

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN  
USE

**DRAFT CONSENSUS GUIDELINE**

**THE COMMON TECHNICAL DOCUMENT FOR THE  
REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE**

**SAFETY**

Released for Consultation  
at *Step 2* of the ICH Process  
on 20 July 2000  
by the ICH Steering Committee

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.*

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

**THE COMMON TECHNICAL DOCUMENT FOR THE  
REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:**

**NONCLINICAL SUMMARIES AND ORGANISATION OF MODULE IV**

**Draft ICH Consensus Guideline**

Released for Consultation, 20 July 2000, at *Step 2* of the ICH Process

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## **GUIDELINE ON THE NONCLINICAL OVERALL SUMMARY AND NONCLINICAL SUMMARIES IN MODULE II OF THE COMMON TECHNICAL DOCUMENT**

### **GENERAL PRINCIPLES**

This guideline provides recommendations for the harmonisation of the Nonclinical Overall Summary, Nonclinical Written Summary, and Nonclinical Tabulated Summaries.

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e. as applicable to labeling) should primarily be addressed in the Overall Summary.

## **NONCLINICAL OVERALL SUMMARY**

This section should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overall Summary should not exceed about 30 pages.

### **GENERAL ASPECTS**

The Nonclinical Overall Summary should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified. The nonclinical testing strategy should be discussed. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, and effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed.

Relevant scientific literature and the properties of related products should be taken into account. The list of references should be presented in accordance with internationally accepted standards or the system used in Chemical Abstracts. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidelines. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overall Summary should contain appropriate reference citations to the Tabulated Summaries, in the following format: (Table X.X, Study/Report Number).

### **CONTENT AND STRUCTURAL FORMAT**

The Nonclinical Overall Summary should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics

## Toxicology

### Integrated overview and conclusions

### List of literature citations

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, anti-product antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, C<sub>max</sub>, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, the dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to:

- pharmacodynamics
- toxic signs
- causes of death
- pathologic findings
- genotoxic activity - the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- fertility, embryofetal development, peri/post-natal toxicity
- the consequences of use before and during pregnancy and during lactation
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- the carcinogenic risk to humans - if epidemiologic data are available, they should be taken into account
- local tolerance
- other toxicity studies/ studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect / phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- animal species used
- numbers of animals used

- routes of administration employed
- dosages used
- duration of treatment or of the study
- systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended.
- the effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

## **THE NONCLINICAL WRITTEN AND TABULATED SUMMARIES**

### **NONCLINICAL WRITTEN SUMMARIES**

#### **1. INTRODUCTION**

This guideline is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It must be emphasised that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

#### **2. GENERAL PRESENTATION ISSUES**

##### **2.1 Order of Presentation of Information within Sections**

When available, in vitro studies should precede in vivo studies.

Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

1. Mouse
2. Rat
3. Hamster
4. Other rodent
5. Rabbit
6. Dog
7. Non-human primate
8. Other non-rodent mammal
9. Non-mammals

Routes of administration should be ordered as follows:

1. The intended route for human use
2. Oral
3. Intravenous
4. Intramuscular
5. Intraperitoneal
6. Subcutaneous
7. Inhalation
8. Topical
9. Other

## **2.2 Use of Tables and Figures**

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures. Examples of formats that might be included in the Written Summaries are shown in Appendix A.

In order to allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

## **2.3 Length of Nonclinical Written Summaries**

Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100-150 pages.

## **2.4 Sequence of Written Summaries and Tabulated Summaries**

The following order is recommended:

1. Introduction
2. Written Summary of Pharmacology
3. Tabulated Summary of Pharmacology
4. Written Summary of Pharmacokinetics
5. Tabulated Summary of Pharmacokinetics
6. Written Summary of Toxicology
7. Tabulated Summary of Toxicology

### **3. CONTENT OF NONCLINICAL WRITTEN SUMMARY**

#### **3.1 Introduction**

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

1. Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties.
2. Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

#### **3.2 The Pharmacology Written Summary**

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief Summary
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

##### **3.2.1 Brief Summary**

The principal findings from the pharmacology studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

##### **3.2.2 Primary Pharmacodynamics**

Studies on primary pharmacodynamics\* should be summarised and evaluated. Where possible, it is helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

##### **3.2.3 Secondary Pharmacodynamics**

Studies on secondary pharmacodynamics\* should be summarised by organ system, where appropriate, and evaluated in this section.

##### **3.2.4 Safety Pharmacology**

Safety pharmacology studies\* should be summarised and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary pharmacodynamic studies should be considered along with safety pharmacology studies.

### **3.2.5 Pharmacodynamic Drug Interactions**

If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.

### **3.2.6 Discussion and Conclusions**

This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise.

### **3.2.7 Tables and Figures**

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

## **3.3 The Pharmacokinetics Written Summary**

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Methods of Analysis
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

### **3.3.1 Brief Summary**

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasising, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

### **3.3.2 Methods of Analysis**

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

### **3.3.3 Absorption**

The following data should be summarised in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies)

### **3.3.4 Distribution**

The following data should be summarised in this section:

- Tissue distribution studies
- Protein binding and distribution in blood cells
- Placental transfer studies

### **3.3.5 Metabolism (inter-species comparison)**

The following data should be summarised in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Pre-systemic metabolism (GI/hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition

### **3.3.6 Excretion**

The following data should be summarised in this section:

- Routes and extent of excretion
- Excretion in milk

### **3.3.7 Pharmacokinetic Drug Interactions**

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarised in this section.

### **3.3.8 Other Pharmacokinetic Studies**

If studies have been performed in nonclinical models of disease (e.g., renal-impaired), they should be summarised in this section.

### **3.3.9 Discussion and Conclusions**

This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.

### **3.3.10 Tables and Figures**

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

### 3.4 The Toxicology Written Summary

The sequence of the Toxicology Written Summary should be as follows:

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproduction Toxicity
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

#### 3.4.1 Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than 6). In this section, the extent of the toxicologic evaluation can be indicated by the use of a table listing the principal toxicologic studies (results should not be presented in this table), for example:

#### TOXICOLOGY PROGRAMME

Study type and duration	Route of administration	Species	Compound administered*
Single-dose toxicity	po and iv	Rat and mouse	Parent drug
Single-dose toxicity	po and iv	Rat and mouse	Metabolite X
Repeat-dose toxicity			
1 month	po	Rat and dog	Parent drug
6 months	po	Rat	“        “
9 months, etc.	po	Dog	“        “

\* This column required only if metabolite(s) are investigated.

The scope of the toxicologic evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

### **3.4.2 Single-Dose Toxicity**

The single-dose data should be very briefly summarised, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.

### **3.4.3 Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)**

Studies should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/response relationships, no observed adverse effect levels, etc.). Non-pivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).

### **3.4.4 Genotoxicity**

Studies should be briefly summarised in the following order:

- in vitro non-mammalian cell system
- in vitro mammalian cell system
- in vivo mammalian system (including supportive toxicokinetics evaluation)
- other systems

### **3.4.5 Carcinogenicity (including supportive toxicokinetics evaluations)**

A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarised in the following order:

- Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Other studies

### **3.4.6 Reproduction Toxicity (including range-finding studies and supportive toxicokinetics evaluations)**

Studies should be summarised in the following order, giving brief details of the methodology and highlighting important findings:

- Fertility and early embryonic development
- Embryo-fetal development
- Prenatal and postnatal development, including maternal function

If modified study designs are used, the sub-headings should be modified accordingly.

### **3.4.7 Local Tolerance**

If such studies have been performed, they should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.

### **3.4.8 Other Toxicity Studies (if available)**

If other studies have been performed, they should be summarised. When appropriate, the rationale for conducting the studies should be provided.

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Studies on metabolites
- Studies on impurities
- Other studies

### **3.4.9 Discussion and Conclusions**

This section should provide an opportunity to discuss the toxicologic evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.

### **3.4.10 Tables and Figures**

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

## **3.5 Examples of Tables and Figures for Written Summaries (Appendix A)**

The tables and figures in Appendix A are presented merely as examples. Applicants should provide tables and figures using a format appropriate to the product.

Study references should be included in the table or text.

Tables should include statistics, if appropriate.

## **NONCLINICAL TABULATED SUMMARIES**

It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined in this Guideline. Applicants can modify the format if needed to provide the best possible presentation of the information, to facilitate the understanding and evaluation of the results.

This Guideline is not intended to indicate what studies are requested, but solely to instruct how to tabulate study results if the study was performed. Applicants might need to add or delete some items to or from the cited format where appropriate. One tabular format can contain results from several studies.

Alternatively, the data resulting from one study may have to be cited in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are provided in Appendices B and C, which follow. Appendix B contains templates for use in preparation of the tables. The templates are annotated (in italics) to provide guidance on their preparation. (The italicized information should be deleted when the tables are prepared.) Appendix C provides examples of the summary tables. The purpose of the examples is to provide additional guidance on the suggested content and format of the Tabulated Summaries. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product. Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information. Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

## **THE ORGANISATION OF MODULE IV: NONCLINICAL STUDY REPORTS**

This guideline presents an agreed format for the organisation of the nonclinical reports in the Common Technical Document for applications that will be submitted to Regulatory Authorities.

### **A. Table of Contents**

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

### **B. Study Reports**

The study reports should be presented in the following order:

1. Pharmacology
  - 1.1 Primary Pharmacodynamics
  - 1.2 Secondary Pharmacodynamics
  - 1.3 Safety Pharmacology
  - 1.4 Pharmacodynamic Drug Interactions
  
2. Pharmacokinetics
  - 2.1 Analytical Methods and Validation Reports (if separate reports are available)
  - 2.2 Absorption
  - 2.3 Distribution
  - 2.4 Metabolism
  - 2.5 Excretion
  - 2.6 Pharmacokinetic Drug Interactions (nonclinical)
  - 2.7 Other Pharmacokinetic Studies
  
3. Toxicology
  - 3.1 Single-Dose Toxicity (in order by species, by route)
  - 3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluation)
  - 3.3 Genotoxicity
    - 3.3.1 *In vitro*
    - 3.3.2 *In vivo* (including supportive toxicokinetics evaluations)

- 3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
  - 3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 3.4.3 Other studies
- 3.5 Reproduction Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
  - 3.5.1 Fertility and early embryonic development
  - 3.5.2 Embryo-fetal development
  - 3.5.3 Prenatal and postnatal development, including maternal function
- 3.6 Local Tolerance
- 3.7 Other Toxicity Studies (if available)
  - 3.7.1 Antigenicity
  - 3.7.2 Immunotoxicity
  - 3.7.3 Mechanistic studies (if not included elsewhere)
  - 3.7.4 Dependence
  - 3.7.5 Metabolites
  - 3.7.6 Impurities
  - 3.7.7 Other

## **C. Key Literature References**

## **APPENDIX A**

### Examples of Tables and Figures for Written Summaries

The tables and figures in Appendix A are presented merely as examples. Applicants should provide tables and figures using a format appropriate to the product.

Study references should be included in the table or text.

Tables should include statistics, if appropriate.

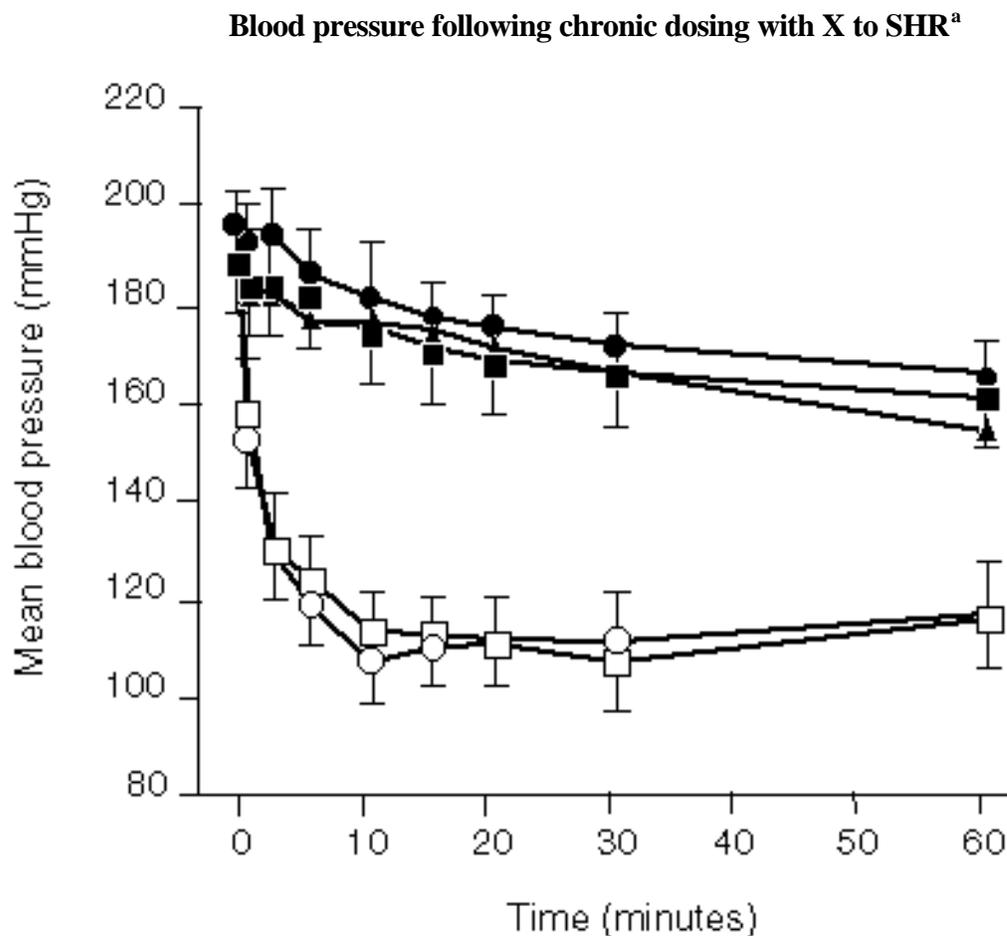
**Table X**

**Binding of X and its Major Metabolites and Comparators  
to Human X<sub>2</sub> and X<sub>3</sub> Receptors**

Compound	X <sub>2</sub>	X <sub>2</sub>	X <sub>3</sub>	X <sub>3</sub>
	K <sub>i1</sub> (nM)	K <sub>i2</sub> (nM)	K <sub>i1</sub> (nM)	K <sub>i2</sub> (nM)
<b>1</b>	538	2730	691	4550
<b>2</b>	2699	1050	2.0	181
<b>3</b>	578	14.4	141	10400
<b>4</b>	20	100	10.7	7.9
<b>5</b>	2100	3.1	281	28
<b>6</b>	7.5	8.4	44	2.8
<b>7</b>	3.11	3.76	1.94	1.93

K<sub>i1</sub> and K<sub>i2</sub> represent the high and low affinity binding sites respectively (Data from Study Number).

Figure X



**Blood pressure following chronic dosing with X to SHR<sup>a</sup>[ref].** Hypotensive effect of saline i.v. infusion over 5 min (▲) compared to X, 3 mg/kg i.v. infusion to SHR pretreated twice daily with saline, 1 mL/kg p.o., for 7 (○) or 14 (□) days or X, 25 mg/kg p.o., for 7 (●) or 14 (■) days. Saline pretreated statistical significances:  $p < 0.05$ , all other points after challenge  $p < 0.01$ . Values represent mean  $\pm$  s.e.m.

