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**ICH M4S
COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF
PHARMACEUTICALS FOR HUMAN USE - SAFETY**

ICH Step 5

**COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF
PHARMACEUTICALS FOR HUMAN USE
NONCLINICAL OVERVIEW AND NONCLINICAL SUMMARIES
OF MODULE 2
ORGANISATION OF MODULE 4**

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Note:

The sequence of M4 *Common Technical Document for the Registration of Pharmaceuticals for Human Use* is:

- M4 - Organisation of Common Technical Document
- M4 Quality - Quality overall summary of Module 2 and Module 3: Quality
- M4 Safety - Nonclinical Overview and Nonclinical Summaries of Module 2 and Organisation of Module 4
- M4 Efficacy - Clinical overview and Clinical summary of Module 2 and Module 5: Clinical Study reports

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The document as presented may be subject to further editorial changes and is for information only.

Details on how to prepare a submission dossier based on the CTD format including information on the content of Module I are included in the revision of the Notice to Applicants.

ICH M4S - COMMON TECHNICAL DOCUMENT FOR THE
REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: SAFETY
NONCLINICAL OVERVIEW AND NONCLINICAL SUMMARIES OF
MODULE 2
ORGANISATION OF MODULE 4

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MODULE 2 : COMMON TECHNICAL DOCUMENT SUMMARIES

General Principles of Nonclinical Overview and Summaries

This guideline provides recommendations for the harmonisation of the Nonclinical Overview, 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 the 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 be addressed in the Overview.

2.4 NONCLINICAL OVERVIEW

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

General Aspects

The Nonclinical Overview 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 and justified. 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, or 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. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. 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 Overview 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 Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics

Toxicology

Integrated overview and conclusions

List of literature references

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, toxicokinetic, 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_{max}, 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, their 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
- 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
- fertility, embryofetal development, pre-and post-natal toxicity
- studies in juvenile animals
- the consequences of use before and during pregnancy, during lactation, and during pediatric development
- 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).

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Nonclinical Written Summaries

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 should 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.

General Presentation Issues

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:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Non-human primate
- Other non-rodent mammal
- Non-mammals

Routes of administration should be ordered as follows :

- The intended route for human use

- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

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.

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).

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.

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Content of Nonclinical Written and Tabulated Summaries

2.6.1 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:

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

2.6.2 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)

2.6.2.1 *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).

2.6.2.2 *Primary Pharmacodynamics*

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

2.6.2.3 *Secondary Pharmacodynamics*

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

2.6.2.4 *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.

2.6.2.5 *Pharmacodynamic Drug Interactions*

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

2.6.2.6 *Discussion and Conclusions*

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

2.6.2.7 *Tables and Figures*

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

2.6.3 Pharmacology Tabulated Summary (see Appendix B)

2.6.4 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)

* See ICH Guideline S7, *Safety Pharmacology Studies for Human Pharmaceuticals*, Note 2. p. 8, for definitions.

2.6.4.1 *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.

2.6.4.2 *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.

2.6.4.3 *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)

2.6.4.4 *Distribution*

The following data should be summarised in this section:

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

2.6.4.5 *Metabolism (interspecies 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

2.6.4.6 *Excretion*

The following data should be summarised in this section:

- Routes and extent of excretion
- Excretion in milk

2.6.4.7 *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.

2.6.4.8 *Other Pharmacokinetic Studies*

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

2.6.4.9 *Discussion and Conclusions*

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

2.6.4.10 *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.

2.6.5 Pharmacokinetics Tabulated Summary (see Appendix B)

2.6.6 Toxicology Written Summary

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

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

2.6.6.1 *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.

2.6.6.2 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.

2.6.6.3 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).

2.6.6.4 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

2.6.6.5 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

2.6.6.6 Reproductive and Developmental 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
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted.

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

2.6.6.7 Local Tolerance

If local tolerance 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.

2.6.6.8 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

2.6.6.9 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.

2.6.6.10 Tables and Figures

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

2.6.7 Toxicology Tabulated Summary (see Appendix B)

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 and to facilitate the understanding and evaluation of the results.

This Guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed. Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study 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.

When a juvenile-animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

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

MODULE 4: 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. 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 appropriate location for individual-animal data is in the study report or as an appendix to the study report.

4.1 Table of Contents of Module 4

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.

4.2 Study Reports

The study reports should be presented in the following order:

- 4.2.1 Pharmacology.
 - 4.2.1.1 Primary Pharmacodynamics
 - 4.2.1.2 Secondary Pharmacodynamics
 - 4.2.1.3 Safety Pharmacology
 - 4.2.1.4 Pharmacodynamic Drug Interactions
- 4.2.2 Pharmacokinetics
 - 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
 - 4.2.2.2 Absorption
 - 4.2.2.3 Distribution
 - 4.2.2.4 Metabolism
 - 4.2.2.5 Excretion
 - 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
 - 4.2.2.7 Other Pharmacokinetic Studies
- 4.2.3 Toxicology
 - 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
 - 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
 - 4.2.3.3 Genotoxicity
 - 4.2.3.3.1 In vitro
 - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
 - 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
 - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

- 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
 - 4.2.3.5.1 Fertility and early embryonic development
 - 4.2.3.5.2 Embryo-fetal development
 - 4.2.3.5.3 Prenatal and postnatal development, including maternal function
 - 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies (if available)
 - 4.2.3.7.1 Antigenicity
 - 4.2.3.7.2 Immunotoxicity
 - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
 - 4.2.3.7.4 Dependence
 - 4.2.3.7.5 Metabolites
 - 4.2.3.7.6 Impurities
 - 4.2.3.7.7 Other

4.3 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.

