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

ICH HARMONISED TRIPARTITE GUIDELINE

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: SAFETY – M4S(R2)

NONCLINICAL OVERVIEW AND NONCLINICAL SUMMARIES OF MODULE 2 ORGANISATION OF MODULE 4

Current *Step 4* version
dated 20 December 2002

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

M4S(R2)
Document History

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Current *Step 4* version

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In order to facilitate the implementation of the M4S guideline, the ICH Experts have developed a series of Q&As which can be downloaded from the ICH web site: http://www.ich.org

M4S Questions & Answers History

M4S Q&As	Approval by the Steering Committee.	24 May 2001	M4S Q&As
M4S Q&As	Approval by the Steering Committee of the newly added questions.	12 September 2002	M4S Q&As (R1)
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THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:

SAFETY

NONCLINICAL OVERVIEW AND NONCLINICAL SUMMARIES OF MODULE 2

ORGANISATION OF MODULE 4

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 9 November 2000, this guideline is recommended for adoption to the three regulatory parties to ICH
(Numbering and Section Headers have been edited for consistency and use in e-CTD as agreed at the Washington DC Meeting, September 11-12, 2002)

(This document includes the typographic correction on page 46 : to read point 2.6.7.3, agreed by the Steering Committee on 20 December 2002).

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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, Cmax, 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 Pharmacokinetcs
- 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

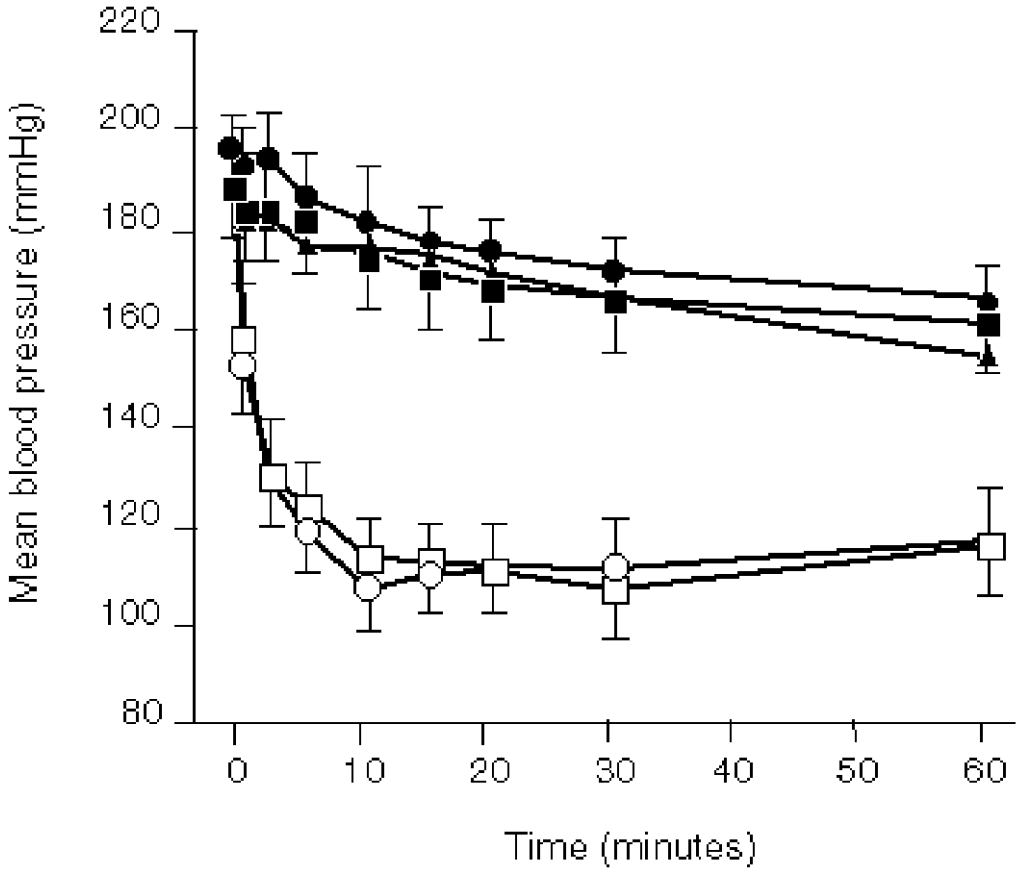
Binding of X and its Major Metabolites and Comparators to Human X_2 and X_3 Receptors

Compound	X_2 K_i1(nM)	X_2 K_i2(nM)	X_3 K_i1(nM)	X_3 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]



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

[a]SHR= spontaneous hypertensive rat (n=5 per group)

Table X

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

Parameter (units)	**Parameter value**					
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 [^{14}C]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 [^{14}C]X at 1.75 mg/kg [refs]

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

* - ng of X free base equivalent/g.
N= 5 animals/time point
ND - Not detected

Table X

Excretion of radioactive material following single doses of [^{14}C]X to male rats [refs]

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

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

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.