<sup>a</sup>SHR= spontaneous hypertensive rat (n=5 per group)

**Table X**

**Model-independent pharmacokinetic parameters for X in mice following single oral doses at 2, 10 and 30 mg/kg [ref]**

Parameter (units)	Parameter value					
	Males			Females		
Sex						
Dose (mg/kg)	2	10	30	2	10	30
C <sub>max</sub> (ng/mL)	4.9	20.4	30.7	5.5	12.9	28.6
T <sub>max</sub> (h)	0.8	0.4	0.3	0.4	0.5	0.3
AUC <sub>0-t</sub> (ng.h/mL)	21.6	80.5	267	33.3	80	298
AUC <sub>0-inf</sub> (ng.h/mL)	28.3	112	297	40.2	90	327

Pharmacokinetic parameters were determined in pooled plasma from three animals at each time

**Table X**

**Excretion of radioactive material following single doses of [<sup>14</sup>C]X to male mice [ref]**

Dose (mg/kg)/ route		Percentage of administered dose		
		Urine*	Faeces	Total <sup>+</sup>
2.8	i.v.	88.1 ± 7.4	5.5 ± 0.7	93.6 ± 6.9
8.8	p.o.	89.4 ± 4.7	6.9 ± 1.4	95.3 ± 3.4

Excretion was determined over 168 hours after dosing

Values are means ± S.D. (n= 5 for p.o. and 5 for i.v.)

\* - includes radioactivity in cage wash (22.1% after p.o. and 21.7% after i.v.)

+ - includes radioactivity in the carcass

**Table X**  
**Concentrations of radioactive material in the tissues of male rats after a single intravenous dose of [<sup>14</sup>C]X at 1.75 mg/kg [refs]**

Tissue	Concentration (ng equiv.*/g)				
	1 h	6 h	24 h	48 h	72 h
Blood	105	96.6	2.34	2.34	3.65
Plasma	142	175	3.12	ND	ND
Adrenals	656	49.2	14.3	9.63	ND
Bone marrow	359	31.5	ND	ND	ND
Brain	116	9.37	ND	ND	ND
Eyes	124	28.9	4.69	ND	ND
Fat	490	44.0	10.2	6.25	5.47
Heart	105	26.6	ND	ND	ND
Kidneys	1280	651	21.6	13.3	9.63
Large intestine	570	2470	39.3	12.0	ND
Liver	875	380	133	87.7	64.6
Lungs	234	59.1	7.55	ND	ND

\* - ng of X free base equivalent/g.

N= 5 animals/time point

ND - Not detected

**Table X**

**Excretion of radioactive material following single doses of [<sup>14</sup>C]X to male rats [refs]**

Dose (mg/kg)/ route		Percentage of administered dose			
		Urine	Faeces	Bile	Total
1.75	i.v.	61.3 ± 9.3	30.3 ± 4.1	-	95.2 ± 5.0
1.75	p.o.	57.4 ± 3.8	37.0 ± 3.4	-	95.2 ± 1.5
2	p.o.	72.3 ± 0.8	26.9 ± 1.9	-	99.5 ± 1.1
20	p.o.	23.5 ± 6.3	0.5 ± 0.2	76.0 ± 5.9	100 ± 0.8
220	p.o.	67.1 ± 9.0	24.8 ± 5.0	-	93.3 ± 6.8

Excretion was determined over 168 h period in Wistar rats: Values are means ± S.D. (n=5); - not assayed; Total includes radioactivity in the carcass and cage washings

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Table X

Comparative pharmacokinetic data and systemic exposure to X following oral administration to mice, rats, dogs and patients [ref]

Species (formulation)	Dose (mg/kg/day)	Systemic (plasma) exposure		References
		C <sub>max</sub> (ng/mL)	AUC (ng.h/mL)#	
Man (tablet)	0.48 <sup>\$</sup>	36.7	557	X
Mouse (solution)	8.8	68.9 (1.9)*	72.7 (0.2)*	Y
	21.9	267 (7.3)*	207 (0.5)*	
	43.8	430 (11.7)*	325 (0.7)*	
Rat (solution)	50	479 (13.0)*	1580 (2.8)*	Z
Dogs (solution)	1.5	5.58 (0.2)*	15.9 (<0.1)*	V
	5	24.8 (0.7)*	69.3 (0.1)*	
	15	184 (5.0)*	511 (0.9)*	

Data presented are for male and female animals and are after daily repeated oral administration (at the end of the 60-day mouse study, 14 day rat study, and 1 year dog study). Data for man are extrapolated from dose normalised data obtained in male and female patients following t.i.d regimen.

# - AUC<sub>0-6</sub> in the mouse, AUC<sub>0-t</sub> in the rat and in the dog and dose normalised AUC<sub>0-τ</sub> x 24 in man. \$ - calculated from the total daily dose assuming a bodyweight of 50 kg for man. \* - Numbers in parentheses represent ratios of exposure in animals to those in patients

**Table X**

**Incidence of Proliferative Interstitial (Leydig) Cell Lesions in Rats [ref]**

---

<b>Lesion</b>	<b>Dose Groups</b>			
	<b>Control</b>	<b>3 mg/kg</b>	<b>30 mg/kg</b>	<b>100 mg/kg</b>
Hyperplasia (only)	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)
Adenoma (only)	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)
Adenoma + Hyperplasia	x/50 (%)	x/50 (%)	x/50(%)	x/50 (%)
Total*	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)

---

\* Adenoma and/or Hyperplasia

**APPENDIX B**

**THE NONCLINICAL TABULATED SUMMARIES – TEMPLATES**

## **THE NONCLINICAL TABULATED SUMMARIES – TEMPLATES**

### **I. Pharmacology**

1. Pharmacology: Overview
  - 1.1 Primary Pharmacodynamics\*
  - 1.2 Secondary Pharmacodynamics\*
  - 1.3 Safety Pharmacology

### **II. Pharmacokinetics**

- 2A Pharmacokinetics: Overview
  - 2.1 Analytical Methods and Validation Reports\*
    - 2.2.1 Pharmacokinetics: Absorption after a Single Dose
    - 2.2.2 Pharmacokinetics: Absorption after Repeated Doses
    - 2.3.1 Pharmacokinetics: Distribution
    - 2.3.2 Pharmacokinetics: Protein Binding
    - 2.3.3 Pharmacokinetics: Study in Pregnant or Nursing Animals
    - 2.3.4 Pharmacokinetics: Other Distribution Study
    - 2.4.1 Pharmacokinetics: Metabolism In Vivo
    - 2.4.2 Pharmacokinetics: Metabolism In Vitro
    - 2.4.3 Pharmacokinetics: Possible Metabolic Pathways
    - 2.4.4 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes
    - 2.5.1 Pharmacokinetics: Excretion
    - 2.5.2 Pharmacokinetics: Excretion into Bile
  - 2.5 Pharmacokinetics: Drug-Drug Interactions
  - 2.6 Pharmacokinetics: Other

### **III. Toxicology**

- 3A Toxicology: Overview
- 3B Toxicokinetics: Overview of Toxicokinetics Studies
- 3C Toxicokinetics: Overview of Toxicokinetics Data
- 3D Toxicology: Drug Substance
  - 3.1 Single-Dose Toxicity
    - 3.2.1 Repeat-Dose Toxicity: Non-Pivotal Studies
    - 3.2.2 Repeat-Dose Toxicity: Pivotal Studies
    - 3.3.1 Genotoxicity: In Vitro
    - 3.3.2 Genotoxicity: In Vivo

### 3.4 Carcinogenicity

3.5.1 Reproduction Toxicity: Non-Pivotal Studies

3.5.2 Reproduction Toxicity – Fertility and Early Embryonic Development to Implantation (Pivotal)

3.5.3 Reproduction Toxicity – Effects on Embryo-Fetal Development (Pivotal)

3.5.4 Reproduction Toxicity – Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)

### 3.6 Local Tolerance

### 3.7 Other Toxicity Studies

\* : Tabulated Summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.

**1 Pharmacology**

**Overview**

**Test Article: (1)**

<u>Type of Study</u>	<u>Test System</u>	<u>Method of Administration</u>	<u>Testing Facility</u>	<u>Study Number(4)</u>	<u>Location Vol. Page</u>
1.1 Primary Pharmacodynamics (2)					(3)
1.2 Secondary Pharmacodynamics					
1.3 Safety Pharmacology					
1.4 Pharmacodynamic Drug Interactions					

Notes: (1) International Nonproprietary Name (INN)

(2) There should be one line for each pharmacology report, in the same order as the CTD. Reports that contain a GLP Compliance Statement should be identified in a footnote.

(3) The location of the Technical Report in the CTD should be indicated.

(4) Or Report Number (on all tables).

**1.3 Safety Pharmacology (1)**

**Test Article: (2)**

<u>Organ Systems Evaluated</u>	<u>Species/ Strain</u>	<u>Method Admin.</u>	<u>of</u>	<u>Doses<sup>a</sup> (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>Noteworthy Findings</u>	<u>GLP Compliance</u>	<u>Study Number(3)</u>
--------------------------------	------------------------	----------------------	-----------	----------------------------------	---------------------------------	----------------------------	-----------------------	------------------------

Notes: (1) All safety-pharmacology studies should be summarized.

(2) International Nonproprietary Name (INN).

(3) Or Report Number (on all tables).

a - Single dose unless specified otherwise.

**2A Pharmacokinetics**

**Overview**

**Test Article: (1)**

<u>Type of Study</u>	<u>Test System</u>	<u>Method of Administration</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location</u>	
					<u>Vol.</u>	<u>Page</u>
2.1 Kinetics (2)						(3)
2.2 Tissue Distribution						
2.3 Metabolism						
2.4 Pharmacokinetic Drug Interactions						

- Notes:
- (1) International Nonproprietary Name (INN).
  - (2) There should be one line for each pharmacokinetics report, in the same order as the CTD. Reports that contain a GLP Compliance Statement should be identified in a footnote.
  - (3) The location of the Technical Report in the CTD should be indicated.

**2.2.1 Pharmacokinetics: Absorption after a Single Dose**

**Test Article: (1)**

Species

Gender (M/F) / Number of animals

(4)

Feeding condition

Vehicle/Formulation

Method of Administration

Dose (mg/kg)

Sample (Whole blood, plasma, serum etc.)

Analyte

Assay (2)

PK parameters:

Study number

Location in CTD

---

Additional Information: (3)

Notes: (1) *International Nonproprietary Name (INN).*

(2) *For example, HPLC, LSC with <sup>14</sup>C-labeled compound.*

(3) *For example, brief textual results, species differences, gender differences, dose dependency, or special comments.*

(4) *There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included.*

---

**2.2.2 Pharmacokinetics: Absorption after Repeated Doses**

**Test Article:**

[Data may be tabulated as in the format of 2.1.1 if applicable.]

**Format A**

**2.3.1 Pharmacokinetics: Organ Distribution**

**Test Article:**

Location in CTD: Vol. Page  
Study No.

Species:

Gender (M/F)/Number of animals:

Feeding condition:

Vehicle/Formulation:

Method of Administration:

Dose (mg/kg):

Radionuclide:

Specific Activity:

Sampling time:

Tissues/organs	Concentration (unit)					
	T(1)	T(2)	T(3)	T(4)	T(5)	t <sub>1/2</sub>

---

Additional information:

---

**Alternate Format B**

**2.3.1 Pharmacokinetics: Organ Distribution**

**Test Article:**

Location in CTD: Vol. Page  
Study No.

Species:

Gender (M/F) / Number of animals:

Feeding condition:

Vehicle/Formulation:

Method of Administration:

Dose (mg/kg):

Radionuclide:

Specific Activity:

Analyte/Assay (unit):

Sampling time:

Tissues/organs

	C <sub>t</sub>		Last time-point			
	conc.	T/P <sup>1)</sup>	conc.	T/P <sup>1)</sup>	Time	AUC
						t <sub>1/2</sub> <sup>2)</sup>

---

Additional information:

---

<sup>1)</sup> [Tissue]/[Plasma]

**2.3.2 Pharmacokinetics: Plasma Protein Binding**

**Test Article:**

Study system:

Target entity, Test system and method:

<u>Species</u>	<u>Conc. tested</u>	<u>% Bound</u>	<u>Study No.</u>	<u>Location in CTD</u>	
				<u>Vol.</u>	<u>Page</u>

---

Additional Information:

---

**2.3.3 Pharmacokinetics: Study in Pregnant or Nursing Animals (1)**

**Test Article: (2)**

**Placental transfer**

Location in CTD: Vol. Page  
Study No.

Species:

Gestation day / Number of animals:

Vehicle/Formulation:

Method of Administration:

Dose (mg/kg):

Analyte:

Assay:

Time (hr)

Concentration / Amount (% of dose)

Dam (3):

Fetus (3):

---

Additional Information:

---

Location in CTD: Vol. Page  
Study No.

**Excretion into milk**

Species:

Lactating date / Number of animals:

Feeding condition:

Vehicle/Formulation:

Method of Administration:

Dose (mg/kg):

Analyte:

Assay:

Time [hr]

Concentration:

Milk:

Plasma:

Milk / plasma:

Neonates:

---

Additional Information:

**Notes for Table 2.3.3**

- (1) Even if the data are obtained in reproduction toxicology studies, they should be presented in this table.
- (2) International Nonproprietary Name (INN).
- (3) The tissue sampled should be described; e.g., plasma for dams, fetal concentrations.

**2.3.4 Pharmacokinetics: Other Distribution Study**

**Test Article:**

**2.4.1 Pharmacokinetics: Metabolism *In Vivo***

**Test Article:**

Gender(M/F) / Number of animals:

Feeding condition:

Vehicle/Formulation:

Method of Administration:

Dose (mg/kg):

Radionuclide:

Specific Activity:

<u>Species</u>	<u>Sample</u>	<u>Sampling Time or Period</u>	<u>% of Dose in Sample</u>	<u>% of Compound in Sample</u>			<u>Study No.</u>	<u>Location in CTD</u>	
				<u>Parent</u>	<u>M1</u>	<u>M2</u>		<u>Vol</u>	<u>Page</u>
	Plasma								
	Urine								
	Bile								
	Feces								
	Plasma								
	Urine								
	Bile								
	Feces								
	Plasma								
	Urine								
	Bile								
	Feces								

**Additional Information:**

Note: Human data should be included for comparison, if available.

**2.4.2 Pharmacokinetics: Metabolism *In Vitro***

**Test Article:**

**Location in CTD: Vol. Page  
Study No.**

**Study system:**

**Time**

**Concentration:**

**Compounds**

**Parent**

**M-1**

**M-2**

---

**Additional Information:**

*Note: Human data should be included for comparison, if available.*

---

**2.4.3 Pharmacokinetics: Possible Metabolic Pathways**

**Test Article:**

*(Illustrate possible metabolic map indicating species in which metabolic reactions occur.)*

**2.4.4 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes**

**Test Article:**

**Location in CTD: Vol. Page  
Study No.**

*Note: Nonclinical studies only.*

**Type of study:**

**Method:**

**Tabulated results:**

**Additional Information:**

**2.5.1 Pharmacokinetics: Excretion**

**Test Article: (1)**

Species	_____											
Gender (M/F) / Number of animals	(3)											
Feeding condition												
Vehicle/Formulation												
Method of Administration												
Dose (mg/kg)												
Analyte												
Assay												
Excretion route (4)	<u>Urine</u>	<u>Feces</u>	<u>Total</u>									
Time												
0 - T hr												
Study number												
Location in CTD												

---

**Additional Information: (2)**

- Notes:
- (1) International Nonproprietary Name (INN).
  - (2) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
  - (3) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included. May be combined with the Absorption Table, if appropriate.
  - (4) Other routes (e.g., biliary, respiratory) should be added, if performed.
-

**2.5.2 Pharmacokinetics: Excretion into Bile**

**Test Article:**

[Data may be tabulated as in the format of 2.2.1 if applicable.]