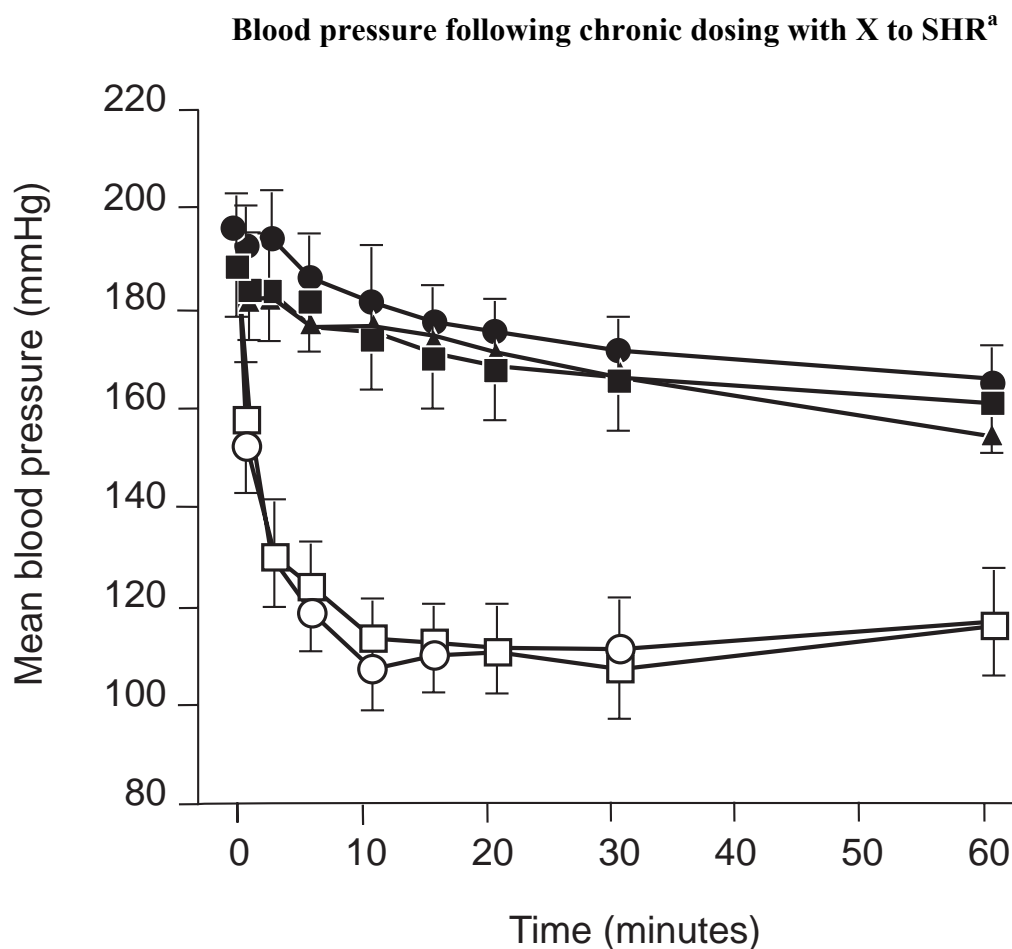
Table X

**Binding of X and its Major Metabolites and Comparators
to Human X₂ and X₃ Receptors**

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

K_{i1} and K_{i2} represent the high and low affinity binding sites respectively (Data from Study Number).

Figure X



Blood pressure following chronic dosing with X to SHR^a[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.

^aSHR= 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					
	Sex	Males			Females	
Dose (mg/kg)	2	10	30	2	10	30
C _{max} (ng/mL)	4.9	20.4	30.7	5.5	12.9	28.6
T _{max} (h)	0.8	0.4	0.3	0.4	0.5	0.3
AUC _{0-t} (ng.h/mL)	21.6	80.5	267	33.3	80	298
AUC _{0-inf} (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 [¹⁴C]X to male mice [ref]

Dose (mg/kg)/ route	Percentage of administered dose		
	Urine*	Faeces	Total ⁺
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 [¹⁴C]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 [¹⁴C]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

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 _{max} (ng/mL)	AUC (ng.h/mL)#	
Man (tablet)	0.48 ^{\$}	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.

- AUC₀₋₆ in the mouse, AUC_{0-t} in the rat and in the dog and dose normalised AUC_{0-τ} 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]**

Lesion	Dose Groups			
	Control	3 mg/kg	30 mg/kg	100 mg/kg
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

2.6.3 Pharmacology

- 2.6.3.1 Pharmacology: Overview
- 2.6.3.2 Primary Pharmacodynamics*
- 2.6.3.3 Secondary Pharmacodynamics*
- 2.6.3.4 Safety Pharmacology
- 2.6.3.5 Pharmacodynamic Drug Interactions*

2.6.5 Pharmacokinetics

- 2.6.5.1 Pharmacokinetics: Overview
- 2.6.5.2 Analytical Methods and Validation Reports*
- 2.6.5.3 Pharmacokinetics: Absorption after a Single Dose
- 2.6.5.4 Pharmacokinetics: Absorption after Repeated Doses
- 2.6.5.5 Pharmacokinetics: Organ Distribution
- 2.6.5.6 Pharmacokinetics: Plasma Protein Binding
- 2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
- 2.6.5.8 Pharmacokinetics: Other Distribution Study
- 2.6.5.9 Pharmacokinetics: Metabolism In Vivo
- 2.6.5.10 Pharmacokinetics: Metabolism In Vitro
- 2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways
- 2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes
- 2.6.5.13 Pharmacokinetics: Excretion
- 2.6.5.14 Pharmacokinetics: Excretion into Bile
- 2.6.5.15 Pharmacokinetics: Drug-Drug Interactions
- 2.6.5.16 Pharmacokinetics: Other

2.6.7 Toxicology

- 2.6.7.1 Toxicology: Overview
- 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies
- 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data
- 2.6.7.4 Toxicology: Drug Substance
- 2.6.7.5 Single-Dose Toxicity
- 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies
- 2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies
- 2.6.7.8 Genotoxicity: In Vitro

- 2.6.7.9 Genotoxicity: In Vivo
- 2.6.7.10 Carcinogenicity
- 2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies
- 2.6.7.12 Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation (Pivotal)
- 2.6.7.13 Reproductive and Developmental Toxicity – Effects on Embryo-Fetal Development (Pivotal)
- 2.6.7.14 Reproductive and Developmental Toxicity – Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)
- 2.6.7.15 Studies in Juvenile Animals^a
- 2.6.7.16 Local Tolerance
- 2.6.7.17 Other Toxicity Studies

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

^a : When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 2.6.7.15.

2.6.3.1 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. Section</u>
Primary Pharmacodynamics (2)					(3)
Secondary Pharmacodynamics					
Safety Pharmacology					
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).

2.6.3.4 Safety Pharmacology(1)

Test Article: (2)

<u>Organ Systems Evaluated</u>	<u>Species/ Strain</u>	<u>Method of Admin.</u>	<u>Doses^a (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.

