 evaluable patients then 75+25/125 with explanatory footnote.
   ii) Patients scored as clinical cures or improvements but where microbiological failures should be clearly identified in the comments section of the table.

4. Microbiological Cure Rates: Cure rates are to be calculated as eradicated pathogens / evaluable pathogens. In the case of multiple pathogens at a single site all pathogens must be eradicated to be scored as a cure. Multiple pathogens at different sites or multiple pathogens requiring additional therapy to be excluded. These patients can be included in a separate summary table so labelled.

5. Pathogen Cure: Cure rates are to be calculated as eradicated pathogens / evaluable pathogens. In the case of multiple pathogens at a single site all pathogens must be eradicated to be scored as a cure. Multiple pathogens at different sites or multiple pathogens requiring additional therapy to be excluded. These patients can be included in a separate summary table so labelled.

6. Comments: This section is for explanatory comments regarding the presentation of the data from the protocol, e.g., a brief discussion of the definitions used if different from the above.

TABLE 14. NUMBER AND RATE OF ADVERSE REACTIONS

Integrated summary of safety information

	Double-blind placebo-controlled				Doubled-blind standard-controlled				Open	
	Studies (# 1, 2, ...)[a]				Studies (# 5,6 ...)[a]				Studies (#11,12..)[a]	
	Placebo	Test drug			Standard		Test drug		Test drug	
Adverse reaction	N=200	Dose 1 N=100	Dose 2 N=150	Dose 3 N=80	Dose 1 N=75	Dose 2 N=95	Dose 1 N=75	Dose 2 N=130	Dose 1 N=125	Dose 2 N=175
CNS										
Dizziness	22(11%)	3(3%)	13(9%)	20(25%)	2(3%)	13(14%)	4(5%)	15(12%)	3(2%)	12(7%)
.										
.										
.										
CV										
hypotension										
.										
.										
.										
GI										
diarrhea										
.										
.										
.										
etc.										

a: Studies included in the table should be listed and referenced as to the location of the full report

Table 15. FREQUENCY OF A CLINICALLY SERIOUS ADVERSE EVENT BY TIME OF OCCURRENCE FOR ALL SUBJECTS STUDIED

Integrated summary of safety information

Time interval of occurrence (month)	Test drug Cumulative			Control Cumulative		
	# Exposed	# Event	Rate	# Exposed	# Event	Rate
0-1	50	3[a]				
1-2	46	6[b]				
2-3						
3-4						
4-5						
5-6						
CRUDE RATE						