**2.6 Pharmacokinetics: Drug-Drug Interactions**

**Test Article:**

**Location in CTD:** Vol.    Page  
**Study No.**

**Type of study:**

**Method:**

**Tabulated results:**

**Additional Information:**

**2.7 Pharmacokinetics: Other**

**Test Article:**

**Location in CTD:** Vol.    Page  
**Study No.**

**Type of study:**

**Method:**

**Tabulated results:**

**Additional Information:**

**3A Toxicology**

**Overview**

**Test Article: (1)**

<u>Type of Study</u>	<u>Species and Strain</u>	<u>Method of Administration</u>	<u>Duration of Dosing</u>	<u>Doses (mg/kg<sup>a</sup>)</u>	<u>GLP Compliance</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol. Page</u>
3.1 Single-Dose Toxicity	(2)							(3)
3.2 Repeat-Dose Toxicity								
3.3 Genotoxicity								
3.4 Carcinogenicity								
3.5 Reproduction Toxicity								
3.6 Local Tolerance								
3.7 Other Toxicity Studies								

Notes: (1) International Nonproprietary Name (INN).

(2) There should be one line for each toxicology report, in the same order as the CTD.

(3) The location of the Technical Report in the CTD should be indicated.

a - Unless otherwise specified. For Single-Dose Toxicity and Repeat-Dose Toxicity, the NOAEL (No Observed Adverse-Effect Level) should be underlined.

**3B Toxicokinetics**

**Overview of Toxicokinetics Studies**

**Test Article: (1)**

<u>Type of Study</u>	<u>Test System</u>	<u>Method of Administration</u>	<u>Doses (mg/kg)</u>	<u>GLP Compliance</u>	<u>Study Number</u>	<u>Location Vol. Page</u>
(2)						(3)

- Notes: (1) International Nonproprietary Name (INN).  
 (2) There should be one line for each toxicokinetics report, in the same order as the CTD (Section 3, Toxicology).  
 (3) The location of the Technical Report in the CTD should be indicated.

**3C Toxicokinetics**

**Overview of Toxicokinetics Data**

**Test Article: (1)**

**(2)**

Notes: (1) International Nonproprietary Name (INN).

(2) A one- to three-page summary (tables and/or figures) of steady-state toxicokinetic data should be prepared in a format that facilitates comparisons across species, including humans.

**3D Toxicology**

**Drug Substance**

**Test Article: (1)**

<u>Batch No.</u>	<u>Purity (%)</u>	<u>Specified Impurities (.)</u>	<u>Study Number</u>	<u>Type of Study</u>
PROPOSED <u>SPECIFICATION:</u>				
(2)				(3)

Notes: (1) International Nonproprietary Name (INN).

(2) All batches used in the Toxicology studies should be listed, in approximate chronological order.

(3) The Toxicology studies in which each batch was used should be identified.

**3.1 Single-Dose Toxicity (1)**

**Test Article: (2)**

<u>Species/ Strain</u>	<u>Method of Administration (Vehicle/ Formulation)</u>	<u>Doses (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>Observed Maximum Non- Lethal Dose (mg/kg)</u>	<u>Approximate Lethal Dose (mg/kg)</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
----------------------------	--	--------------------------	---	--	--	----------------------------	-------------------------

Notes: (1) All single-dose toxicity studies should be summarized, in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual duration, infusion rate, or age of test subjects.

(2) International Nonproprietary Name (INN).

**3.2.1 Repeat-Dose Toxicity Non-Pivotal Studies (1)**

**Test Article: (2)**

<u>Species/ Strain</u>	<u>Method of Administration (Vehicle/ Formulation)</u>	<u>Duration of Dosing</u>	<u>Doses (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>NOAEL<sup>a</sup> (mg/kg)</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
----------------------------	--	-------------------------------	--------------------------	---	--------------------------------------	----------------------------	-------------------------

Notes: (1) All repeat-dose toxicity studies (including all range-finding toxicity studies), other than the definitive GLP studies specified by ICH Guideline M3 should be summarized, in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual age of test subjects.

(2) International Nonproprietary Name (INN).

---

a - No Observed Adverse-Effect Level.

**3.2.2 (1) Repeat-Dose Toxicity (2)**

**Report Title:**

**Test Article: (3)**

Species/Strain:  
Initial Age: Duration of Postdose:  
Date of First Dose:

Duration of Dosing:  
Location in CTD: Vol. Page  
Method of Administration:  
Vehicle/Formulation:

Study No.

GLP Compliance:

Special Features:  
No Observed Adverse-Effect Level:

Daily Dose (mg/kg)	<u>0 (Control)</u>							
Number of Animals	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>
Toxicokinetics: AUC ( ) (4)	(5)							

**Noteworthy Findings**

**Died or Sacrificed Moribund**

**Body Weight (%<sup>a</sup>)**

**Food Consumption (%<sup>a</sup>)** (5)

**Water Consumption ( )** (5)

**Clinical Observations**

**Ophthalmoscopy**

**Electrocardiography**

- No noteworthy findings.      + Mild      ++ Moderate      +++ Marked      (6)

(7) \* - p<0.05      \*\* - p<0.01

a - At end of dosing period. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

(Continued)

**3.2.2 (1) Repeat-Dose Toxicity**

**Study No. (Continued)**

Daily Dose (mg/kg)	<u>0 (Control)</u>							
Number of Animals	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>
Hematology								
Serum Chemistry								
Urinalysis								
Organ Weights <sup>a</sup> (%)								
Gross Pathology								
<hr/> Histopathology	<i>(11)</i>							
<hr/> Additional Examinations								
Postdose Evaluation:								
Number Evaluated	<i>(8)</i>							

- No noteworthy findings.

(7) \* - p<0.05      \*\* - p<0.01

a - Both absolute and relative weights differed from controls in the direction indicated. Number should indicate percent difference for the absolute organ weights.

**Notes for Table 3.2.2**

- (1) The tables should be numbered consecutively: 3.2.2A, 3.2.2B, 3.2.2C etc.
- (2) There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.
- (3) International Nonproprietary Name (INN).
- (4) Steady-state AUC, C<sub>max</sub>, or other toxicokinetic information supporting the study. If from a separate study, the Study Number should be given in a footnote.
- (5) **ONLY NOTEWORTHY FINDINGS SHOULD BE PRESENTED.** If additional parameters (other than those in the Template) showed noteworthy changes, these should be added to the tables. In general, data at end of dosing period can be shown; however, if there were additional noteworthy findings at earlier timepoints, these should be included. Footnotes should be used as needed to provide additional information about the tests or the results.
- (6) Or other scale, as appropriate.
- (7) Methods of statistical analyses should be indicated.
- (8) All parameters that still show drug-related changes should be listed. This section should be deleted if the study does not include a Postdose Evaluation.
- (9) When appropriate, information on animals that were necropsied early should be presented separately.

**3.3.1 (1) Genotoxicity: In Vitro**

**Report Title:**

**Test Article: (2)**

**Test for Induction of:**

**Strains:**

**Metabolizing System:**

**Vehicles: For Test Article:**

**Treatment:**

**Cytotoxic Effects:**

**Genotoxic Effects:**

**No. of Independent Assays:**

**No. of Replicate Cultures:**

**No. of Cells Analyzed/Culture:**

**For Positive Controls:**

**Study No.**

**Location in CTD: Vol. Page**

**GLP Compliance:**

**Date of Treatment:**

Metabolic  
Activation

Test  
Article

Concentration or  
Dose Level  
((3))

\_\_\_\_\_

Without  
Activation

(4)

With  
Activation

- Notes: (1) The tables should be numbered consecutively: 3.3.1A, 3.3.1B, etc. Results of replicate assays should be shown on subsequent pages.  
 (2) International Nonproprietary Name (INN).  
 (3) Units should be inserted.  
 (4) If precipitation is observed, this should be inserted in a footnote.  
 (5) Methods of statistical analyses should be indicated.

(5) \* - p<0.05      \*\* - p<0.01

**3.3.2 (1) Genotoxicity: In Vivo**

**Report Title:**

**Test Article: (2)**

Test for Induction of:

Species/Strain:

Age:

Cells Evaluated:

No. of Cells Analyzed/Animal:

Special Features:

Toxic/Cytotoxic Effects:

Genotoxic Effects:

Evidence of Exposure:

Treatment Schedule:

Sampling Time:

Method of Administration:

Vehicle/Formulation:

Study No.

Location in CTD: Vol. Page

GLP Compliance:

Date of Dosing:

<u>Test Article</u>	<u>Dose (mg/kg)</u>	<u>No. of Animals</u>				

Notes: (1) The tables should be numbered consecutively: 3.3.2A, 3.3.2B, etc.

(2) International Nonproprietary Name (INN).

(3) Methods of statistical analysis should be indicated.

(3) \* - p<0.05      \*\* - p<0.01).

**3.4 (1) Carcinogenicity**

**Report Title:**

**Test Article: (2)**

Species/Strain:

Initial Age:

Date of First Dose:

Basis for High-Dose Selection: (3)

Special Features:

Duration of Dosing:

Method of Administration:

Vehicle/Formulation:

Treatment of Controls:

Study No.

Location in CTD: Vol. Page

GLP Compliance:

Daily Dose (mg/kg)

Gender

Toxicokinetics: AUC ( ) (4)

Number of Animals

At Start

Died/Sacrificed Moribund

Terminal Sacrifice

Survival (%)

Body Weight (%<sup>a</sup>)

Food Consumption (%<sup>a</sup>)

	0 (Control)							
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>

(5)

(6) \* - p<0.05    \*\* - p<0.01

a - At 6 months. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

(Continued)

**3.4 (1) Carcinogenicity**

**Study No.**

**(Continued)**

Daily Dose (mg/kg)	____ (Control)	____ 0 (Control)							
Number Evaluated	<u>M:</u> <u>F:</u>	<u>M:</u> <u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u>	<u>F:</u>	<u>M:</u> <u>F:</u>
<b><u>Number of Animals</u></b>									
<b><u>with Neoplastic Lesions:</u></b>									
(7)									
<b><u>Noteworthy Findings:</u></b>									
Gross Pathology									
Histopathology - Non-Neoplastic Lesions									

- No noteworthy findings.

\* - p<0.05      \*\* - p<0.01

**(a) Notes for Table 3.4**

- (1) Tables should be numbered consecutively: 3.4A, 3.4B, etc. There should be one table for each carcinogenicity study.
- (2) International Nonproprietary Name (INN).
- (3) From ICH Guideline S1C.
- (4) Steady-state AUC, C<sub>max</sub>, C<sub>ss</sub>, or other toxicokinetic information supporting the study. If the information is from a separate study, the Study Number should be given in a footnote.
- (5) If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.
- (6) Methods of statistical analysis should be indicated.
- (7) Drug-related lesions should be listed first. Then other lesions should be listed by alphabetically ordered organs/tissues.

**3.5.1 Reproduction Toxicity**

**Non-Pivotal Studies (1)**

**Test Article: (2)**

<u>Species/ Strain</u>	<u>Method of Administration (Vehicle/ Formulation)</u>	<u>Dosing Period</u>	<u>Doses mg/kg</u>	<u>No. per Group</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
----------------------------	--	--------------------------	------------------------	----------------------	----------------------------	-------------------------

---

Notes: (1) All reproduction toxicity studies (including all relevant range-finding studies) other than the definitive GLP studies specified by ICH Guideline M3 should be summarized, in the same order as the CTD. However, investigative studies should be summarized using a more detailed template.

(2) International Nonproprietary Name (INN).

**3.5.2 (1) Reproduction Toxicity -  
Fertility and Early Embryonic  
Development to Implantation (3)**

**Report Title:**

**Test Article: (2)**

Design similar to ICH 4.1.1?  
Species/Strain:  
Initial Age:  
Date of First Dose:  
Special Features:  
No Observed Adverse-Effect Level:  
    F<sub>0</sub> Males:  
    F<sub>0</sub> Females:  
    F<sub>1</sub> Litters:

Duration of Dosing: M:  
Day of Mating: (8) F:  
Day of C-Section:  
Method of Administration:  
Vehicle/Formulation:

Study No.  
Location in CTD: Vol. Page  
  
GLP Compliance:

**Daily Dose (mg/kg)**

**0 (Control)**

**Males** Toxicokinetics: AUC ( ) (4)

No. Evaluated  
No. Died or Sacrificed Moribund  
Clinical Observations  
Necropsy Observations  
Body Weight (%<sup>a</sup>)  
Food Consumption (%<sup>a</sup>)  
Mean No. Days Prior to Mating  
No. of Males that Mated  
No. of Fertile Males

(5)

- No noteworthy findings.   + Mild   ++Moderate   +++Marked (6)

(7) \* - p<0.05   \*\* - p<0.01

a - After 4 weeks of dosing. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences). (Continued)

**3.5.2 (1) Reproduction Toxicity  
(Continued)**

**Study No.**

**Daily Dose (mg/kg)**

**0 (Control)**

**Females** Toxicokinetics: AUC ( ) (4)

No. Evaluated  
No. Died or Sacrificed Moribund  
Clinical Observations  
Necropsy Observations  
Premating Body Weight (%<sup>a</sup>)  
Gestation Body Weight (%<sup>a</sup>)  
Premating Food Consumption (%<sup>a</sup>)  
Gestation Food Consumption (%<sup>a</sup>)  
Mean No. Estrous Cycles/14 days  
Mean No. Days Prior to Mating  
No. Of Females Sperm-Positive  
No. Of Pregnant Females  
No. Aborted or with Total Resorption of Litter  
Mean No. Corpora Lutea  
Mean No. Implantations  
Mean % Preimplantation Loss  
Mean No. Live Conceptuses  
Mean No. Resorptions  
No. Dead Conceptuses  
Mean % Postimplantation Loss

- No noteworthy findings.    + Mild    ++Moderate    +++Marked    (6)

(7) \* - p<0.05    \*\* - p<0.01

a - At end of premating or gestation period. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

**Notes for Tables 3.5.2, 3.5.3, and 3.5.4**

- (1) If there are multiple studies of this type, the tables should be numbered consecutively: 3.5.2A, 3.5.2B, 3.5.3A, 3.5.3B, etc.
- (2) International Nonproprietary Name (INN).
- (3) If a modified study design is used, tables should be modified accordingly.
- (4) Steady-state AUC, C<sub>max</sub>, or other toxicokinetic information supporting the study. If the information is from a separate study, the Study Number should be given in a footnote.
- (5) POSSIBLE PRESENTATIONS OF THE RESULTS ARE SHOWN IN THESE TEMPLATES. DATA PRESENTATION SHOULD BE FLEXIBLE AND APPROPRIATE ACCORDING TO OPTIMAL STATISTICAL ANALYSIS AND THE DESIGN OF THE STUDY. If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.
- (6) Or other scale as appropriate.

Methods of statistical analysis should be indicated.

- (8) Day of mating should be indicated; e.g., Day 0 or Day 1

**3.5.3 (1) Reproduction Toxicity -  
Effects on Embryo-Fetal  
Development (3)**

**Report Title:**

**Test Article: (2)**

Design similar to ICH 4.1.3?

Duration of Dosing:

Study No.