2.6.5.1 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 Vol. Section</u>
Absorption (2)					(3)
Distribution					
Metabolism					
Excretion					
Pharmacokinetic Drug Interactions					
Other					

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.

2.6.5.3 Pharmacokinetics: Absorption after a Single Dose

Test Article: (1)
Location in CTD: Vol. Section
Study No.

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:	_____	_____	_____	_____	_____

Additional Information: (3)

- Notes: (1) *International Nonproprietary Name (INN).*
(2) *For example, HPLC, LSC with ¹⁴C-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.*
-

2.6.5.4 Pharmacokinetics: Absorption after Repeated Doses

Test Article:

[Data may be tabulated as in the format of 2.6.5.3 if applicable.]

Format A

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article:

**Location in CTD: Vol. Section
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_{1/2}?

Additional information:

Alternate Format B

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. Section
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_t		Last time-point			AUC	t_{1/2?}
conc.	T/P¹⁾	conc.	T/P¹⁾	Time		

Additional information:

¹⁾ [Tissue]/[Plasma]

2.6.5.6 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>Section</u>
----------------	---------------------	----------------	------------------	--

Additional Information:

2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals (1)

Test Article: (2)
Location in CTD: Vol. Section
Study No.

Placental transfer

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. Section
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:

- (2) International Nonproprietary Name (INN).
- (3) The tissue sampled should be described; e.g., plasma for dams, fetal concentrations.

2.6.5.9 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>Section</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.*

2.6.5.10 Pharmacokinetics: Metabolism *In Vitro*

Test Article:
Location in CTD: Vol. Section
Study No.

Study system:

Time
Concentration:
Compounds
Parent
M-1
M-2

Additional Information:

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

2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways

Test Article:

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

2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes

Test Article:
Location in CTD: Vol. Section
Study No.

Note: Nonclinical studies only.

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.5.13 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>	<u>Urine</u>	<u>Feces</u>	<u>Total</u>	<u>Urine</u>	<u>Feces</u>	<u>Total</u>	<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.
-

[Data may be tabulated as in the format of 2.6.5.13 if applicable.]

Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.7.1 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^a)</u>	<u>GLP Compliance</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol. Section</u>
Single-Dose Toxicity	(2)							(3)
Repeat-Dose Toxicity								
Genotoxicity								
Carcinogenicity								
Reproductive and Developmental Toxicity								
Local Tolerance								
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 Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

2.6.7.2 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. Section</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.

(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.*

2.6.7.4 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.

2.6.7.5 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).

2.6.7.6 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^a (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.

2.6.7.7 (1) Repeat-Dose Toxicity (2)

Report Title:

Test Article: (3)

**Species/Strain:
Initial Age:**

Duration of Dosing:

Study No.

Duration of Postdose:

Location in CTD:

Date of First Dose:

Vol. Section

Method of Administration:

Vehicle/Formulation:

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)							
<u>Noteworthy Findings</u>								
Died or Sacrificed Moribund								
Body Weight (%^a)								
Food Consumption (%^a)	(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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

2.6.7.7 (1) Repeat-Dose Toxicity

Study No. (Continued)

Daily Dose (mg/kg)	0 (Control)		M:	E:	M:	E:	M:	E:
	M:	E:						
Number of Animals								
Hematology								
Serum Chemistry								
Urinalysis								
Organ Weights^a (%)								
Gross Pathology								
Histopathology								
Additional Examinations								
Postdose Evaluation:								
Number Evaluated								
(8)								

- No noteworthy findings.

(7) * - 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.

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_{max}, C_{ss}, 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.

2.6.7.8 (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. Section

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: 2.6.7.8A, 2.6.7.8B, 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

2.6.7.9 (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. Section
GLP Compliance:
Date of Dosing:

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

*Notes: (1) The tables should be numbered consecutively: 2.6.7.9A, 2.6.7.9B, etc.
(2) International Nonproprietary Name (INN).
(3) Methods of statistical analysis should be indicated.*

(3) * - p<0.05 ** - p<0.01).

2.6.7.10 (1)Carcinogenicity

Report Title:

Test Article: (2)

**Species/Strain:
Initial Age:
Date of First Dose:**

**Duration of Dosing:
Method of Administration:
Vehicle/Formulation:
Treatment of Controls:**

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

**Basis for High-Dose Selection: (3)
Special Features:**

GLP Compliance:

Daily Dose (mg/kg)	<u>0 (Control)</u>							
Gender	<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)								
Number of Animals								
At Start								
Died/Sacrificed Moribund								
Terminal Sacrifice								
Survival (%)	(5)							
Body Weight (%^a)								
Food Consumption (%^a)								

(6) * - p<0.05 ** - p<0.01

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

(Continued)

2.6.7.10 (1) Carcinogenicity

Study No. (Continued)

Daily Dose (mg/kg)
Number Evaluated
Number of Animals
with Neoplastic Lesions:
 (7)

 (Control)
M: E:

 0 (Control)
M: E:

M:

E:

M:

E:

M:

E:

Noteworthy Findings:
Gross Pathology
Histopathology - Non-Neoplastic Lesions

- No noteworthy findings.
- * - p<0.05 ** - p<0.01

- (2) International Nonproprietary Name (INN).
- (3) From ICH Guideline S1C.
- (4) Steady-state AUC, C_{max}, C_{ss}, 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.