a: list of serious adverse events
b: list of serious adverse events

Table 16. TOTAL NUMBER (PERCENT) OF DEATHS OR ADVERSE DROPOUTS IN CONTROLLED CLINICAL STUDIES

Integrated summary of safety information

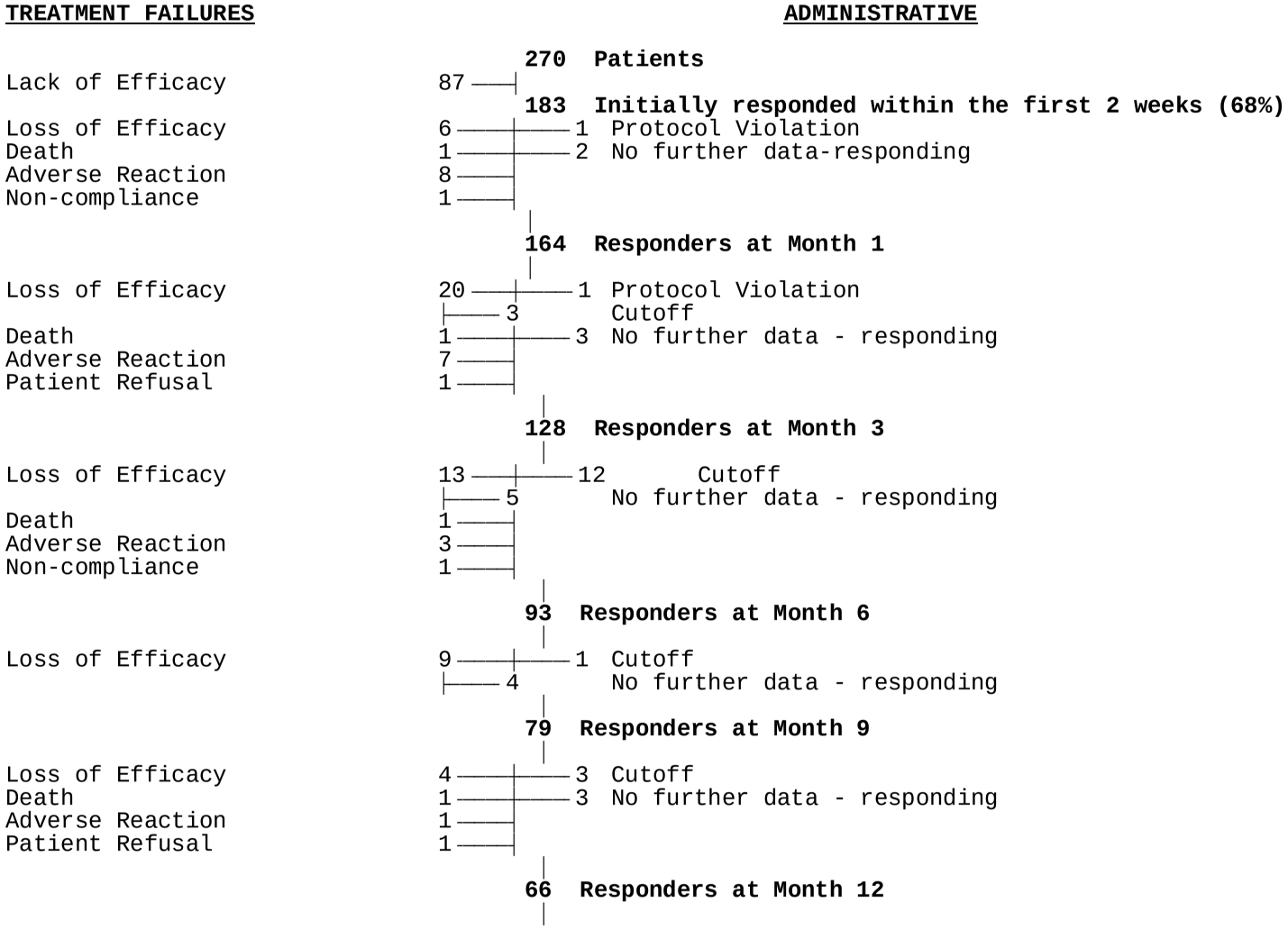
	Treatment group			
	Test drug 162 (100)	**Control 163 (100)**	**P-value**	**Comments**
Deaths and adverse dropouts	45 (28)	40 (25)		
Deaths according to cause				
Acute MI				
Stroke				
GI bleed				
.				
.				
.				
Adverse dropouts according to body system				
Digestive system				
GI pain				
Dyspepsia				
.				
.				
.				
Skin and appendages				
Rash				
Alopecia	63 (39)	7 (4)	0.001	
.				
.				
.				
Etc.				

TABLE 17. SUMMARY OF CLINICAL LABORATORY ABNORMALITES

Laboratory parameter:

	Normal	**Low**	**High**
Normal	70	-	20
Low	-	5	-
High	3	-	4

FIGURE 1. PATIENT DISPOSITION FLOW-CHART



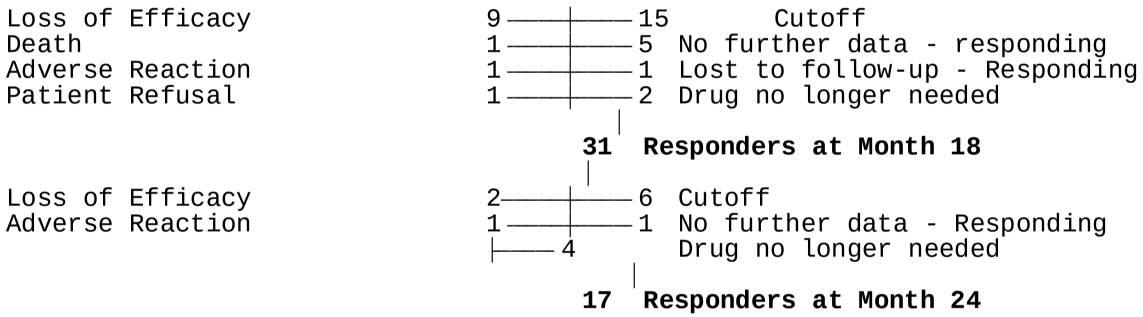

Loss of Efficacy
Death
Adverse Reaction
Patient Refusal
9
1
1
1
15
5
1
2
Cutoff
No further data - responding
Lost to follow-up - Responding
Drug no longer needed
31 Responders at Month 18
Loss of Efficacy
Adverse Reaction
2
1
4
6
1
Cutoff
No further data - Responding
Drug no longer needed
17 Responders at Month 24