Species/Strain:

Day of Mating: (8)

Location in CTD: Vol. Page

Initial Age:

Day of C-Section:

Date of First Dose:

Method of Administration:

Special Features:

Vehicle/Formulation:

GLP Compliance:

No Observed Adverse-Effect Level:

F<sub>0</sub> Females:

F<sub>1</sub> Litters:

**Daily Dose (mg/kg)**

**0 (Control)**

**Dams/Does:** Toxicokinetics: AUC ( ) (4)

No. Pregnant

No. Died or Sacrificed Moribund

No. Aborted or with Total Resorption of Litter

(5)

Clinical Observations

Necropsy Observations

Body Weight (%<sup>a</sup>)

Food Consumption (%<sup>a</sup>)

Mean No. Corpora Lutea

Mean No. Implantations

Mean % Preimplantation Loss

- No noteworthy findings.    + Mild    ++Moderate    +++Marked (6)    G = Gestation day

(7) \* - p<0.05    \*\* - p<0.01

a - At end of dosing period. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

(Continued)

**3.5.3 (1) Reproduction Toxicity  
(Continued)**

**Study No.**

**Daily Dose (mg/kg)**

**0 (Control)**

Litters: No. Litters Evaluated  
No. Live Fetuses  
Mean No. Resorptions  
No. of Litters with Dead Fetuses  
Mean % Postimplantation Loss  
Mean Fetal Body Weight (g)  
Fetal Sex Ratios  
Fetal Anomalies:  
    Gross External  
    Visceral Anomalies  
    Skeletal Anomalies  
Total Affected Fetuses (Litters)

---

- No noteworthy findings.

\* - p<0.05   \*\* - p<0.01

**3.5.4 (1) Reproduction Toxicity -  
Effects on Pre- and Postnatal  
Development, Including Maternal Function (3)**

**Report Title:**

**Test Article: (2)**

Design similar to ICH 4.1.2?

Duration of Dosing:

Study No.

Species/Strain:

Day of Mating: (8)

Location in CTD: Vol. Page

Initial Age

Method of Administration:

Date of First Dose:

Vehicle/Formulation:

Special Features:

Litters Culled/Not Culled:

GLP Compliance:

No Observed Adverse-Effect Level:

F<sub>0</sub> Females:

F<sub>1</sub> Males:

F<sub>1</sub> Females:

**Daily Dose (mg/kg)**

**0 (Control)**

F<sub>0</sub> Females: Toxicokinetics: AUC ( ) (4)  
 No. Pregnant  
 No. Died or Sacrificed Moribund  
 No. Aborted or with Total Res. Of Litter  
 Clinical Observations  
 Necropsy Observations  
 Gestation Body Weight (%<sup>a</sup>)  
 Lactation Body Weight (%<sup>a</sup>)  
 Gestation Food Consumption (%<sup>a</sup>)  
 Lactation Food Consumption (%<sup>a</sup>)  
 Mean Duration of Gestation (days)  
 Abnormal Parturition

(5)

- No noteworthy findings.    + Mild    ++Moderate    +++Marked (6)    G = Gestation day

(7) \* - p<0.05    \*\* - p<0.01)

L = Lactation day

a - At end of gestation or lactation. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

(Continued)

**3.5.4 (1) Reproduction Toxicity  
(Continued)**

**Study No.**

**Daily Dose (mg/kg)**

**0 (Control)**

F<sub>1</sub> Litters:  
(Preweaning) No. Litters Evaluated  
Mean No. of Implantations  
Mean No. Pups/Litter  
Mean No. Liveborn Pups/Litter  
No. of Litters with Stillborn Pups  
Postnatal Survival to Day 4  
Postnatal Survival to Weaning  
No. of Total Litter Losses  
Change in Pup Body Weights<sup>a</sup> (g)  
Pup Sex Ratios  
Pup Clinical Signs  
Pup Necropsy Obs.

F<sub>1</sub> Males:  
(Postweaning) No. Evaluated Postweaning  
Per Litter  
No. Died or Sacrificed Moribund  
Clinical Observations  
Necropsy Observations  
Body-Weight Change<sup>b</sup> (g)  
Food Consumption (%<sup>c</sup>)  
Preputial Separation  
Sensory Function  
Motor Activity  
Learning and Memory  
Mean No. Days Prior to Mating  
No. of Males that Mated  
No. of Fertile Males

- No noteworthy findings.    + Mild    ++Moderate    +++Marked (6)

(7)\* - p<0.05    \*\* - p<0.01

a - From birth to weaning.

b - From weaning to mating.

c - At end of postweaning period. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

**3.5.4 (1) Reproduction Toxicity  
(Continued)**

**Study No.**

**Daily Dose (mg/kg)**

**0 (Control)**

F<sub>1</sub> Females: (Postweaning) No. Evaluated Postweaning  
 No. Died or Sacrificed Moribund  
 Clinical Observations  
 Necropsy Observations  
 Premating Body-Weight Change<sup>a</sup> (g)  
 Gestation Body-Weight Change (g)  
 Premating Food Consumption (%<sup>b</sup>)  
 Gestation Food Consumption (%<sup>b</sup>)  
 Mean Age of Vaginal Patency (days)  
 Sensory Function  
 Motor Activity  
 Learning and Memory  
 Mean No. Days Prior to Mating  
 No. of Females Sperm-Positive  
 No. of Pregnant Females  
 Mean No. Corpora Lutea  
 Mean No. Implantations  
 Mean % Preimplantation Loss

F<sub>2</sub> Litters: Mean No. Live Conceptuses/Litter  
 Mean No. Resorptions  
 No. of Litter with Dead Conceptuses  
 No. Dead Conceptuses  
 Mean % Postimplantation Loss  
 Fetal Body Weights (g)  
 Fetal Sex Ratios (% males)  
 Fetal Anomalies

- No noteworthy findings.    + Mild    ++Moderate    +++Marked    (6)

(7)\* - p<0.05    \*\* - p<0.01

a - From weaning to mating

b - At end of premating or gestation period. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

**3.5.4 (1) Reproduction Toxicity  
(Continued)**

**Study No.**

**Daily Dose (mg/kg)**

**0 (Control)**

F<sub>1</sub> Females: No. Evaluated Postweaning  
(Postweaning) No. Died or Sacrificed Moribund  
Clinical Observations  
Necropsy Observations  
Premating Body-Weight Change<sup>a</sup> (g)  
Gestation Body-Weight Change (g)  
Premating Food Consumption (%<sup>b</sup>)  
Gestation Food Consumption (%<sup>ab</sup>)  
Mean Age of Vaginal Patency (days)  
Sensory Function  
Motor Activity  
Learning and Memory  
Mean No. Days Prior to Mating  
No. of Females Sperm-Positive  
No. of Pregnant Females  
Mean Duration of Gestation  
Abnormal Parturition

*Note: Alternate  
Format for  
Natural Parturition.*

F<sub>2</sub> Litters: No. Litters Evaluated  
Mean No. of Implantations  
Mean No. Pups/Litter  
Mean No. Liveborn Pups/Litter  
Mean No. Stillborn Pups/Litter  
Postnatal Survival to Day 4  
Postnatal Survival to Weaning  
Change in Pup Body Weights<sup>a</sup> (g)  
Pup Sex Ratios  
Pup Clinical Signs  
Pup Necropsy Obs.

- No noteworthy findings.    + Mild    ++Moderate    +++Marked    (6)

(7)\* - p<0.05    \*\* - p<0.01

a - From birth to mating.

b - At end of premating or gestation period. For controls, group means should be shown. For treated groups, percent differences from controls should be shown. Statistical significance based on actual data (not on the percent differences).

**3.6 Local Tolerance (1)**

**Test Article: (2)**

<u>Species/ Strain</u>	<u>Method of Administration</u>	<u>Doses (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
----------------------------	-------------------------------------	--------------------------	-------------------------------------	----------------------------	-------------------------

Notes: (1) All local-tolerance studies should be summarized.  
(2) International Nonproprietary Name (INN).

**3.7 Other Toxicity Studies (1)**

**Test Article: (2)**

<u>Species/ Strain</u>	<u>Method of Administration</u>	<u>Duration of Dosing</u>	<u>Doses (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
----------------------------	-------------------------------------	-------------------------------	--------------------------	-------------------------------------	----------------------------	-------------------------

Notes: (1) All supplementary toxicity studies should be summarized.

(2) International Nonproprietary Name (INN).

## **Appendix C**

### The Nonclinical Tabulated Summaries - Examples

EXAMPLE

**1 Pharmacology  
Sodium**

**Overview**

**Test Article: Curitol**

<u>Type of Study</u>	<u>Test System</u>	<u>Method of Administration</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol.</u>	<u>Page</u>
<b>1.1 Primary Pharmacodynamics</b>						
Antiviral activity vs. VZV	Human embryonic lung	In vitro	Sponsor Inc.	95401	1	1
Antiviral activity vs. VZV	fibroblasts	In vitro	Sponsor Inc.	95402	1	20
Antiviral activity vs. HSV	Clinical isolates	In vitro	Sponsor Inc.	95406	1	30
Antiviral activity vs. CMV	Human embryonic lung	In vitro	Sponsor Inc.	95408	1	45
Antiviral activity vs. VZV	fibroblasts	Gavage	Sponsor Inc.	95411	1	55
Antiviral activity vs. SVV	Human embryonic lung	Nasogastric Intubation	Sponsor Inc.	95420	1	100
	ICR mice					
	African Green monkeys					
<b>1.2 Secondary Pharmacodynamics</b>						
Antimicrobial activity	Gram-positive and gram-negative bacteria; yeasts	In vitro	Sponsor Inc.	95602	1	200
<b>1.3 Safety Pharmacology</b>						
Effects on central nervous system <sup>a</sup>	Mice, rats, rabbits, and cats	Gavage	Sponsor Inc.	95703	2	1
Effects on cardiovascular system	Dogs	Gavage, i.v.	Sponsor Inc.	95706	2	75
<b>1.4 Pharmacodynamic Drug Interactions</b>						
Interactions with anti-HIV activity of AZT	Human T lymphocytes	In vitro	Sponsor Inc.	95425	2	200

a - Report contains a GLP Compliance Statement.

**1.3 Safety Pharmacology Sodium**

EXAMPLE

**Test Article: Curitol**

<u>Organ Systems Evaluated</u>	<u>Species/ Strain</u>	<u>Method of Admin.</u>	<u>Doses<sup>a</sup> (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>Noteworthy Findings</u>	<u>GLP Compliance</u>	<u>Study Number</u>
CNS	CD-1 Mice	Gavage	0, 10, 50, 250	10M	Slight prolongation of hexobarbital anesthesia (¼10 mg/kg). No analgesic, anticonvulsive, or cataleptic properties. No effects on coordination, traction, or spontaneous motility.	Yes	92201
Renal, GI, CNS, and Hemostasis	CD-1 Mice	Gavage	0, 10, 50, 250	6M	Slight increases in urinary excretion of sodium and potassium (¼50 mg/kg). No effects on GI transit time (charcoal meal), pupillary diameter, blood coagulation time, or urine volume.	No	92205
Cardiovascular	Mongrel Dogs	Intravenous	0, 3, 10, 30	3M	Dose-related transient decreases in blood pressure and increases in heart rate and respiratory rate (all doses). Minor ECG changes at 30 mg/kg. No effects on cardiac output, stroke volume, or total peripheral resistance.	Yes	92210

a - Single dose unless specified otherwise.

EXAMPLE

**2A Pharmacokinetics  
Sodium**

**Overview**

**Test Article: Curitol**

<u>Type of Study</u>	<u>Test System</u>	<u>Method of Administration</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol.</u>	<u>Page</u>
<b>2.1 Kinetics</b>						
Absorption and excretion	Rats	Gavage, i.v.	Sponsor Inc.	93302	1	1
Absorption and excretion	Dogs	Gavage, i.v.	Sponsor Inc.	93304	1	25
Absorption and excretion	Monkeys	Gavage, i.v.	Sponsor Inc.	93306	1	50
<b>2.2 Tissue Distribution</b>						
Single-dose tissue distribution	Rats	Gavage	Sponsor Inc.	93307	1	100
Repeat-dose tissue distribution	Rats	Gavage	Sponsor Inc.	93308	1	125
Plasma protein binding	Mice, rats, dogs,	In vitro	Sponsor Inc.	93311	1	150
Plasma protein binding	monkeys, Humans, rats, dogs	Tablets/Gavage/Capsules	Sponsor Inc.	93312	1	200
<b>2.3 Metabolism</b>						
Metabolites in blood, urine, and feces	Rats	Gavage	Sponsor Inc.	93402	1	250
Metabolites in blood, urine, and feces	Dogs	Gavage	<u>Sponsor Inc.</u>	93407	1	300
<b>2.4 Pharmacokinetic Drug Interactions</b>						
Interaction with AZT <sup>a</sup>	Rats	Gavage	<u>Sponsor Inc.</u>	94051	1	350

a - Report contains a GLP Compliance Statement.

EXAMPLE

**2.2.1 Pharmacokinetics: Absorption after a Single Dose**

**Test Article:** Curitol Sodium

Species	<u>Mouse</u>	<u>Rat</u>	<u>Dog</u>	<u>Monkey</u>	<u>Human</u>
Gender (M/F) / Number of animals	4M	3M	4F	2M	6M
Feeding condition	Fed	Fasted	Fasted	Fed	Fasted
Vehicle/Formulation	Suspension 10% acacia	Suspension 10% acacia	Capsule	Suspension 10% acacia	Tablet
Method of Administration	Gavage	Gavage	Capsule	Gavage	Oral
Dose (mg/kg)	15	8	5	5	4 mg
Sample (Whole blood, plasma, serum etc.)	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte	TRA <sup>a</sup>	MM-180801	MM-180801	MM-180801	MM-180801
Assay	LSC	HPLC	HPLC	HPLC	HPLC
PK parameters:					
T <sub>max</sub> (hr)	4.0	1.0	3.3	1.0	6.8
C <sub>max</sub> (ng/ml or ng-eq/ml)	2,260	609	172	72	8.2
AUC (ng or ng-eq x hr/ml)	15,201	2,579	1,923	582	135
(Time for calculation – hr)	(0-72)	(0-24)	(0.5-48)	(0-12)	(0-24)
T 1/2 (hr)	10.6	3.3	9.2	3.2	30.9
(Time for calculation – hr)	(7-48)	(1-24)	(24-96)	(1-12)	(24-120)

Study number 95104

Location in CTD Volume 1, Page 258

**Additional Information:**

A single oral dose was well absorbed in mice, rats, dogs, and monkeys.

In a study examining the concentration of compound in the portal vein and inferior vena cava, 30 minutes after a dose to rats, the concentration of compound was approximately 15-fold higher in the portal circulation compared to systemic circulation. This result indicated extensive metabolism and/or biliary secretion of compound in the rat.

a - Total radioactivity, <sup>14</sup>C

EXAMPLE

**Format A**

**2.3.1 Pharmacokinetics: Organ Distribution Sodium**

**Test Article: Curitol**

**Location in CTD:** Vol. 21 Page 1  
**Study No.** 95207

**Species:** Rat  
**Gender (M/F)/Number of animals:** 3M/each time point  
**Feeding condition:** Fasted  
**Vehicle/Formulation:** Solution/Water  
**Method of Administration:** Oral Gavage  
**Dose (mg/kg):** 10  
**Radionuclide:** <sup>14</sup>C  
**Specific Activity:** 2x10<sup>5</sup> Bq/mg  
**Sampling time:** 0.25, 0.5, 2, 6, 24, 96, and 192 hr

Tissues/organs	Concentration (mcg/mL)					t <sub>1/2</sub> <sup>2</sup>
	0.25	0.5	2	6	24	
Blood	9.2	3.7	1.8	0.9	0.1	
Plasma	16.5	7.1	3.2	1.6	0.2	
Brain	0.3	0.3	0.2	0.1	nd	
Lung	9.6	14.1	7.3	2.9	0.1	
Liver	73.0	54.5	19.9	12.4	3.2	
Kidney	9.6	13.2	4.9	3.8	0.6	
Testis	0.3	0.5	0.6	0.5	0.1	
Muscle	1.0	1.2	0.8	0.3	nd	

**Additional information:**

Heart, thymus, adrenal, spleen, stomach, intestine,....are examined but not shown.

nd = Not detected.