2.6.7.11 Reproductive and Developmental 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).*

2.6.7.12 (1) Reproductive and Developmental 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:

F₀ Males:

F₀ Females:

F₁ 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. Section

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 (%^a)

Food Consumption (%^a)

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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

2.6.7.12 (1) Reproductive and Developmental Toxicity

Study No. (Continued)

Daily Dose (mg/kg)

0 (Control)

Females Toxicokinetics: AUC () (4)

- No. Died or Sacrificed Moribund
- Clinical Observations
- Necropsy Observations
- Premating Body Weight (%^a)
- Gestation Body Weight (%^a)
- Premating Food Consumption (%^a)
- Gestation Food Consumption (%^a)
- 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 pre mating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

- (2) International Nonproprietary Name (INN).
- (3) If a modified study design is used, tables should be modified accordingly.
- (4) Steady-state AUC, C_{max}, 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.
- (7) Methods of statistical analysis should be indicated.
- (8) Day of mating should be indicated; e.g., Day 0 or Day 1

**2.6.7.13 (1) Reproductive and Developmental 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. Section

Initial Age:

Day of C-Section:

Date of First Dose:

Method of Administration:

Special Features:

Vehicle/Formulation:

GLP Compliance:

No Observed Adverse-Effect Level:

F₀ Females:

F₁ Litters:

Daily Dose (mg/kg)

0 (Control)

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

No. Pregnant

No. Died or Sacrificed Moribund

(5)

No. Aborted or with Total Resorption of Litter

Clinical Observations

Necropsy Observations

Body Weight (%^a)

Food Consumption (%^a)

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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

2.6.7.13 (1) Reproductive and Developmental Toxicity

Study No. (Continued)

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

2.6.7.14 (1) Reproductive and Developmental Toxicity - Report Title:
Effects on Pre- and Postnatal Development, Including Maternal Function (3)

Test Article: (2)

Design similar to ICH 4.1.2?

Duration of Dosing:
Day of Mating: (8)
Method of Administration:
Vehicle/Formulation:
Litters Culled/Not Culled:

Study No.

Species/Strain:

Initial Age

Date of First Dose:

Special Features:

No Observed Adverse-Effect Level:

F₀ Females:

F₁ Males:

F₁ Females:

Location in CTD: Vol. Section

GLP Compliance:

Daily Dose (mg/kg)

0 (Control)

F₀ Females: Toxicokinetics: AUC () (4)

No. Pregnant

No. Died or Sacrificed Moribund

No. Aborted or with Total Res. Of Litter

Clinical Observations

Necropsy Observations

(5)

Gestation Body Weight (%^a)

Lactation Body Weight (%^a)

Gestation Food Consumption (%^a)

Lactation Food Consumption (%^a)

Mean Duration of Gestation (days)

Abnormal Parturition

- 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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

2.6.7.14 (1) Reproductive and Developmental Toxicity

Study No. (Continued)

Daily Dose (mg/kg)

0 (Control)

F₁ Litters:
(Prewearing) 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^a (g)
Pup Sex Ratios
Pup Clinical Signs
Pup Necropsy Obs.

F₁ Males:
(Postweaning) No. Evaluated Postweaning
Per Litter
No. Died or Sacrificed Moribund
Clinical Observations
Necropsy Observations
Body-Weight Change^b (g)
Food Consumption (%^c)
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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.14 (1) Reproductive and Developmental Toxicity

Study No. (Continued)

Daily Dose (mg/kg)

0 (Control)

F₁ Females:
 (Postweaning) No. Evaluated Postweaning
 No. Died or Sacrificed Moribund
 Clinical Observations
 Necropsy Observations
 Premating Body-Weight Change^a (g)
 Gestation Body-Weight Change (g)
 Premating Food Consumption (%^b)
 Gestation Food Consumption (%^b)
 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

F₂ 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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.14 (1) Reproductive and Developmental Toxicity

Study No. (Continued)

Daily Dose (mg/kg)

0 (Control)

F₁ Females:
(Postweaning)
No. Evaluated Postweaning
No. Died or Sacrificed Moribund
Clinical Observations
Necropsy Observations
Premating Body-Weight Change^a (g)
Gestation Body-Weight Change (g)
Premating Food Consumption (%^b)
Gestation Food Consumption (%^{ab})
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.*

F₂ 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^a (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 are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.16 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>
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*Notes: (1) All local-tolerance studies should be summarized.
(2) International Nonproprietary Name (INN).*

2.6.7.17 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>
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*Notes: (1) All supplementary toxicity studies should be summarized.
(2) International Nonproprietary Name (INN).*

Appendix C

The Nonclinical Tabulated Summaries - Examples

EXAMPLE

2.6.3.1 Pharmacology

Overview

Test Article: Curitol Sodium

<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. Section</u>
1.1 Primary Pharmacodynamics					
Antiviral activity vs. VZV	Human embryonic lung	In vitro	Sponsor Inc.	95401	1
Antiviral activity vs. VZV	fibroblasts	In vitro	Sponsor Inc.	95402	1
Antiviral activity vs. HSV	Clinical isolates	In vitro	Sponsor Inc.	95406	1
Antiviral activity vs. CMV	Human embryonic lung	In vitro	Sponsor Inc.	95408	1
Antiviral activity vs. VZV	fibroblasts	Gavage	Sponsor Inc.	95411	1
Antiviral activity vs. SVV	Human embryonic lung fibroblasts	Nasogastric Intubation	Sponsor Inc.	95420	1
	ICR mice				
	African Green monkeys				
Secondary Pharmacodynamics					
Antimicrobial activity	Gram-positive and gram-negative bacteria; yeasts	In vitro	Sponsor Inc.	95602	1
Safety Pharmacology					
Effects on central nervous system ^a	Mice, rats, rabbits, and cats	Gavage	Sponsor Inc.	95703	2
Effects on cardiovascular system	Dogs	Gavage, i.v.	Sponsor Inc.	95706	2
Pharmacodynamic Drug Interactions					
Interactions with anti-HIV activity of AZT	Human T lymphocytes	In vitro	Sponsor Inc.	95425	2

a - Report contains a GLP Compliance Statement.

EXAMPLE

2.6.3.4 Safety Pharmacology

Test Article: Curitol Sodium

<u>Organ Systems Evaluated</u>	<u>Species/ Strain</u>	<u>Method of Admin.</u>	<u>Doses^a (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 (≥ 10 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 (≥ 50 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

2.6.5.1 Pharmacokinetics

Overview

Test Article: Curitol Sodium

<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. Section</u>
Absorption					
Absorption and excretion	Rats	Gavage, i.v.	Sponsor Inc.	93302	1
Absorption and excretion	Dogs	Gavage, i.v.	Sponsor Inc.	93304	1
Absorption and excretion	Monkeys	Gavage, i.v.	Sponsor Inc.	93306	1
Distribution					
Single-dose tissue distribution	Rats	Gavage	Sponsor Inc.	93307	1
Repeat-dose tissue distribution	Rats	Gavage	Sponsor Inc.	93308	1
Plasma protein binding	Mice, rats, dogs,	In vitro	Sponsor Inc.	93311	1
Plasma protein binding	monkeys, Humans, rats, dogs	Tablets/Gavage/Capsules	Sponsor Inc.	93312	1
Metabolism					
Metabolites in blood, urine, and feces	Rats	Gavage	Sponsor Inc.	93402	1
Metabolites in blood, urine, and feces	Dogs	Gavage	Sponsor Inc.	93407	1
Excretion					
Absorption and excretion	Rats	Gavage, i.v.	Sponsor Inc.	93302	1
Absorption and excretion	Dogs	Gavage, i.v.	Sponsor Inc.	93304	1
Absorption and excretion	Monkeys	Gavage, i.v.	Sponsor Inc.	93306	1
Pharmacokinetic Drug Interactions					
Interaction with AZT ^a	Rats	Gavage	Sponsor Inc.	94051	1

a - Report contains a GLP Compliance Statement.