- AUC_{0-6} in the mouse, AUC_{0-t} in the rat and in the dog and dose normalised $AUC_{0-\tau}$ 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]

	Dose Groups			
Lesion	**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)

Type of Study	Test System	Method of Administration	Testing Facility	Study Number*(4)*	Location Vol.	Location Section
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)*

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses[a] (mg/kg)	Gender and No. per Group	Noteworthy Findings	*GLP* Compliance	Study Number*(3)*

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)*

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol. (3)	Location Section
Absorption *(2)*						
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 ^{14}C-labeled compound.
(3) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
(4) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included.

2.6.5.4 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:

	Concentration (unit)					
Tissues/organs	**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				
	conc.	T/P[1)]	conc.	T/P[1)]	Time	AUC	$t_{1/2?}$

Additional information:

[1)] **[Tissue]/[Plasma]**

2.6.5.6 Pharmacokinetics: Plasma Protein Binding **Test Article:**

Study system:
Target entity, Test system and method:

Species	Conc. tested	% Bound	Study No.	Location in CTD Vol.	Location in CTD Section

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:

Notes for Table 2.6.5.7

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

2.6.5.8 Pharmacokinetics: Other Distribution Study

Test Article:

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:

				% of Compound in Sample				Location in CTD	
Species	**Sample**	**Sampling Time or Period**	**% of Dose in Sample**	**Parent**	**M1**	**M2**	**Study No.**	**Vol**	**Section**
	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)***	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**
Time												
0 - T hr												

Study number
Location in CTD

Additional Information: ***(2)***

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

2.6.5.14 Pharmacokinetics: Excretion into Bile ***Test Article:***

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

2.6.5.15 Pharmacokinetics: Drug-Drug Interactions

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

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.5.16 Pharmacokinetics: Other

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

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.7.1 Toxicology **Overview** **Test Article:** ***(1)***

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg[a])	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
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)***

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Study Number	Location Vol.	Location Section
(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.

2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** ***(1)***

(2)

Notes: (1) International Nonproprietary Name (INN).
(2) A one- to three-page summary (tables and/or figures) of steady-state toxicokinetic data should be prepared in a format that facilitates comparisons across species, including humans.

2.6.7.4 Toxicology **Drug Substance** **Test Article:** ***(1)***

Batch No.	**Purity (%)**	**Specified Impurities ( )**	**Study Number**	**Type of Study**
PROPOSED SPECIFICATION:				
(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)*

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

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)*

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	NOAEL[a] (mg/kg)	Noteworthy Findings	Study Number

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: **Duration of Dosing:** **Study No.**
Initial Age: **Duration of Postdose:** **Location in CTD:** Vol. Section
Date of First Dose: **Method of Administration:**
Vehicle/Formulation: **GLP Compliance:**

Special Features:
No Observed Adverse-Effect Level:

Daily Dose (mg/kg)	0 (Control)							
Number of Animals	M:	F:	M:	F:	M:	F:	M:	F:
Toxicokinetics: AUC ( ) *(4)*	*(5)*							
Noteworthy Findings								
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)							
Number of Animals	M:	F:	M:	F:	M:	F:	M:	F:
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.

Notes for Table 2.6.7.7

(1) The tables should be numbered consecutively: 2.6.7.7A, 2.6.7.7B, 2.6.7.7C etc.

(2) There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.

(3) International Nonproprietary Name (INN).

(4) Steady-state AUC, Cmax, Css, 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: **No. of Independent Assays:** **Study No.**
Strains: **No. of Replicate Cultures:** **Location in CTD:** Vol. Section
Metabolizing System: **No. of Cells Analyzed/Culture:**
Vehicles: **For Test Article:** **For Positive Controls:** **GLP Compliance:**
Treatment: **Date of Treatment:**
Cytotoxic Effects:
Genotoxic Effects:

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:

Test Article	Dose (mg/kg)	No. of Animals	_____	_____	_____	_____

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: **Duration of Dosing:** **Study No.**
Initial Age: **Method of Administration:** **Location in CTD:** Vol. Section
Date of First Dose: **Vehicle/Formulation:**
Treatment of Controls: **GLP Compliance:**

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

Daily Dose (mg/kg)	0 (Control)							
Gender	M	F	M	F	M	F	M	F
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)	(Control)		0 (Control)							
Number Evaluated	M:	F:	M:	F:	M:	F:	M:	F:	M:	F:
Number of Animals with Neoplastic Lesions: *(7)*										
Noteworthy Findings:										
Gross Pathology										
Histopathology - Non-Neoplastic Lesions										

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

Notes for Table 2.6.7.10.

(1) Tables should be numbered consecutively: 2.6.7.10A, 2.6.7.10B, , etc. There should be one table for each carcinogenicity study.

(2) International Nonproprietary Name (INN).

(3) From ICH Guideline S1C.