EXAMPLE

**Alternate Format B**

**2.3.1 Pharmacokinetics: Organ Distribution Sodium**

**Test Article: Curitol**

Location in CTD: Vol. 21 Page 1

Study No. 95207

Species: Rat  
 Gender (M/F) / Number of animals: 3M/each time point  
 Feeding condition: Fed  
 Vehicle/Formulation: Solution/Saline  
 Method of Administration: Intravenous  
 Dose (mg/kg): 1  
 Radionuclide: Non-labeled compound  
 Specific Activity: -  
 Analyte/Assay: Unchanged compound (mcg/mL)/HPLC  
 Sampling time: 10 min, 1, 4, 8, 24, 48, 96, and 168 hr

Tissues/organs	C <sub>1hr</sub>		Last time-point			AUC	t <sub>1/2</sub> <sup>2</sup>
	conc.	T/P <sup>1)</sup>	conc.	T/P <sup>1)</sup>	Time		
Heart	1.4	0.08	0.44	22	48	57.3	37.3
Liver	4.5	6	1.85	92.5	48	290	51.7
Kidney	2.8	0.20	1.07	53.5	48	126	36.3
Spleen	6.5	8.6	3.5	175	48	410	46.9

Additional information:

<sup>1)</sup> [Tissue]/[Plasma]

EXAMPLE

**2.3.2 Pharmacokinetics: Protein Binding**

**Test Article:** Curitol Sodium

**Study system:** In vitro

**Target entity, Test system and method:** Plasma, Ultrafiltration

<u>Species</u>	<u>Conc. tested</u>	<u>% Bound</u>	<u>Study</u>	<u>Location in CTD</u>	
			<u>No.</u>	<u>Vol.</u>	<u>Page</u>
Rat	1 - 100uM	82.1 - 85.4	95301	21	150
Dog	1 - 100uM	83.5 - 88.2	95301	21	150
Human	1 - 100uM	75.2 - 79.4	96-103-03	45	1

---

**Additional Information:**

---

EXAMPLE

**2.3.3 Pharmacokinetics: Study in Pregnant or Nursing Animals**  
Sodium

**Test Article:** Curitol

Location in CTD: Vol. 22 Page 1  
Study No. 95702

Placental transfer

Species: Rat

Gestation day / Number of animals: 14 and 19 days gestation/3 animals at each time point

Vehicle/Formulation: Solution/Water

Method of Administration: Oral gavage

Dose (mg/kg): 5

Analyte: Total radioactivity, <sup>14</sup>C

Assay: LSC

Time (hr)

14 days/30 min

14 days/24 hr

19 days/30 min

19 days/24 hr

Concentration / Amount (% of dose)

Maternal plasma	12.4	0.32	13.9	0.32
Placenta	3.8	0.14	3.3	0.32
Amniotic fluid	0.07	0.04	0.04	0.13
Whole fetus	0.54	0.03	0.39	0.10

**Additional Information:**

Maternal blood, liver, kidney, ovary, uterus were also examined but not shown.

Location in CTD: Vol. 22 Page 102  
Study No. 95703

Excretion into milk

Species: Rat

Lactating date / Number of animals: day 7/3

Feeding condition: Fed

Vehicle/Formulation: Solution/Water

Method of Administration: Oral gavage

Dose (mg/kg): 5

Analyte: Total radioactivity, <sup>14</sup>C

Assay: LSC

Time [hr]

**1**

**2**

**4**

**6**

**8**

**24**

Concentration:

Milk:	0.6	0.8	1.0	1.1	1.3	0.4
Plasma:	1.5	1.4	1.2	0.8	0.6	0.1
Milk / plasma:	0.40	0.57	0.83	1.4	2.2	4.0

Neonates

**Additional Information:**

**2.4.1 Pharmacokinetics: Metabolism *In Vivo* Sodium**

EXAMPLE

**Test Article: Curitol**

Gender (M/F) / Number of animals: Rats: 4M Dogs: 3F Humans: 8M  
 Feeding condition: Fed  
 Vehicle/Formulation: Rats: Solution/water Dogs: Capsules Humans: 75-mg tablets  
 Method of Administration: Rats: Gavage\* Dogs: Oral Capsule\* Humans: Oral Tablet  
 Dose (mg/kg): Rats: 5 mg/kg Dogs: 5 mg/kg Humans: 75 mg  
 Radionuclide: <sup>14</sup>C  
 Specific Activity: 2 x 10<sup>5</sup> Bq/mg

Species	Sample	Sampling Time or Period	% of Dose in Sample	% of Compound in Sample			Study Number	Location in CTD	
				Parent	M1	M2		Vol.	Page
Rats	Plasma	0.5 hr	-	87.2	6.1	3.4	<u>95076</u>	26	101
	Urine	0-24 hr	2.1	0.6	n.d.	0.2			
	Bile	0-4 hr	28.0	15.5	7.2	5.1			
	Feces	-	-	-	-	-			
Dogs	Plasma	0.5 hr	-	92.8	n.d.	7.2	95082	26	301
	Urine	0-24 hr	6.6	6.4	n.d.	n.d.			
	Bile	0-4 hr	32.0	28.5	2.8	n.d.			
	Feces	-	-	-	-	-			
Humans	Plasma	1 hr	-	87.5	trace	12.5	CD-102	42	1
	Urine	0-24 hr	5.5	2.4	2.9	n.d.			
	Bile	-	-	-	-	-			
	Feces	-	-	-	-	-			

Additional Information

\* - Intraduodenal administration for collection of bile.  
 n.d. - None detected.

EXAMPLE

**2.5.1 Pharmacokinetics: Excretion**

**Test Article: Curitol Sodium**

Species	Rat			Rat			Dog			Dog		
	4M			4M			3M			3M		
Gender (M/F) / Number of animals	Fasted			Fasted			Fasted			Fasted		
Feeding condition	Solution			Solution			Capsule			Solution		
Vehicle/Formulation	Water			Saline						Saline		
Method of Administration	Oral			Intravenous			Oral			Intravenous		
Dose (mg/kg)	10			5			10			5		
Analyte	TRA <sup>a</sup>											
Assay	LSC			LSC			LSC			LSC		
Excretion route	Urine	Feces	Total									
Time												
0 - 24 hr	26	57	83	22	63	85	20	29	49	23	42	65
0 - 48 hr	30	65	95	27	69	96	25	65	90	28	78	96
0 - 72 hr	31	65	97	28	70	98	26	73	99	29	72	101
0 - 96 hr	31	67	98	29	70	99	26	74	100	29	73	102

Study number  
Location in CTD

95102  
Volume 20, Page 75

95156  
Volume 20, Page 150

Additional Information:

a - Total radioactivity; percent recovery, <sup>14</sup>C

EXAMPLE

**Test Article:** Curitol Sodium

**2.5.2 Pharmacokinetics: Excretion into Bile**

Species	<u>Rat</u>			<u>Rat</u>		
Gender (M/F) / Number of animals	4M			4M		
Feeding condition	Fasted			Fasted		
Vehicle/Formulation	Solution			Solution		
Method of Administration	Water			Saline		
Dose (mg/kg)	Oral			Intravenous		
Analyte	10			5		
Assay	TRA <sup>a</sup>			TRA <sup>a</sup>		
Excretion route	LSC			LSC		
Time	<u>Bile</u>	<u>Urine</u>	<u>Total</u>	<u>Bile</u>	<u>Urine</u>	<u>Total</u>
0 - 2 hr	37	-	37	75	-	75
0 - 4 hr	50	-	50	82	-	82
0 - 8 hr	62	-	62	86	-	86
0 - 24 hr	79	9	86	87	11	98
0 - 48 hr	83	10	93	88	11	99

Study number 95106

Location in CTD Volume 20, Page 150

a - Total radioactivity; percent recovery, <sup>14</sup>C

EXAMPLE

**3A Toxicology**

**Overview**

**Test Article: Curitol Sodium**

<u>Type of Study</u>	<u>Species and Strain</u>	<u>Method of Administration</u>	<u>Duration of Dosing</u>	<u>Doses (mg/kg<sup>a</sup>)</u>	<u>GLP Compliance</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol.</u>	<u>Page</u>	
<b>3.1 Single-Dose Toxicity</b>	CD-1 Mice	Gavage	-	0, 1000, <u>2000</u> , 5000	Yes	Sponsor Inc.	96046	1	1	
		Intravenous	-	0, <u>100</u> , 250, 500	Yes	CRO Co.	96047	1	100	
	Wistar Rats	Gavage	-	0, <u>1000</u> , 2000, 5000	Yes	Sponsor Inc.	96050	1	200	
		Intravenous	-	0, 100, <u>250</u> , 500	Yes	CRO Co.	96051	1	300	
	<b>3.2 Repeat-Dose Toxicity</b>	CD-1 Mice	Diet	3 Months	0, 62.5, <u>250</u> , 1000, 4000, 7000	Yes	CRO Co.	94018	2	1
		Wistar Rats	Diet	2 Weeks	0, <u>1000</u> , 2000, 4000	No	Sponsor Inc.	94019	3	1
Gavage			2 Weeks	0, <u>500</u> , 1000, 2000	No	Sponsor Inc.	94007	3	200	
Gavage			3 Months	0, <u>200</u> , 600, 1800	Yes	Sponsor Inc.	94214	4	1	
Gavage			6 Months	0, 100, <u>300</u> , 900	Yes	Sponsor Inc.	95001	5	1	
Beagle Dogs		Capsules	1 Month	0, 10, <u>40</u> , 100	Yes	Sponsor Inc.	94020	6	1	
		Capsules	9 Months	0, <u>5</u> , 20, 50	Yes	Sponsor Inc.	96041	7	1	
Cynomolgus Monkeys		Gavage	5 Days	0, <u>500</u> , 1000	No	CRO Co.	94008	8	1	
<b>3.3 Genotoxicity</b>		S. typhimurium and E. coli	In Vitro	-	0, 500, 1000, 2500, and/or 5000 mcg/plate	Yes	Sponsor Inc.	96718	9	1
			In Vitro	-		Yes	CRO Co.	97634	9	100
	Human Lymphocytes	Gavage	3 Days	0, 2.5, 5, 10, 20, and 40 mcg/ml	Yes	Sponsor Inc.	96037	9	200	
	Wistar Rats			0, 1000, 2000						

a - Unless otherwise specified. For Single-Dose Toxicity and Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

Continued

EXAMPLE

**3A Toxicology  
Sodium**

**Overview (Continued)**

**Test Article: Curitol**

<u>Type of Study</u>	<u>Species and Strain</u>	<u>Method of Administration</u>	<u>Duration of Dosing</u>	<u>Doses (mg/kg)</u>	<u>GLP Compliance</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol.</u>	<u>Page</u>
<b>3.4 Carcinogenicity</b>	CD-1 Mice	Diet	21 Months	0, 0, 25, 100, 400	Yes	CRO Co.	95012	10	1
	Wistar Rats	Gavage	24 Months	0, 0, 25, 100, 400	Yes	Sponsor Inc.	95013	12	1
<b>3.5 Reproduction Toxicity</b>	Wistar Rats	Gavage	a	0, 5, 30, 180	Yes	CRO Co.	96208	14	1
	Wistar Rats	Gavage	F: G6 - G15 <sup>b</sup>	0, 10, 100, 1000	Yes	Sponsor Inc.	94211	15	1
	NZW Rabbits	Gavage	F: G6 - G18 <sup>b</sup>	0, 1, 5, 25	Yes	CRO Co.	97028	16	1
	Wistar Rats	Gavage	F: G6 - L21 <sup>b</sup>	0, 7.5, 75, 750	Yes	Sponsor Inc.	95201	17	1
<b>3.6 Local Tolerance</b>	NZW Rabbits	Dermal	1 Hour	0, 15 mg	No	Sponsor Inc.	95015	18	1
<b>3.7 Other Toxicity Studies</b>									
<b>3.7.1 Antigenicity</b>	Guinea Pigs	Subcutaneous	Weekly for 3 weeks	0, 5 mg	No	CRO Co.	97012	18	20
<b>3.7.2 Impurities</b>	Wistar Rats	Gavage	2 Weeks	0, 1000, 2000	Yes	Sponsor Inc.	97025	18	200

a - Males: 4 weeks prior to mating. Females - 2 weeks prior to mating through Gestation Day 7.

b - G = Gestation Day L = Lactation Day

EXAMPLE

**3B Toxicokinetics  
Sodium**

**Overview of Toxicokinetics Studies**

**Test Article: Curitol**

<b><u>Type of Study</u></b>	<b><u>Test System</u></b>	<b><u>Method of Administration</u></b>	<b><u>Doses (mg/kg)</u></b>	<b><u>GLP Compliance</u></b>	<b><u>Study Number</u></b>	<b><u>Location Vol.</u></b>	<b><u>Page</u></b>
Three-month range-finding study	Mice	Diet	62.5, 250, 1000, 4000, 7000	Yes	94018	2	1
Two-week toxicity study	Rats	Gavage	500, 1000, 2000	No	94007	3	200
Six-month toxicity study	Rats	Gavage	100, 300, 900	Yes	95001	5	1
One-month toxicity study	Dogs	Capsules	10, 40, 100	Yes	94020	6	1
Nine-month toxicity study	Dogs	Capsules	5, 20, 50	Yes	96041	7	1
Carcinogenicity study	Mice	Diet	25, 100, 400	Yes	95012	10	1
Carcinogenicity study	Rats	Gavage	25, 100, 400	Yes	95013	12	1
Toxicokinetics study	Rabbits	Gavage	1, 5, 25	No	97231	16	1

EXAMPLE

**3C Toxicokinetics  
Sodium**

**Overview of Toxicokinetics Data**

**Test Article: Curitol**

Daily Dose (mg/kg)	Steady-State AUC (mcg-hr/ml)						
	Mice <sup>a</sup>		Rats <sup>b</sup>		Dogs <sup>c</sup>	Female Rabbits <sup>b</sup>	Humans <sup>f</sup>
	M	F	M	F			
1						9	3
5					3	25	
10					4		
20					10		
25	10	12	6	8		273	
40					10		
50					12		
62.5	35	40					
100	40	48	25 <sup>d</sup> , 20 <sup>e</sup>	27 <sup>d</sup> , 22 <sup>e</sup>	40		
250	120	135					
300			68	72			
400	815	570	90	85			
500			125	120			
900			200	190			
1000	2,103	1,870	250	240			
2000			327	321			
4000	4,975	3,987					
7000	8,241	7,680					

a - In diet.

b - By gavage.

c - In capsules. Males and females combined.

d - Six-month toxicity study.

e - Carcinogenicity study.