EXAMPLE

2.6.5.3 Pharmacokinetics: Absorption after a Single Dose

Test Article: Curitol Sodium
Location in CTD Volume 1, Section
Study number 95104

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 ^a	MM-180801	MM-180801	MM-180801	MM-180801
Assay	LSC	HPLC	HPLC	HPLC	HPLC
PK parameters:					
Tmax (hr)	4.0	1.0	3.3	1.0	6.8
Cmax (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)

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, ¹⁴C

EXAMPLE

Format A

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: Curitol Sodium

Location in CTD: Vol. 21 Section
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: ¹⁴C
Specific Activity: 2x10⁵ Bq/mg
Sampling time: 0.25, 0.5, 2, 6, 24, 96, and 192 hr

Tissues/organs	Concentration (mcg/mL)					t _{1/2}
	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

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: Curitol Sodium

Location in CTD: Vol. 21 Section
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 _{1hr}		Last time-point			AUC	t _{1/2}
	conc.	T/P ¹⁾	conc.	T/P ¹⁾	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:

¹⁾ [Tissue]/[Plasma]

EXAMPLE

2.6.5.6 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 No.</u>	<u>Location in CTD Vol. Section</u>
Rat	1 - 100uM	82.1 - 85.4	95301	21
Dog	1 - 100uM	83.5 - 88.2	95301	21
Human	1 - 100uM	75.2 - 79.4	96-103-03	45

Additional Information:

EXAMPLE

2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals

Test Article: Curitol Sodium

Location in CTD: Vol. 22 Section
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, ¹⁴C

Assay: LSC

Time (hr)

Concentration / Amount (% of dose)

	<u>14 days/30 min</u>	<u>14 days/24 hr</u>	<u>19 days/30 min</u>	<u>19 days/24 hr</u>
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 Section
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, ¹⁴C

Assay: LSC

Time [hr]

Concentration:

	1	2	4	6	8	24
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

Additional Information:

EXAMPLE

2.6.5.9 Pharmacokinetics: Metabolism *In Vivo*

Test Article: Curitol Sodium

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: ¹⁴C
 Specific Activity: 2 x 10⁵ 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.	Section
Rats	Plasma	0.5 hr	-	87.2	6.1	3.4	95076	26	
	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	
	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	
	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

2.6.5.13 Pharmacokinetics: Excretion

Test Article: Curitol Sodium

Species	<u>Rat</u>			<u>Rat</u>			<u>Dog</u>			<u>Dog</u>		
	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 ^a			TRA ^a			TRA ^a			TRA ^a		
Assay	LSC			LSC			LSC			LSC		
Excretion route	<u>Urine</u>	<u>Feces</u>	<u>Total</u>	<u>Urine</u>	<u>Feces</u>	<u>Total</u>	<u>Urine</u>	<u>Feces</u>	<u>Total</u>	<u>Urine</u>	<u>Feces</u>	<u>Total</u>
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

95102

95156

Location in CTD

Volume 20, Section

Volume 20, Section

Additional Information:

a - Total radioactivity; percent recovery, ¹⁴C

EXAMPLE

2.6.5.14 Pharmacokinetics: Excretion into Bile

Test Article: Curitol Sodium

	<u>Rat</u>			<u>Rat</u>		
Species	4M			4M		
Gender (M/F) / Number of animals	Fasted			Fasted		
Feeding condition	Solution			Solution		
Vehicle/Formulation	Water			Saline		
Method of Administration	Oral			Intravenous		
Dose (mg/kg)	10			5		
Analyte	TRA ^a			TRA ^a		
Assay	LSC			LSC		
Excretion route	<u>Bile</u>	<u>Urine</u>	<u>Total</u>	<u>Bile</u>	<u>Urine</u>	<u>Total</u>
Time						
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, Section

a - Total radioactivity; percent recovery, ¹⁴C

EXAMPLE

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

Overview (Continued)

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)</u>	<u>GLP Compliance</u>	<u>Testing Facility</u>	<u>Study Number</u>	<u>Location Vol. Section</u>
Carcinogenicity	CD-1 Mice	Diet	21 Months	0, 0, 25, 100, 400	Yes	CRO Co.	95012	10
	Wistar Rats	Gavage	24 Months	0, 0, 25, 100, 400	Yes	Sponsor Inc.	95013	12
Reproduction Toxicity	Wistar Rats	Gavage	a	0, 5, 30, 180	Yes	CRO Co.	96208	14
	Wistar Rats	Gavage	F: G6 - G15 ^b	0, 10, 100, 1000	Yes	Sponsor Inc.	94211	15
	NZW Rabbits	Gavage	F: G6 - G18 ^b	0, 1, 5, 25	Yes	CRO Co.	97028	16
	Wistar Rats	Gavage	F: G6 - L21 ^b	0, 7.5, 75, 750	Yes	Sponsor Inc.	95201	17
Local Tolerance	NZW Rabbits	Dermal	1 Hour	0, 15 mg	No	Sponsor Inc.	95015	18
Other Toxicity Studies								
Antigenicity	Guinea Pigs	Subcutaneous	Weekly for 3 weeks	0, 5 mg	No	CRO Co.	97012	18
Impurities	Wistar Rats	Gavage	2 Weeks	0, 1000, 2000	Yes	Sponsor Inc.	97025	18