TABLE 18. PROTOCOL COVER SHEET

Name of Drug:

Study Dosage(s): Route of Administration:

Objective:

Tract and pathogens if there is a specific target pathogen:
(if applicable)

Patient Population:

Structure: Parallel Group Duration of treatment period:

Crossover: # of treatments: # of sequences:
# of periods: Duration of periods:
Washout between periods: Yes No
Duration of washout:
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) Dose:

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

FIGURE 2. FLOW CHART OF STUDY

Study #

	Single Blind								Double-Blind Treatment Period								
	Screening Period				Placebo Period				25 mg C bid					Standard Treatment			
									12.5 mg C bid								
Visit	1	(7d)	2	(7d)	3	(7d)	4	(7d)	6.25 mg C bid					(1d)	(6d)	8	
									Placebo bid								
									5	(7d)	6	(7d)	7				
Consent	X																
History	X																
Physical	X																
Capsule count			X		X		X		X		X		X			X	
Concomitant medication			X		X		X		X		X		X			X	
Efficacy evaluation			X		X		X		X		X		X			X	
Adverse experiences			X		X		X		X		X		X			X	
CBC	X								X				X				
Clinical chemistry	X								X				X				
Urinalysis	X								X				X				
Blood levels									X				X				
Discharge non-qualified patients	X		X		X		X		X								
Assign patient number									X								

Table 19. DISPOSITION OF PATIENTS

Study #

			Number of patients completing each period of study		
	Randomized	**Treated**	**Week 1**	**Week 2**	**Week 4**
Test Drug	#	# (%)			
Active Control					
Placebo					
Total					
Comparability test (p-value)					

Table 20. LISTING OF PATIENTS WHO DISCONTINUED STUDY

Study #

Investigator:

Treatment	Patient #	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	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 21. NUMBER OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Study #

Test Drug N =

	Duration of treatment (week/month)			
Reason	**1**	**2**	**4**	**8**
Total				

Similar tables should be prepared for the other treatment groups, i.e., placebo and/or standard drug.

TABLE 22. ADVERSE REACTION: NUMBER AND RATE, WITH PATIENT IDENTIFICATIONS

Treatment Group X N=50

	Mild		Moderate		Severe		Total	
	Related[a]	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%)
	005**	021	031	038	048	058		
	009	022	033		049			
	011							
	014							
Event 2								

a = according to the investigator
NR*= not related; this could be expanded, e.g., as definite, probable, possible
** = Patient identification number

Table 23. ADVERSE EVENT LISTING

Study #

Individual patient data listing

Investigator	Patient	Demographic variables Age	Sex	Treatment dose at onset	Time on Rx at onset	Adverse event	Duration of event	Severity of event	Action taken	Outcome	Relation to Rx
A	005	47	M	Drug 40 mg							
	007	32	F	Drug 40 mg							

TABLE 24. CLINICAL LABORATORY TESTS

Study #

Individual patient data listing

								Laboratory Test	
Investigator	Treatment	Patient	Time (weeks, month)	Age	Sex	Weight	Dose	AST (SGOT)	ALT (SGPT)
A	Test drug	005	0	47	M	80kg	40 mg	..*.	....
			1					....	....
			2					....	....
			3					....	....
		007	0	32	F	55kg	40 mg	....	....
			1					....	....
			2					....	....
			3					....	....

*= value of a particular test

Table 25. KEY DEMOGRAPHIC VARIABLES, BASELINE CHARACTERISTICS AND SCREENING VARIABLES

Study #

Individual patient data listing

			Demographic variables								All screening variables	Baseline characteristics	
			V1	V2...	V6	Duration	Prior	Concurrent	Concomitant medications		V7...	V8...	V11
Investigator	Patient	Treatment	Sex	Age	Wt	of illness	therapy	illness	Baseline	During study	Disease/State	SSBP	
A	005		M	47									
	007		F	32									