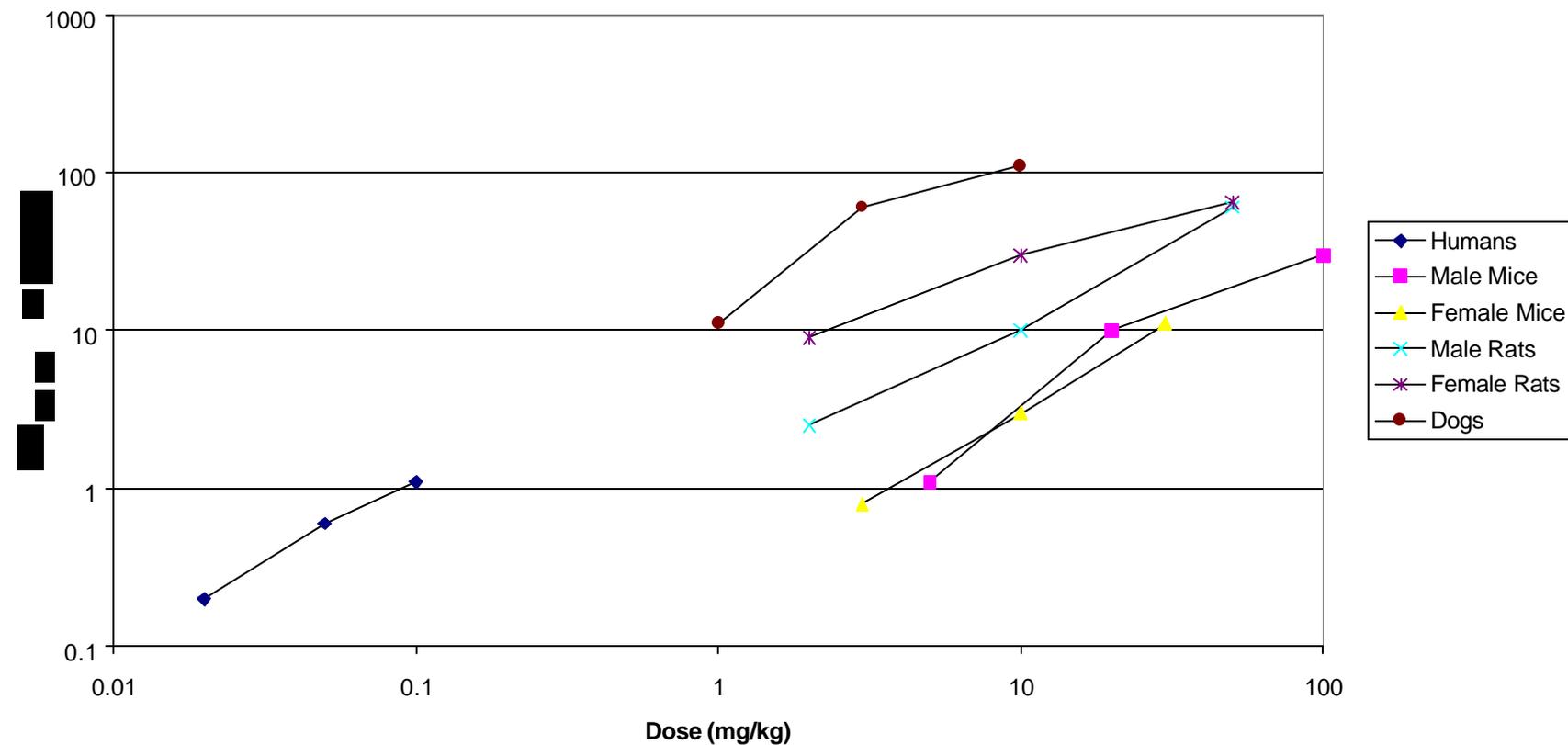
f - Protocol 147-007.

EXAMPLE

3C Toxicokinetics

Overview of Toxicokinetics Data

Test Article : Curitol Sodium



Steady-state  $AUC_{24hr}$  values of unchanged MM-180801 in humans after repeated oral administration of 1, 2.5, and 5 mg OD, in comparison with those in mice in the carcinogenicity study, rats in the 6-month toxicity study, and dogs in the 9-month toxicity study.

EXAMPLE

**3D Toxicology**

**Batches Used**

**Test Article: Curitol Sodium**

<u>Batch No.</u>	<u>Purity (%)</u>	<u>Specified Impurities<sup>a</sup></u>			<u>Study Number</u>	<u>Type of Study</u>
		<u>A</u>	<u>B</u>	<u>C</u>		
PROPOSED <u>SPECIFICATION:</u>	<u>&gt;95</u>	<u>¼ 0.1</u>	<u>¼ 0.2</u>	<u>¼ 0.3</u>	-	-
LN125	98.2	0.1	0.1	0.2	94007 94008 96718	Two-Week Oral Range-Finding Study in Rats Five-Day Oral Range-Finding Study in Monkeys Ames Test
94NA103	99.1	0.2	0.1	0.2	96046 96050 94214 94020 97634	Single-Dose Oral Study in Mice Single-Dose Oral Study in Rats Three-Month Oral Study in Rats One-Month Oral Study in Dogs Human Lymphocytes Assay <u>In Vitro</u>
95NA215	97.3	0.1	0.3	0.1	96047 96051 96037 94211 97028	Single-Dose Intravenous Study in Mice Single-Dose Intravenous Study in Rats Micronucleus Test in Rats Embryo-Fetal Development Study in Rats Embryo-Fetal Development Study in Rabbits
95NB003	94.6	0.2	0.3	0.4	94019 97012	Two-Week Palatability Study in Rats Antigenicity Study in Hamsters
96NB101	99.0	0.4	0.1	0.0	94018 95001 95002 95012 95013 96208 95015	Three-Month Dietary Range-Finding Study in Mice Six-Month Oral Study in Rats One-Year Oral Study in Dogs Dietary Carcinogenicity Study in Mice Oral Carcinogenicity Study in Rats Fertility and Early Embryonic Development Study in Rats Dermal Irritation Study in Rabbits

a - Area percent.

EXAMPLE

**3.1 Single-Dose Toxicity Sodium**

**Test Article: Curitol**

<b>Species/ Strain</b>	<b>Method of Administration (Vehicle/ Formulation)</b>	<b>Doses (mg/kg)</b>	<b>Gender and No. per Group</b>	<b>Observed Maximum Non- Lethal Dose (mg/kg)</b>	<b>Approximate Lethal Dose (mg/kg)</b>	<b>Noteworthy Findings</b>	<b>Study Number</b>																								
CD-1 Mice	Gavage (Water)	0, 1000, 2000, 5000	10M	¼5000	>5000	¾2000: Transient body-weight losses.  5000: Decreased activity, convulsions, collapse.	96046																								
			10F	¼5000					Intravenous (Saline)	0, 100, 250, 500	10M	250	>250 <500	¾250: Body-weight losses. 500: 3M and 2F died.	96047	10F	250	Wistar Rats	Gavage (CMC Suspension)	0, 1000, 2000, 5000	5M	2000	>2000 <5000	¾2000: Transient body-weight losses; inactivity; chromorhinorrhea. 5000: 2M died.	96050	5F	¼5000		Intravenous (5% Dextrose)	0, 100, 250, 500	5M
	Intravenous (Saline)	0, 100, 250, 500	10M	250	>250 <500	¾250: Body-weight losses. 500: 3M and 2F died.	96047																								
			10F	250				Wistar Rats	Gavage (CMC Suspension)	0, 1000, 2000, 5000	5M	2000	>2000 <5000	¾2000: Transient body-weight losses; inactivity; chromorhinorrhea. 5000: 2M died.	96050	5F	¼5000		Intravenous (5% Dextrose)	0, 100, 250, 500	5M	250	>250 <500	¾250: Body-weight losses in males. 500: 3M died.	96051	5F	¼500				
Wistar Rats	Gavage (CMC Suspension)	0, 1000, 2000, 5000	5M	2000	>2000 <5000	¾2000: Transient body-weight losses; inactivity; chromorhinorrhea. 5000: 2M died.	96050																								
			5F	¼5000					Intravenous (5% Dextrose)	0, 100, 250, 500	5M	250	>250 <500	¾250: Body-weight losses in males. 500: 3M died.	96051	5F	¼500														
	Intravenous (5% Dextrose)	0, 100, 250, 500	5M	250	>250 <500	¾250: Body-weight losses in males. 500: 3M died.	96051																								
			5F	¼500																											

EXAMPLE

**3.2.1 Repeat-Dose Toxicity**

**Non-Pivotal Studies**

**Test Article: Curitol Sodium**

<b>Species/ Strain</b>	<b>Method of Administration (Vehicle/ Formulation)</b>	<b>Duration of Dosing</b>	<b>Doses (mg/kg)</b>	<b>Gender and No. per Group</b>	<b>NOAEL<sup>a</sup> (mg/kg)</b>	<b>Noteworthy Findings</b>	<b>Study Number</b>
CD-1 Mice	Diet	3 Months	0, 62.5, 250, 1000, 4000, and 7000	10M, 10F	M:4000 F: 1000	¼4000: Lower body weights; gastric erosions/ulcers in some mice. 7000: 4M and 6F died/ sacrificed; lower body weights; single-cell necrosis in liver.	94018
Wistar Rats	Diet	2 Weeks	0, 1000, 2000, and 4000	5M, 5F	1000	¼2000: Lower body weights. 4000: 2M and 1F sacrificed moribund.	94019
	Gavage (Water)	2 Weeks	0, 500, 1000, and 2000	5M, 5F	1000	2000: Lower body weights; single-cell necrosis in liver.	94007
Beagle Dogs	Gavage (CMC Suspension)	5 Days	0, 500, and 1000	1M, 1F	<500	¼500: Weight losses, inappetence.	94008

a - No Observed Adverse-Effect Level.

EXAMPLE #1

**3.2.2A Repeat-Dose Toxicity Report Title:** MM-180801: Three-Month Oral Toxicity Study in Rats **Test Article:** Curitol Sodium

**Species/Strain:** Wistar Rats  
**Initial Age:** 5 Weeks  
**Date of First Dose:** 15 Jan 94

**Duration of Dosing:** 3 Months  
**Duration of Postdose:** 1 Month  
**Method of Administration:** Gavage  
**Vehicle/Formulation:** Aqueous Solution

**Study No.** 94214  
**Location in CTD:** Vol. 4 Page 1

**GLP Compliance:** Yes

**Special Features:** None

**No Observed Adverse-Effect Level:** 200 mg/kg

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
<b>Number of Animals</b>								
<b>Toxicokinetics: AUC (mcg-hr/ml):</b>								
Day 1	-	-	30	28	130	125	328	302
Day 28	-	-	52	47	145	140	400	380
Day 90	-	-	50	51	160	148	511	475
<b>Noteworthy Findings</b>								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (% <sup>a</sup> )	394 g	244 g	0	-1	-10*	-11*	-25**	-45**
Food Consumption (% <sup>a</sup> )	20.4 g	17.2 g	0	-1	-1	-8*	-30**	-50**
<b>Clinical Observations</b>								
Hyperactivity	-	-	-	-	-	+	-	++
Chromorhinorrhea, reddish-stained coat, white feces	-	-	-	-	-	-	++	++
Emaciated, piloerection, stilted gait	-	-	-	-	-	-	-	++
Ophthalmoscopy	-	-	-	-	-	-	-	-

- No noteworthy findings. + Mild ++ Moderate +++ Marked

Dunnett's Test: \* - p<0.05 \*\* - p<0.01

a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

(Continued)

EXAMPLE #1

**3.2.2A Repeat-Dose Toxicity**

**Study No. 94214 (Continued)**

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
<b>Hematology</b>								
Hemoglobin (g/dl)	15.8	15.0	15.7	14.9	15.8	14.6	14.0*	13.1*
Erythrocyte Count (x10 <sup>6</sup> /mm <sup>3</sup> )	8.1	-	7.9	-	8.1	-	7.4*	-
MCH	-	22	-	21	-	22	-	19*
MCHC	-	34	-	34	-	34	-	30*
Platelet Count (x10 <sup>3</sup> /mm <sup>3</sup> )	846	799	825	814	914	856	931*	911*
<b>Serum Chemistry</b>								
Creatinine (IU/L)	0.7	0.7	0.7	0.7	0.7	0.7	1.1*	1.1*
Proteins g/dl)	-	6.7	-	6.6	-	6.6	-	5.0**
Cholesterol (mg/dl)	96	-	86	-	90	-	105*	-
ALT (IU/L)	67	56	60*	52	55*	47*	53*	58
AST (IU/L)	88	92	96	90	87*	84*	85*	93
Bilirubin (mg/dl)	0.18	0.20	0.17	0.20	0.18	0.20	0.22**	0.26**
Calcium (mEq/L)	-	10.7	-	10.8	-	10.8	-	9.8**
Phosphorus (mEq/L)	9.3	-	9.3	-	9.3	-	8.2*	-
<b>Urinalysis</b>								
Protein Conc. (mg/dl)	260	49	102	34	123	54	126*	22*
pH	7.5	-	7.5	-	7.2	-	6.3**	-
Glucose (mg/dl)	-	0	-	0	-	20	-	98**
Urine Volume (ml)	-	18	-	18	-	16	-	12*

- No noteworthy findings.

Dunnett's Test: \*- p<0.05    \*\*- p<0.01

(Continued)

EXAMPLE #1

3.2.2A Repeat-Dose Toxicity

Study No. 94214 (Continued)

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
<b>Number of Animals</b>								
<b>Organ Weights<sup>b</sup> (%)</b>								
Kidney	3.01 g	1.75 g	0	+5*	+1	+8**	+12**	+20**
Liver	15.9 g	8.01 g	0	+1	+10*	+12*	+12*	+20**
<b>Gross Pathology</b>								
Number examined	20	20	20	20	20	20	20	20
Kidneys: Pallor	0	0	0	0	0	5	1	2
Glandular Stomach: Discoloration	0	0	0	0	0	1	1	4
<b>Histopathology</b>								
Number examined	20	20	20	20	20	20	20	20
Kidneys: Tubular dilatation	0	0	0	0	0	6	3	4
Mild	0	0	0	0	0	6	1	0
Moderate	0	0	0	0	0	0	2	4
Glandular Stomach: Erosions	0	0	0	0	0	2	2	9
<b>Additional Examinations</b>	-	-	-	-	-	-	-	-
<b>Postdose Evaluation:</b>								
Number Evaluated	10	10	0	0	0	0	10	10
Body Weight <sup>a</sup> (%)	422 g	265 g	-1	-2	-3	-4	-10*	-20**
Kidney Weight <sup>b</sup> (%)	3.24 g	1.81 g	0	-1	-1	0	+8*	+10

- No noteworthy findings.

Dunnett's Test: \* - p<0.05      \*\* - p<0.01

a - At end of postdose recovery period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

b - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

EXAMPLE #2

**3.2.2B Repeat-Dose Toxicity Report Title:** MM-180801: One-Month Oral Toxicity Study in Dogs **Test Article:** Curitol Sodium

**Species/Strain:** Beagle Dogs  
**Initial Age:** 5-6 Months  
**Date of First Dose:** 2 Feb 94

**Duration of Dosing:** 1 Month  
**Duration of Postdose:** None  
**Method of Administration:** Oral  
**Vehicle/Formulation:** Gelatin Capsules

**Study No.** 94020  
**Location in CTD:** Vol. 6 Page 1

**GLP Compliance:** Yes

**Special Features:** Hepatic enzyme induction evaluated at termination.

**No Observed Adverse-Effect Level:** 10 mg/kg

Daily Dose (mg/kg)	0 (Control)		10		40		100	
	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
<b>Number of Animals</b>								
<b>Toxicokinetics: AUC (mcg-hr/ml):</b>								
Day 1	-	-	5	6	10	12	40	48
Day 28	-	-	4	5	8	11	35	45
<b>Noteworthy Findings</b>								
<b>No. Died or Sacrificed Moribund</b>	0	0	0	0	0	0	0	0
<b>Body Weight (%<sup>a</sup>)</b>	9.8 kg	9.2 kg	0	0	-1	-19**	0	-18**
<b>Clinical Observations:</b>								
Hypoactivity (after dosing)	-	-	-	-	-	-	+	++
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
<b>Serum Chemistry</b>								
ALT (IU/L): Week 2	22	25	24	27	21	24	48*	69**
Week 4	25	27	26	25	23	25	54*	84**

- No noteworthy findings. + Mild ++ Moderate +++ Marked

Dunnett's Test: \* - p<0.05 \*\* - p<0.01

a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

(Continued)

EXAMPLE #2

**3.2.2B Repeat-Dose Toxicity**

**Study No. 94020 (Continued)**

Daily Dose (mg/kg)	0 (Control)		10		40		100	
	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
<b>Number of Animals</b>								
<b>Organ Weights<sup>a</sup> (%)</b>								
Liver	339 g	337 g	+1	-1	+17**	+16**	+23**	+21**
<b>Gross Pathology</b>	-	-	-	-	-	-	-	-
<b>Histopathology</b>								
Number Examined	3	3	3	3	3	3	3	3
Liver: Centrilobular hypertrophy	0	0	0	0	0	0	2	3
<b>Additional Examinations</b>								
Hepatic Enzyme Induction	-	-	-	-	-	-	-	-

- No noteworthy findings.