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

2.6.7.2 Toxicokinetics

Overview of Toxicokinetics Studies

Test Article: Curitol Sodium

<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. Section</u>
Three-month range-finding study	Mice	Diet	62.5, 250, 1000, 4000, 7000	Yes	94018	2
Two-week toxicity study	Rats	Gavage	500, 1000, 2000	No	94007	3
Six-month toxicity study	Rats	Gavage	100, 300, 900	Yes	95001	5
One-month toxicity study	Dogs	Capsules	10, 40, 100	Yes	94020	6
Nine-month toxicity study	Dogs	Capsules	5, 20, 50	Yes	96041	7
Carcinogenicity study	Mice	Diet	25, 100, 400	Yes	95012	10
Carcinogenicity study	Rats	Gavage	25, 100, 400	Yes	95013	12
Toxicokinetics study	Rabbits	Gavage	1, 5, 25	No	97231	16

EXAMPLE

2.6.7.3 Toxicokinetics

Overview of Toxicokinetics Data

Test Article: Curitol Sodium

Daily Dose (mg/kg)	Steady-State AUC (mcg-hr/ml)					Female Rabbits ^b	Humans ^f
	Mice ^a		Rats ^b		Dogs ^c		
	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 ^d , 20 ^e	27 ^d , 22 ^e	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.

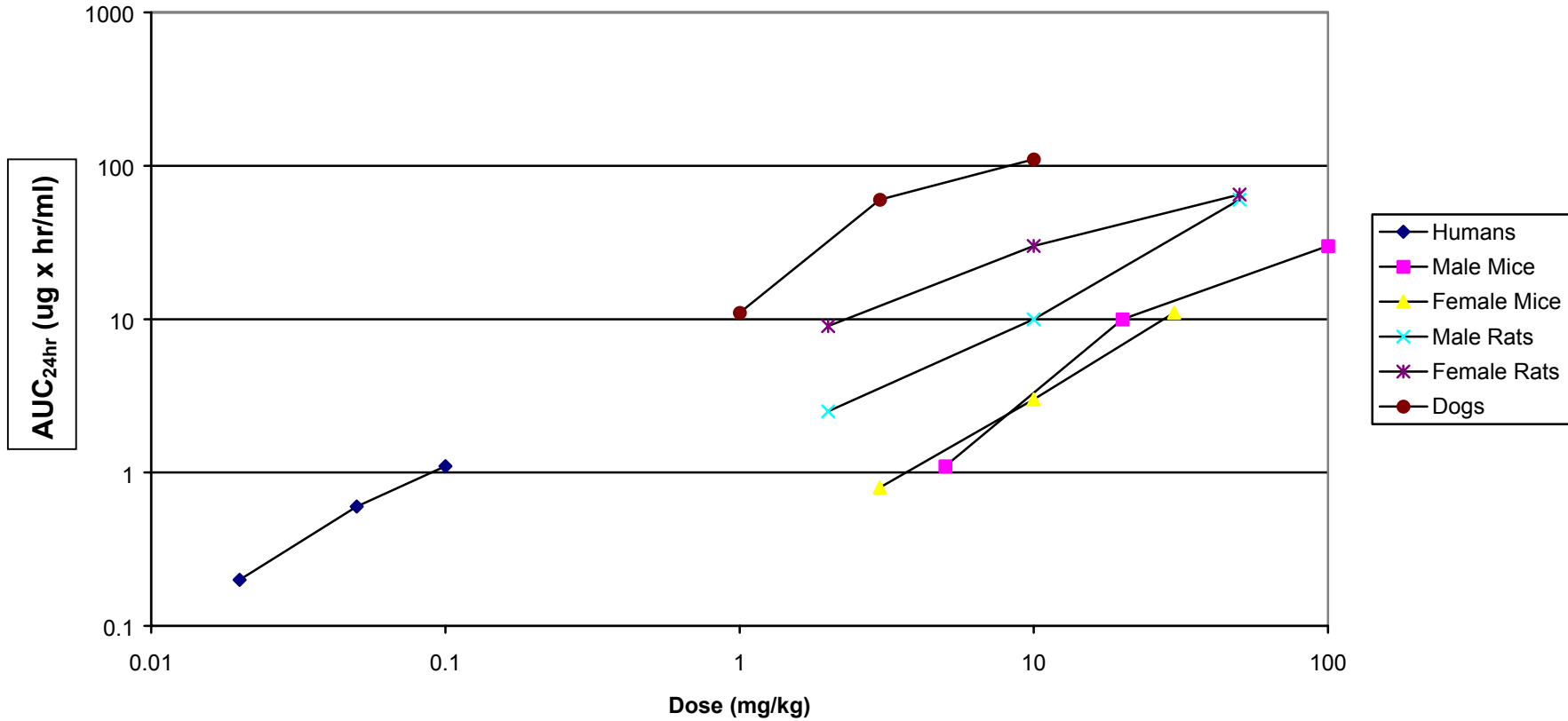
f - Protocol 147-007.

EXAMPLE

2.6.7.3 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
2.6.7.4 Toxicology

Drug Substance

Test Article: Curitol Sodium

Batch No.	Purity (%)	Specified Impurities^a			Study Number	Type of Study
		<u>A</u>	<u>B</u>	<u>C</u>		
<u>PROPOSED SPECIFICATION:</u>	<u>>95</u>	<u>≤ 0.1</u>	<u>≤ 0.2</u>	<u>≤ 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

2.6.7.5 Single-Dose Toxicity

Test Article: Curitol Sodium

<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>
CD-1 Mice	Gavage (Water)	0, 1000, 2000, 5000	10M 10F	≥5000 ≥5000	>5000	≥2000: Transient body-weight losses. 5000: Decreased activity, convulsions, collapse.	96046
	Intravenous (Saline)	0, 100, 250, 500	10M 10F	250 250	>250 <500	≥250: Body-weight losses. 500: 3M and 2F died.	96047
Wistar Rats	Gavage (CMC Suspension)	0, 1000, 2000, 5000	5M 5F	2000 ≥5000	>2000 <5000	≥2000: Transient body-weight losses; inactivity; chromorhinorrhea. 5000: 2M died.	96050
	Intravenous (5% Dextrose)	0, 100, 250, 500	5M 5F	250 ≥500	>250 <500	≥250: Body-weight losses in males. 500: 3M died.	96051

EXAMPLE

2.6.7.6 Repeat-Dose Toxicity

Non-Pivotal Studies

Test Article: Curitol Sodium

<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^a (mg/kg)</u>	<u>Noteworthy Findings</u>	<u>Study Number</u>
CD-1 Mice	Diet	3 Months	0, 62.5, 250, 1000, 4000, and 7000	10M, 10F	M:4000 F: 1000	≥4000: 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	≥2000: 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	≥500: Weight losses, inappetence.	94008

^a - No Observed Adverse-Effect Level.