Dunnett's Test: \* - p<0.05      \*\* - p<0.01

a - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

EXAMPLE #1

**3.3.1A Genotoxicity: In Vitro Report Title:** MM-180801: Ames Reverse-Mutation Study in **Test Article:** Curitol Sodium Salmonella and E. Coli

**Test for Induction of:** Reverse mutation in bacterial cells

**No. of Independent Assays:** 2

**Study No.** 96669

**Strains:** S. typhimurium and E. coli

**No. of Replicate Cultures:** 3

**Location in CTD:** Vol. 10 Page 211

**Metabolizing System:** Arochlor-induced rat liver S9, 7.1%

**No. of Cells Analyzed/Culture:** -

**Vehicles:** Test Article: DMSO

**Positive Controls:** DMSO

**GLP Compliance:** Yes

**Treatment:** Plate incorporation for 48 hr.

**Date of Treatment:** Feb. 1996

**Cytotoxic Effects:** None.

**Genotoxic Effects:** None.

Metabolic Activation	Test Article	Dose Level (mcg/plate)	Assay #1 Revertant Colony Counts (Mean ±SD)					
			TA 98	TA 100	TA 1535	TA 1537	WP2 uvrA	
Without Activation	DMSO	100 mcl/plate	24 ± 9	129 ± 4	15 ± 4	4 ± 2	17 ± 3	
		MM-180801	312.5	24 ± 6	128 ± 11	12 ± 4	4 ± 2	14 ± 2
		625	32 ± 9	153 ± 9	9 ± 2	8 ± 2	17 ± 5	
		1250	30 ± 4	152 ± 12	9 ± 3	9 ± 2	18 ± 4	
		2500	27 ± 5	140 ± 6	9 ± 3	5 ± 1	19 ± 1	
		5000 <sup>a</sup>	30 ± 3	137 ± 21	15 ± 1	7 ± 2	13 ± 4	
		2-Nitrofluorene	2	696				
		Sodium azide	1		542	468		
		9-Aminoacridine	100			515		
		MMS	2.5 mcl/plate				573	
With Activation	DMSO	100 mcl/plate	27 ± 6	161 ± 12	12 ± 5	5 ± 1	21 ± 8	
		MM-180801	312.5	31 ± 4	142 ± 8	12 ± 5	4 ± 2	17 ± 3
		625	30 ± 1	156 ± 15	17 ± 2	9 ± 5	23 3	
		1250	33 ± 2	153 ± 13	13 ± 3	8 ± 2	18 ± 3	
		2500	35 ± 8	160 ± 4	10 ± 2	8 ± 2	19 ± 5	
		5000 <sup>a</sup>	31 ± 4	153 ± 5	9 ± 4	7 ± 1	17 ± 4	
		2-Aminoanthracene	2.5	1552	1487	214	61	
			10					366

a - Precipitation.

EXAMPLE #2

**3.3.1B Genotoxicity: In Vitro Report Title:** MM-180801: Cytogenetics Study in Primary Human Lymphocytes **Test Article:** Curitol Sodium

**Test for Induction of:** Chromosome aberrations

**No. of Independent Assays:** 1

**Study No.** 96668

**Strains:** Primary human lymphocytes

**No. of Replicate Cultures:** 2

**Location in CTD:** Vol. 10 Page 245

**Metabolizing System:** Arochlor-induced rat liver S9, 5%

**No. of Cells Analyzed/Culture:** 100

**Vehicles:** Test Article: DMSO

**Positive Controls:** DMSO

**GLP Compliance:** Yes

**Treatment:** Continuous treatment for 24-hr without S9; pulse treatment 5 hr and recovery time 24 hr with and without S9.

**Date of Treatment:** Aug. 1996

**Cytotoxic Effects:** Dose-related decreases in mitotic indices.

**Genotoxic Effects:** Chromosome aberrations without S9 at 10 and 20 µg/ml, and with S9 at 50 and 200 µg/ml.

<u>Metabolic Activation</u>	<u>Test Article</u>	<u>Concentration (mcg/ml)</u>	<u>Cytotoxicity<sup>a</sup> (% of control)</u>	<u>Aberrant Cells Mean %</u>	<u>Abs/Cell</u>	<u>Total polyploid cells</u>
Without Activation	DMSO	-	100	2.0	0.02	4
	MM-180801	2.5	78	3.0	0.03	3
		5	59	4.0	0.05	4
		10	36	16.5**	0.20	2
		20	32	35.0**	0.55	3
		MITOMYCIN	0.10	52	38.5**	0.64
With Activation	DMSO	-	100	4.0	0.04	3
	MM-180801	2.5	91	4.5	0.05	3
		10	88	4.5	0.05	2
		50	80	9.5*	0.10	4
		200	43	34.0**	0.66	3
		CYCLOPHOSPHAMIDE	4	68	36.5**	0.63

Dunnett's Test: \* - p<0.05      \*\* - p<0.01

a - Based on mitotic indices.

EXAMPLE #1

**3.3.2A Genotoxicity: In Vivo Report Title:** MM-180801: Oral Micronucleus Study in Rats **Test Article:** Curitol Solution

**Test for Induction of:** Bone-marrow micronuclei

**Species/Strain:** Wistar Rats

**Age:** 5 Weeks

**Cells Evaluated:** Polychromatic erythrocytes

**No. of Cells Analyzed/Animal:** 2000

**Special Features:** None.

**Toxic/Cytotoxic Effects:** At 2000 mg/kg, clinical signs, two deaths, and decreases in bone-marrow PCEs.

**Genotoxic Effects:** None.

**Evidence of Exposure:** Overt toxicity at 2000 mg/kg.

**Treatment Schedule:** Three daily doses.

**Sampling Time:** 24 hr after last dose.

**Method of Administration:** Gavage.

**Vehicle/Formulation:** Aqueous solution.

**Study No:** 96683

**Location in CTD:** Vol. 10 Page 502

**GLP Compliance:** Yes

**Date of Dosing:** July 1996

<u>Test Article</u>	<u>Dose (mg/kg)</u>	<u>No. of Animals</u>	<u>Mean % PCEs (+SD)</u>	<u>Mean % MN-PCEs (+SD)</u>
Vehicle	0	5M	52 ± 1.9	0.20 ± 0.12
MM-180801	2	5M	54 ± 3.7	0.25 ± 0.16
	20	5M	49 ± 3.1	0.20 ± 0.07
	200	5M	50 ± 2.1	0.26 ± 0.08
	2000	3M	31 ± 2.5	0.12 ± 0.03
Cyclophosphamide	7	5M	51 ± 2.3	2.49 ± 0.30**

Dunnett's Test: \* - p<0.05      \*\* - p<0.01

EXAMPLE #2

**3.3.2B Genotoxicity: In Vivo Report Title:** MM-180801: Oral DNA Repair Study in Rats **Test Article:** Curitol Solution

**Test for Induction of:** Unscheduled DNA synthesis

**Species/Strain:** Wistar Rats

**Age:** 5 Weeks

**Cells Evaluated:** Hepatocytes.

**No. of Cells Analyzed/Animal:** 100

**Special Features:** None.

**Toxic/Cytotoxic Effects:** None.

**Genotoxic Effects:** None.

**Evidence of Exposure:** Toxicokinetics - See Study No. 94007, Two-Week Oral Toxicity Study in Rats.

**Treatment Schedule:** Single dose.

**Sampling Time:** 2 and 16 hr.

**Method of Administration:** Gavage.

**Vehicle/Formulation:** Aqueous solution.

**Study No:** 51970

**Location in CTD:** Vol. 11 Page 2

**GLP Compliance:** Yes

**Date of Dosing:** Jan. 1997

<u>Test Article</u>	<u>Dose (mg/kg)</u>	<u>No. of Animals</u>	<u>Time hr</u>	<u>Nuclear Mean ± SD</u>	<u>Cytoplasm Mean ± SD</u>	<u>NG Mean ± SD</u>	<u>% IR Mean ± SD</u>	<u>NGIR Mean ± SD</u>
Vehicle	0	3M	16	3.5 ± 0.2	7.3 ± 0.3	-3.8 ± 0.4	0 ± 0	-
MM-180801	2	3M	2	3.0 ± 1.1	5.5 ± 1.4	-2.6 ± 0.4	0 ± 0	-
	2	3M	16	4.1 ± 0.5	6.5 ± 0.8	-2.4 ± 0.2	0 ± 0	-
	20	3M	2	3.9 ± 0.2	6.9 ± 0.3	-3.0 ± 0.1	1 ± 0	5.7 ± 0.4
	20	3M	16	3.6 ± 0.3	6.3 ± 0.4	-2.7 ± 0.2	0 ± 0	-
	200	3M	2	4.2 ± 0.2	7.5 ± 0.3	-3.4 ± 0.2	0 ± 0	-
	200	3M	16	3.1 ± 0.3	5.3 ± 0.3	-2.2 ± 0.1	0 ± 0	-
	2000	3M	2	4.8 ± 0.4	8.2 ± 0.7	-3.4 ± 0.4	0 ± 0	-
	2000	3M	16	2.7 ± 0.1	4.8 0.3	-2.1 ± 0.3	0 ± 0	-
DMN	10	3M	2	10.7 ± 3.0	5.8 ± 1.0	4.9 ± 2.1	41 ± 15	11.4 ± 0.4

Nuclear = Nuclear grain count; the number of grains over the nucleus.

Cytoplasm = Cytoplasmic grain count; the highest grain count from 2 nuclear-sized areas adjacent to the nucleus.

NG = Net grains/nucleus; the nuclear count minus the cytoplasmic count.

% IR = Percentage of cells with at least 5 NG.

NGIR = Average net grains/nucleus of cells in repair.

EXAMPLE

**3.4A Carcinogenicity Report Title:** MM-180801: Dietary Carcinogenicity Study in Mice **Test Article:** Curitol Sodium

**Species/Strain:** CD-1 Mice  
**Initial Age:** 6 Weeks  
**Date of First Dose:** 20 Sep 95

**Duration of Dosing:** 21 months  
**Method of Administration:** Diet  
**Vehicle/Formulation:** In Diet  
**Treatment of Controls:** Drug-Free Diet

**Study No.** 95012  
**Location in CTD:** Vol. 4 Page 1

**GLP Compliance:** Yes

**Basis for High-Dose Selection:** Toxicity-based endpoint.

**Special Features:** 12 additional males and 12 additional females per drug-treated group bled at 6 months for toxicokinetic monitoring and then removed from the study.

Daily Dose (mg/kg)	0 (Control)		25		100		400	
	M	F	M	F	M	F	M	F
Gender								
Toxicokinetics:								
AUC on Day 28 (mcg-hr/ml <sup>a</sup> )	-	-	10	12	40	48	815	570
Css on Day 180 (mcg/ml)	-	-	0.4	0.5	1.7	0.3	34	24
Number of Animals:								
At Start	60	60	60 <sup>c</sup>	60	60	60	60	60
Died/Sacrificed Moribund	16	16	15	13	18	20	27	25
Terminal Sacrifice	44	44	44 <sup>c</sup>	47	42	40	33	35
Survival (%)	67	73	75	80	71	68	56	59
Body Weight (% <sup>b</sup> )	33g	31g	0	0	-7*	0	-13**	-19**
Food consumption (% <sup>b</sup> )	6g/day	5g/day	0	0	-9*	-8*	-17**	-15**

Dunnett's Test: \* - p<0.05    \*\* - p<0.01

a - From Study No. 95013.

b - At 6 months. For controls, group means are shown. For treated groups, percent differences from controls. Statistical significance based on actual data (not on the percent differences)

c - One missing mouse could not be evaluated.

(Continued)

EXAMPLE

3.4A Carcinogenicity

Study No. 95012 (Continued)

Daily Dose (mg/kg)	0 (Control)		25		100		400	
	M: 60	F: 60	M: 59	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Number Evaluated</b>								
<b>Number of Animals</b>								
<b>with Neoplastic Lesions:</b>								
<b>Skin: Hemangioma</b>	0	1	1	0	6 <sup>b</sup>	1	13 <sup>b</sup>	0
<b>Hemangiosarcoma</b>	1	3	2	2	9	11	18 <sup>a</sup>	24 <sup>a</sup>
<b>Adrenal: Adrenocortical adenoma</b>	4	1	2	0	4	3	3	1
<b>Adrenocortical adenocarcinoma</b>	0	0	0	0	0	1	0	0
<b>Adenoma + Adenocarcinoma</b>	4	1	2	0	4	3	3	1
<b>Pheochromocytoma</b>	0	0	0	0	1	1	0	1
<b>Bone: Osteochondrosarcoma</b>	0	1	0	1	0	0	0	0
<b>Osteoma</b>	0	1	0	0	0	0	0	0
<b>Epididymis: Sarcoma, undifferentiated</b>	0	0	1	0	0	0	1	0
<b>Gallbladder: Adenoma</b>	0	0	1	0	0	0	0	0
<b>Harderian gland: Adenoma</b>	4	2	3	1	3	4	3	1
<b>Kidney: Renal cell adenoma</b>	1	2	0	0	2	0	0	0
<b>Liver: Hepatocellular adenoma</b>	3	1	4	2	3	1	4	1
<b>Hepatocellular carcinoma</b>	2	1	1	2	3	1	0	1
<b>Hepatocellular adenoma + carcinoma</b>	3	2	4	3	5	2	4	1
<b>Lung: Alveolar/bronchiolar adenoma</b>	13	10	11	11	14	7	13	4
<b>Alveolar/bronchiolar carcinoma</b>	4	0	1	1	2	2	1	1
<b>Adenoma + carcinoma</b>	15	10	11	12	15	9	13	5

a - Trend analysis, p<0.005

b - Trend analysis, p<0.025

(Continued)

EXAMPLE

**3.4A Carcinogenicity**

**Study No. 95012 (Continued)**

Daily Dose (mg/kg)	0 (Control)		25		100		400	
	M: 60	F: 60	M: 59	F: 60	M: 60	F: 60	M: 60	F: 60
Number Evaluated								
Mediastinum: Sarcoma, undifferentiated	0	1	0	0	0	1	0	0
Oviduct: Adenoma		1		1		0		0
Pancreas: Islet cell adenoma	1	0	0	0	0	0	0	0
Peritoneum: Osteosarcoma	1	0	0	0	1	0	0	1
Seminal vesicle: Adenoma	0		1		0		0	
Stomach: Osteochondrosarcoma	0	0	0	1	0	0	0	0
Thymus: Thymoma	0	1	0	0	0	0	0	0
Thyroid: Follicular cell adenoma	0	1	0	0	0	1	0	0
Uterus: Papillary cystadenoma		1		0		2		0
Whole animal: Lymphosarcoma	6	13	4	11	3	12	5	11
Whole animal: Histiocytic sarcoma	1	0	0	0	0	1	0	0
<b>Noteworthy Findings:</b>								
Gross Pathology	-	-	-	-	-	-	-	-
<b>Histopathology - Non-Neoplastic Lesions</b>								
Liver: Hepatocellular hypertrophy	4	2	3	2	4	1	40**	45**
Testes: Hypospermatogenesis	1		2		15*		30**	

- No noteworthy findings.

Fisher Exact Test: \* - p<0.05

\*\* - p<0.01

EXAMPLE

**3.5.1 Reproduction Toxicity**

**Non-Pivotal Studies**

**Test Article:** Curitol Sodium

<b><u>Species/ Strain</u></b>	<b><u>Method of Administration (Vehicle/ Formulation)</u></b>	<b><u>Dosing Period</u></b>	<b><u>Doses mg/kg</u></b>	<b><u>No. per Group</u></b>	<b><u>Noteworthy Findings</u></b>	<b><u>Study Number</u></b>
Wistar Rats	Gavage (Water)	G6 through G15	0, 500, 1000, 2000	8 Pregnant Females	¼1000: Deaths; weight losses; decreased food consumption; clinical signs; resorptions.	94201
NZW Rabbits	Gavage (CMC Suspension)	13 Days	0, 5,15, 45	6 Nonpregnant Females	¼15: Decreased weight gain and food consumption. 45: Four does died.	97020

G – Gestational day

EXAMPLE

**3.5.2 Reproduction Toxicity - Sodium Fertility and Early Embryonic Development to Implantation**

**Report Title:** MM-180801: Oral Study of Effects on Fertility and **Test Article:** Curitol

Early Embryonic Development in Rats

**Design similar to ICH 4.1.1?** Yes

**Species/Strain:** Wistar Rats

**Initial Age:** 10 Weeks

**Day of Mating:** Day 0

**Date of First Dose:** 3 Mar 97

**Special Features:** None

**No Observed Adverse-Effect Level:**

**F<sub>0</sub> Males:** 100 mg/kg

**F<sub>0</sub> Females:** 100 mg/kg

**F<sub>1</sub> Litters:** 1000 mg/kg

**Duration of Dosing:** M: 4 weeks prior to mating  
F: 2 weeks prior to mating, through day 7 of gestation

**Study No.** 97072

**Location in CTD:** Vol. 6 Page 1

**Day of C-Section:** Day 16 of gestation

**GLP Compliance:** Yes

**Method of Administration:** Gavage

**Vehicle/Formulation:** Aqueous solution.

<u>Daily Dose (mg/kg)</u>	<u>0 (Control)</u>	<u>10</u>	<u>100</u>	<u>1000</u>
<u>Males</u> Toxicokinetics: AUC <sup>b</sup> (mcg-hr/ml)	-	1.8	25	320
No. Evaluated	22	22	22	22
No. Died or Sacrificed Moribund	0	0	0	0
Clinical Observations:				
Salivation	-	-	+	++
Necropsy Observations	-	-	-	-
Body Weight (% <sup>a</sup> )	452 g	0	0	-12*
Mean No. Days Prior to Mating	2.7	2.5	2.3	2.8
No. of Males that Mated	22	21	22	22
No. of Fertile Males	21	21	21	21

- No noteworthy findings.      + Mild      ++Moderate      +++Marked

Dunnett's Test    \* - p<0.05    \*\* - p<0.01

a - After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

b - From Study No. 94220.

(Continued)

EXAMPLE

**3.5.2 Reproduction Toxicity**

**Study No. 97072 (Continued)**

<b>Daily Dose (mg/kg)</b>	<b>0 (Control)</b>	<b>10</b>	<b>100</b>	<b>1000</b>
<b>Females</b> Toxicokinetics: AUC <sup>b</sup> (mcg-hr/ml)	-	2.1	27	310
No. Evaluated	22	22	22	22
No. Died or Sacrificed Moribund	0	1	0	0
Clinical Observations				
Salivation	-	-	-	+
Necropsy Observations	-	-	-	-
Premating Body Weight (% <sup>a</sup> )	175 g	0	0	-5*
Gestation Body Weight (% <sup>a</sup> )	225 g	0	0	-12**
Premating Food Consumption (% <sup>a</sup> )	14 g	0	0	-6*
Gestation Food Consumption (% <sup>a</sup> )	15 g	0	0	-15**
Mean No. Estrous Cycles/14 days	3.9	3.8	3.8	3.9
Mean No. Days Prior to Mating	2.1	2.3	2.5	2.2
No. of Females Sperm-Positive	21	22	22	21
No. of Pregnant Females	21	21	22	20
Mean No. Corpora Lutea	15.9	15.8	16.8	15.3
Mean No. Implantations	14.5	14.0	15.3	13.8
Mean % Preimplantation Loss	8.8	11.4	8.9	9.8
Mean No. Live Conceptuses	13.3	13.3	14.3	12.8
Mean No. Resorptions	1.2	0.7	1.0	1.0
No. Dead Conceptuses	0	0	0	0
Mean % Postimplantation Loss	8.3	5.0	6.5	7.2

- No noteworthy findings.      + Mild      ++Moderate      +++Marked

Dunnett's Test    \* - p<0.05    \*\* - p<0.01

a - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown.  
 Statistical significance based on actual data (not on the percent differences).

b - From Study No. 94220.

EXAMPLE

**3.5.3 Reproduction Toxicity - Effects on Embryo-Fetal Development**

**Report Title:** MM-180801: Oral Study of Effects on Embryo-Fetal Development in Rabbits **Test Article:** Curitol Sodium

**Design similar to ICH 4.1.3?** Yes

**Day of Mating:** Day 0

**Species/Strain:** NZW Rabbits

**Initial Age:** 5 months

**Date of First Dose:** 7 Aug 97

**Special Features:** None.

**No Observed Adverse-Effect Level:**

**F<sub>0</sub> Females:** 1 mg/kg

**F<sub>1</sub> Litters:** 5 mg/kg

**Duration of Dosing:** G6-G18

**Day of C-Section:** G29

**Method of Administration:** Gavage

**Vehicle/Formulation:** Aqueous Solution

**Study No.** 97028

**Location in CTD:** Vol. 6 Page 200

**GLP Compliance:** Yes

<b>Daily Dose (mg/kg)</b>	<b>0 (Control)</b>	<b>1</b>	<b>5</b>	<b>25</b>
<b>Dams/Does:</b> Toxicokinetics: AUC <sup>b</sup> (mcg-hr/ml)	-	2.6	31	345
No. Pregnant	20	19	20	20
No. Died or Sacrificed Moribund	0	1	1	0
No. Aborted or with Total Resorption of Litter	0	0	0	3
Clinical Observations	-	-	-	++
Necropsy Observations	-	-	-	-
Body Weight (% <sup>a</sup> )	3.2 kg	0	-15*	-20**
Food Consumption (% <sup>a</sup> )	60 g/day	0	-9*	-16**
Mean No. Corpora Lutea	9.4	9.3	9.4	10.4
Mean No. Implantations	7.9	8.1	9.1	9.4
Mean % Preimplantation Loss	15.8	13.1	4.0	8.9

- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day

Dunnett's Test \* - p<0.05 \*\* - p<0.01

a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

b - From Study No. 97231.

(Continued)

EXAMPLE

**3.5.3 Reproduction Toxicity**

**Study No. 97028 (Continued)**

<b>Daily Dose (mg/kg)</b>	<b>0 (Control)</b>	<b>1</b>	<b>5</b>	<b>25</b>
<b>Litters:</b> No. Litters Evaluated	18	16	17	18
No. Live Fetuses	140	126	148	86*
Mean No. Resorptions	0.2	0.3	0.4	4.7**
No. Dead Fetuses	1	0	0	0
Mean % Postimplantation Loss	4.3	2.8	5.4	49.0**
Mean Fetal Body Weight (g)	44.82	42.44	42.14	42.39
Fetal Sex Ratios (% males)	46.3	57.7	57.4	52.8
<b>Fetal Anomalies:</b>				
<b>Gross External</b>				
Lower jaw: Short				
No. Fetuses (%)	0	0	0	7 (8.0)*
No. Litters (%)	0	0	0	5 (27.8)**
<b>Visceral Anomalies</b>				
Tongue: Absent				
No. Fetuses (%)	0	0	0	6 (6.9)*
No. Litters (%)	0	0	0	6 (33.3)**
<b>Skeletal Anomalies</b>				
Mandible: Cleft				
No. Fetuses (%)	0	0	0	10 (11.5)**
No. Litters (%)	0	0	0	8 (44.4)**
Ribs: Cervical				
No. Fetuses (%)	2 (1.4)	0	1 (0.7)	0
No. Litters (%)	1 (5.6)	0	1 (5.9)	0
Sternebrae: Misshapen				
No. Fetuses (%)	2 (1.4)	1 (0.8)	0	1 (1.2)
No. Litters (%)	2 (11.1)	1 (6.3)	0	1 (5.6)

- No noteworthy findings.

Fisher Exact Test \* - p<0.05 \*\* - p<0.01

EXAMPLE

**3.5.4 Reproduction Toxicity - Sodium Effects on Pre- and Postnatal Development, Including Maternal Function**

**Report Title:** MM-180801: Oral Study of Effects on **Test Article:** Curitol  
Pre- and Postnatal Development in Rats

**Design similar to ICH 4.1.2?** Yes

**Duration of Dosing:** G6 - L21

**Study No.** 95201

**Day of Mating:** Day 0

**Species/Strain:** Wistar Rats

**Method of Administration:** Gavage

**Location in CTD:** Vol. 10 Page 1

**Initial Age:** 9-10 Weeks

**Vehicle/Formulation:** Water

**Date of First Dose:** 8 Oct 95

**Litters Culled/Not Culled:** Culled to 4/sex/litter

**GLP Compliance:** Yes

**Special Features:** None

**No Observed Adverse-Effect Level:**

**F<sub>0</sub> Females:** 7.5 mg/kg

**F<sub>1</sub> Males:** 75 mg/kg

**F<sub>1</sub> Females:** 75 mg/kg

<u>Daily Dose (mg/kg)</u>	<u>0 (Control)</u>	<u>7.5</u>	<u>75</u>	<u>750</u>
<u>F<sub>0</sub> Females:</u> Toxicokinetics: AUC <sup>b</sup> (mcg-hr/ml)	-	2.4	21	150
No. Pregnant	23	21	22	23
No. Died or Sacrificed Moribund	0	0	0	8
Clinical Observations	-	-	++	+++
Necropsy Observations	-	-	-	-
Gestation Body Weight (% <sup>a</sup> )	225 g	0	0	-25**
Lactation Body Weight (% <sup>a</sup> )	210 g	0	0	0
Gestation Food Consumption (% <sup>a</sup> )	15 g	0	0	-12*
Lactation Food Consumption (% <sup>a</sup> )	16 g	0	0	0
Mean Duration of Gestation (days)	22.1	22.2	22.1	23.5 <sup>+</sup>
Abnormal Parturition	-	-	-	-

- No noteworthy findings.

+ Mild

++Moderate

+++Marked

G = Gestation day

Dunnett's Test \* - p<0.05 \*\* - p<0.01

L = Lactation day

Kruskal-Wallis with Dunn's procedure + - p<0.05

a - At end of gestation or lactation. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

b - From Study No. 97227.

(Continued)

EXAMPLE

**3.5.4 Reproduction Toxicity**

**Study No. 95201 (Continued)**

<b>Daily Dose (mg/kg)</b>		<b>0 (Control)</b>	<b>7.5</b>	<b>75</b>	<b>750</b>
<b>F<sub>1</sub> Litters:</b> (Prewearing)	No. Litters Evaluated	23	21	22	15
	Mean No. Pups/Litter	13.6	13.8	14.9	11.2 <sup>++</sup>
	Mean No. Liveborn Pups/Litter	13.5	13.8	14.6	9.4 <sup>++</sup>
	Mean No. Stillborn Pups/Litter	0.1	0.0	0.3	1.8 <sup>+</sup>
	Postnatal Survival to Day 4	-	-	-	-
	Postnatal Survival to Weaning	-	-	-	-
	Change in Pup Body Weights <sup>a</sup> (g)	60	58	62	53 <sup>*</sup>
	Pup Sex Ratios (% males)	51	53	49	51
	Pup Clinical Signs	-	-	-	-
	Pup Necropsy Obs.	-	-	-	-
<b>F<sub>1</sub> Males:</b> (Postweaning)	No. Evaluated Postweaning	23	21	22	15
	No. Died or Sacrificed Moribund	-	-	-	-
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Change <sup>b</sup> (g)	200	195	195	186 <sup>*</sup>
	Food Consumption (% <sup>b</sup> )	15 g	0	0	-11 <sup>*</sup>
	Preputial Separation	-	-	-	-
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	2.4	3.3	2.9	3.5
	No. of Males that Mated	23	21	21	23
	No. of Fertile Males	23	21	19	20

- No noteworthy findings.      + Mild      ++Moderate      +++Marked

Dunnett's Test \* - p<0.05      \*\* - p<0.01

Kruskal-Wallis with Dunn's procedure      + - p<0.05      ++ - p<0.01

a - From birth to weaning.

b - From weaning to mating. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

(Continued)

EXAMPLE

**3.5.4 Reproduction Toxicity**

**Study No. 95201 (Continued)**

<u>Daily Dose (mg/kg)</u>		<u>0 (Control)</u>	<u>7.5</u>	<u>75</u>	<u>750</u>
<u>F<sub>1</sub> Females:</u> (Postweaning)	No. Evaluated Postweaning	23	21	22	23
	No. Died or Sacrificed Moribund	0	1	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Premating Body-Weight Change <sup>a</sup> (g)	226	230	235	196*
	Gestation Body-Weight Change (g)	153	160	144	158
	Premating Food Consumption (% <sup>b</sup> )	15 g	0	0	-13*
	Gestation Food Consumption (% <sup>b</sup> )	16 g	0	0	0
	Mean Age of Vaginal Patency (days)	-	-	-	-
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	2.4	3.3	3.1	3.5
	No. of Females Sperm-Positive	23	21	21	23
	No. of Pregnant Females	23	21	20	21
	Mean No. Corpora Lutea	16.4	16.2	15.8	15.5
	Mean No. Implantations	15.8	15.2	14.4	14.9
Mean % Preimplantation Loss	3.8	6.3	12.3	3.7	
<u>F<sub>2</sub> Litters:</u>	Mean No. Live Conceptuses/Litter	15.0	14.9	13.6	14.4
	Mean No. Resorptions	0.8	0.3	0.8	0.5
	No. Dead Conceptuses	0	0	0	0
	Mean % Postimplantation Loss	5.1	2.2	5.2	3.4
	Fetal Body Weights (g)	3.69	3.65	3.75	3.81
	Fetal Sex Ratios (% males)	53	49	54	54
	Fetal Anomalies	-	-	-	-

- No noteworthy findings.      + Mild      ++Moderate      +++Marked

Dunnett's Test \* - p<0.05      \*\* - p<0.01

a - From weaning to mating

b - During postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences). (Continued)

EXAMPLE

**3.7 Other Toxicity Studies**

**Test Article: Curitol Sodium**

<u>Species/ Strain</u>	<u>Method of Administration</u>	<u>Duration of Dosing</u>	<u>Doses (mg/kg)</u>	<u>Gender and No. per Group</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
<b>3.7.1 Antigenicity</b>						
Guinea Pigs	Subcutaneous	Weekly for 3 weeks; challenge 1 week later.	0, 5 mg	5M, 5F	Mildly positive delayed hypersensitivity reaction. No evidence of passive cutaneous anaphylaxis or systemic anaphylaxis.	97012
<b>3.7.2 Impurities</b>						
WISTAR Rats	Gavage	2 Weeks	0, 1000, 2000	10M, 10F	MM-180801 fortified with 2% of the Z- isomer impurity; toxicologic effects comparable to MM-180801 without impurity.	97025