EXAMPLE #1

2.6.7.7A 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 Section

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
Number of Animals								
Toxicokinetics: AUC (mcg-hr/ml):								
Day 1	-	-	30	28	130	125	328	302
Day 28	-	-	52	47	145	140	400	380
Day 90	-	-	50	51	160	148	511	475
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (% ^a)	394 g	244 g	0	-1	-10*	-11*	-25**	-45**
Food Consumption (% ^a)	20.4 g	17.2 g	0	-1	-1	-8*	-30**	-50**
Clinical Observations								
Hyperactivity	-	-	-	-	-	+	-	++
Chromorrhinorrhea, 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 is based on actual data (not on the percent differences).

(Continued)

EXAMPLE #1

2.6.7.7A 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
Number of Animals								
Hematology								
Hemoglobin (g/dl)	15.8	15.0	15.7	14.9	15.8	14.6	14.0*	13.1*
Erythrocyte Count (x10 ⁶ /mm ³)	8.1	-	7.9	-	8.1	-	7.4*	-
MCH	-	22	-	21	-	22	-	19*
MCHC	-	34	-	34	-	34	-	30*
Platelet Count (x10 ³ /mm ³)	846	799	825	814	914	856	931*	911*
Serum Chemistry								
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*	-
Urinalysis								
Protein Conc. (mg/dl)								
pH	260	49	102	34	123	54	126*	22*
Glucose (mg/dl)	7.5	-	7.5	-	7.2	-	6.3**	-
Urine Volume (ml)	-	0	-	0	-	20	-	98**
	-	18	-	18	-	16	-	12*

- No noteworthy findings.

Dunnett's Test: *- p<0.05

**- p<0.01

(Continued)

EXAMPLE #1

2.6.7.7A 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
Number of Animals								
Organ Weights^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**
Gross Pathology								
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
Histopathology								
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
Additional Examinations	-	-	-	-	-	-	-	-
Postdose Evaluation:								
Number Evaluated	10	10	0	0	0	0	10	10
Body Weight^a (%)	422 g	265 g	-1	-2	-3	-4	-10*	-20**
Kidney Weight^b (%)	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 is 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

2.6.7.7B Repeat-Dose Toxicity

Report Title: MM-180801: One-Month Oral Toxicity Study in Dogs

Test Article: Curitol Sodium

Species/Strain: Beagle Dogs

Duration of Dosing: 1 Month

Study No. 94020

Initial Age: 5-6 Months

Duration of Postdose: None

Location in CTD: Vol. 6 Section

Date of First Dose: 2 Feb 94

Method of Administration: Oral

Vehicle/Formulation: Gelatin Capsules

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
Number of Animals								
Toxicokinetics: AUC (mcg-hr/ml):								
Day 1	-	-	5	6	10	12	40	48
Day 28	-	-	4	5	8	11	35	45
Noteworthy Findings								
No. Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%^a)	9.8 kg	9.2 kg	0	0	-1	-19**	0	-18**
Clinical Observations:								
Hypoactivity (after dosing)	-	-	-	-	-	-	+	++
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Chemistry								
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 is based on actual data (not on the percent differences).

(Continued)

EXAMPLE #2

2.6.7.7B 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
Number of Animals								
Organ Weights^a (%)								
Liver	339 g	337 g	+1	-1	+17**	+16**	+23**	+21**
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology								
Number Examined	3	3	3	3	3	3	3	3
Liver: Centrilobular hypertrophy	0	0	0	0	0	0	2	3
Additional Examinations								
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

2.6.7.8A Genotoxicity: In Vitro

Report Title: MM-180801: Ames Reverse-Mutation Study in Salmonella and E. Coli

Test Article: Curitol Sodium

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 Section

Metabolizing System: Aroclor-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
		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 ^a	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
		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 ^a	31 ± 4	153 ± 5	9 ± 4	7 ± 1	17 ± 4
	2-Aminoanthracene	2.5	1552	1487	214	61	
		10					366

a - Precipitation.

EXAMPLE #2

2.6.7.8B 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 Section

Metabolizing System: Aroclor-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^a (% 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	5
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	6

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

a - Based on mitotic indices.

EXAMPLE #1

2.6.7.9A 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 Section

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

2.6.7.9B 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 Section

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

2.6.7.10 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 Section
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^a)	-	-	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 ^c	60	60	60	60	60
Died/Sacrificed Moribund	16	16	15	13	18	20	27	25
Terminal Sacrifice	44	44	44 ^c	47	42	40	33	35
Survival (%)	67	73	75	80	71	68	56	59
Body Weight (%^b)	33g	31g	0	0	-7*	0	-13**	-19**
Food consumption (%^b)	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 are shown. Statistical significance is based on actual data (not on the percent differences)

c - One missing mouse could not be evaluated.

(Continued)

EXAMPLE

2.6.7.10 Carcinogenicity

Study No. 95012 (Continued)

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

a - Trend analysis, p<0.005

b - Trend analysis, p<0.025

(Continued)

EXAMPLE

2.6.7.10 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
<u>Noteworthy Findings:</u>								
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology - Non-Neoplastic Lesions								
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

2.6.7.11 Reproductive and Developmental Toxicity

Non-Pivotal Studies

Test Article: Curitol Sodium

<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>
Wistar Rats	Gavage (Water)	G6 through G15	0, 500, 1000, 2000	8 Pregnant Females	≥1000: Deaths; weight losses; decreased food consumption; clinical signs; resorptions.	94201
NZW Rabbits	Gavage (CMC Suspension)	13 Days	0, 5, 15, 45	6 Nonpregnant Females	≥15: Decreased weight gain and food consumption. 45: Four does died.	97020

G – Gestation day

EXAMPLE

2.6.7.12 Reproductive and Developmental Toxicity-Report Title: MM-180801: Oral Study of Effects on Fertility and Early Embryonic Development in Rats **Test Article:** Curitol Sodium
Fertility and Early Embryonic Development to Implantation

Design similar to ICH 4.1.1? Yes
Species/Strain: Wistar Rats
Initial Age: 10 Weeks

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 Section

Date of First Dose: 3 Mar 97
Special Features: None
No Observed Adverse-Effect Level:
F₀ Males: 100 mg/kg
F₀ Females: 100 mg/kg
F₁ Litters: 1000 mg/kg

Day of Mating: Day 0
Day of C-Section: Day 16 of gestation
Method of Administration: Gavage
Vehicle/Formulation: Aqueous solution.

GLP Compliance: Yes

<u>Daily Dose (mg/kg)</u>	<u>0 (Control)</u>	<u>10</u>	<u>100</u>	<u>1000</u>
Males Toxicokinetics: AUC ^b (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 (% ^a)	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 is based on actual data (not on the percent differences).

b - From Study No. 94220.

(Continued)

EXAMPLE

2.6.7.12 Reproductive and Developmental Toxicity

Study No. 97072 (Continued)

<u>Daily Dose (mg/kg)</u>	<u>0 (Control)</u>	<u>10</u>	<u>100</u>	<u>1000</u>
Females Toxicokinetics: AUC ^b (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 (% ^a)	175 g	0	0	-5*
Gestation Body Weight (% ^a)	225 g	0	0	-12**
Premating Food Consumption (% ^a)	14 g	0	0	-6*
Gestation Food Consumption (% ^a)	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 pre mating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b - From Study No. 94220.

EXAMPLE

2.6.7.13 Reproductive and Developmental Toxicity - Report Title: MM-180801: Oral Study of Effects on Embryo-Fetal Development

Test Article: Curitol Sodium

Design similar to ICH 4.1.3? Yes

Duration of Dosing: G6-G18

Study No. 97028

Species/Strain: NZW Rabbits

Day of Mating: Day 0

Location in CTD: Vol. 6 Section

Initial Age: 5 months

Day of C-Section: G29

Date of First Dose: 7 Aug 97

Method of Administration: Gavage

Special Features: None.

Vehicle/Formulation: Aqueous Solution

GLP Compliance: Yes

No Observed Adverse-Effect Level:

F₀ Females: 1 mg/kg

F₁ Litters: 5 mg/kg

<u>Daily Dose (mg/kg)</u>	<u>0 (Control)</u>	<u>1</u>	<u>5</u>	<u>25</u>
<u>Dams/Does:</u> Toxicokinetics: AUC ^b (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 (% ^a)	3.2 kg	0	-15*	-20**
Food Consumption (% ^a)	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 is based on actual data (not on the percent differences).

b - From Study No. 97231.

(Continued)

EXAMPLE

2.6.7.13 Reproductive and Developmental Toxicity

Study No. 97028 (Continued)

<u>Daily Dose (mg/kg)</u>	<u>0 (Control)</u>	<u>1</u>	<u>5</u>	<u>25</u>
<u>Litters:</u>	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
Fetal Anomalies:				
Gross External				
Lower jaw: Short				
No. Fetuses (%)	0	0	0	7 (8.0)*
No. Litters (%)	0	0	0	5 (27.8)**
Visceral Anomalies				
Tongue: Absent				
No. Fetuses (%)	0	0	0	6 (6.9)*
No. Litters (%)	0	0	0	6 (33.3)**
Skeletal Anomalies				
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)
Total Affected Fetuses (Litters)	2 (2)	1 (1)	0	15 (10)

- No noteworthy findings.

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

EXAMPLE

2.6.7.14 Reproductive and Developmental Toxicity - Report Title: MM-180801: Oral Study of Effects on Effects on Pre- and Postnatal Development, Including Maternal Function **Test Article:** Curitol Sodium
 Pre- and Postnatal Development in Rats

Design similar to ICH 4.1.2? Yes **Duration of Dosing:** G6 - L21 **Study No.** 95201
Species/Strain: Wistar Rats **Method of Administration:** Gavage **Day of Mating:** Day 0
Initial Age: 9-10 Weeks **Vehicle/Formulation:** Water **Location in CTD:** Vol. 10 Section
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:
F₀ Females: 7.5 mg/kg
F₁ Males: 75 mg/kg
F₁ 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>F₀ Females:</u> Toxicokinetics: AUC ^b (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 (% ^a)	225 g	0	0	-25**
Lactation Body Weight (% ^a)	210 g	0	0	0
Gestation Food Consumption (% ^a)	15 g	0	0	-12*
Lactation Food Consumption (% ^a)	16 g	0	0	0
Mean Duration of Gestation (days)	22.1	22.2	22.1	23.5 ⁺
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 is based on actual data (not on the percent differences).

b - From Study No. 97227.

(Continued)

EXAMPLE

2.6.7.14 Reproductive and Developmental 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>F₁ Litters:</u> (Preweaning)	No. Litters Evaluated	23	21	22	15
	Mean No. Pups/Litter	13.6	13.8	14.9	11.2 ⁺⁺
	Mean No. Liveborn Pups/Litter	13.5	13.8	14.6	9.4 ⁺⁺
	Mean No. Stillborn Pups/Litter	0.1	0.0	0.3	1.8 ⁺
	Postnatal Survival to Day 4	-	-	-	-
	Postnatal Survival to Weaning	-	-	-	-
	Change in Pup Body Weights ^a (g)	60	58	62	53 [*]
	Pup Sex Ratios (% males)	51	53	49	51
	Pup Clinical Signs	-	-	-	-
	Pup Necropsy Obs.	-	-	-	-
<u>F₁ Males:</u> (Postweaning)	No. Evaluated Postweaning	23	21	22	15
	No. Died or Sacrificed Moribund	-	-	-	-
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Change ^b (g)	200	195	195	186 [*]
	Food Consumption (% ^b)	15 g	0	0	-11 [*]
	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 is based on actual data (not on the percent differences).

(Continued)

EXAMPLE

2.6.7.14 Reproductive and Developmental 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>F₁ 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 ^a (g)	226	230	235	196*
Gestation Body-Weight Change (g)	153	160	144	158
Premating Food Consumption (% ^b)	15 g	0	0	-13*
Gestation Food Consumption (% ^b)	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>F₂ 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 is based on actual data (not on the percent differences).

(Continued)

EXAMPLE

2.6.7.17 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>
Antigenicity						
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
Impurities						
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