(4) Steady-state AUC, Cmax, Css, 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)*

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

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? **Duration of Dosing:** M: **Study No.**
Species/Strain: **Day of Mating:** ***(8)*** F: **Location in CTD:** Vol. Section
Initial Age: **Day of C-Section:**
Date of First Dose: **Method of Administration:** **GLP Compliance:**
Special Features: **Vehicle/Formulation:**
No Observed Adverse-Effect Level:
F_0 Males:
F_0 Females:
F_1 Litters:

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. Evaluated	
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 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).

Notes for Tables 2.6.7.12, 2.6.7.13 and 2.6.7.14

(1) If there are multiple studies of this type, the tables should be numbered consecutively: 2.6.7.12A, 2.6.7.12B, 2.6.7.13A, 2.6.7.13B, etc.

(2) International Nonproprietary Name (INN).

(3) If a modified study design is used, tables should be modified accordingly.

(4) Steady-state AUC, Cmax, 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:

Day of Mating: ***(8)***

Study No.

Species/Strain:

Day of C-Section:

Location in CTD: Vol. Section

Initial Age:

Method of Administration:

Date of First Dose:

Vehicle/Formulation:

GLP Compliance:

Special Features:

No Observed Adverse-Effect Level:

F_0 Females:

F_1 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 - Effects on Pre- and Postnatal Development, Including Maternal Function *(3)*

Report Title:

Test Article: *(2)*

Design similar to ICH 4.1.2?

Duration of Dosing:
Day of Mating: ***(8)***

Study No.

Species/Strain:
Initial Age
Date of First Dose:
Special Features:

Method of Administration:
Vehicle/Formulation:
Litters Culled/Not Culled:

Location in CTD: Vol. Section

GLP Compliance:

No Observed Adverse-Effect Level:
F_0 Females:
F_1 Males:
F_1 Females:

Daily Dose (mg/kg)	**0 (Control)**
F_0 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)**
F_1 Litters: (Preweaning)	No. Litters Evaluated	
	Mean No. of Implantations	
	Mean No. Pups/Litter	
	Mean No. Liveborn Pups/Litter	
	No. of Litters with Stillborn Pups	
	Postnatal Survival to Day 4	
	Postnatal Survival to Weaning	
	No. of Total Litter Losses	
	Change in Pup Body Weights[a] (g)	
	Pup Sex Ratios	
	Pup Clinical Signs	
	Pup Necropsy Obs.	
F_1 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)**
F_1 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	
F_2 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)**
F_1 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.*
F_2 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)*

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

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)*

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

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

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Section
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 ICR mice African Green monkeys	Nasogastric Intubation	Sponsor Inc.	95420	1	
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

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses[a] (mg/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
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

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Section
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	**Mouse**	**Rat**	**Dog**	**Monkey**	**Human**
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, ^{14}C

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: ^{14}C
Specific Activity: $2x10^5$ Bq/mg
Sampling time: 0.25, 0.5, 2, 6, 24, 96, and 192 hr

	Concentration (mcg/mL)					
Tissues/organs	**0.25**	**0.5**	**2**	**6**	**24**	**$t_{1/2}$**
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

Species	Conc. tested	% Bound	Study No.	Location in CTD Vol.	Section
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, ^{14}C
Assay: LSC

Time (hr)	**14 days/30 min**	**14 days/24 hr**	**19 days/30 min**	**19 days/24 hr**
Concentration / Amount (% of dose)				
Maternal plasma	12.4	0.32	13.9	0.32
Placenta	3.8	0.14	3.3	0.32
Amniotic fluid	0.07	0.04	0.04	0.13
Whole fetus	0.54	0.03	0.39	0.10

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

Location in CTD: Vol. 22 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, ^{14}C
Assay: LSC

Time [hr]	**1**	**2**	**4**	**6**	**8**	**24**
Concentration:						
Milk:	0.6	0.8	1.0	1.1	1.3	0.4
Plasma:	1.5	1.4	1.2	0.8	0.6	0.1
Milk / plasma:	0.40	0.57	0.83	1.4	2.2	4.0
Neonates						

Additional Information:

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: ^{14}C
Specific Activity: 2 x 10^5 Bq/mg

				% of Compound in Sample				Location in CTD	
Species	**Sample**	**Sampling Time or Period**	**% of Dose in Sample**	**Parent**	**M1**	**M2**	**Study Number**	**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	Rat			Rat			Dog			Dog		
Gender (M/F) / Number of animals	4M			4M			3M			3M		
Feeding condition	Fasted			Fasted			Fasted			Fasted		
Vehicle/Formulation	Solution Water			Solution Saline			Capsule			Solution 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	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**
Time												
0 - 24 hr	26	57	83	22	63	85	20	29	49	23	42	65
0 - 48 hr	30	65	95	27	69	96	25	65	90	28	78	96
0 - 72 hr	31	65	97	28	70	98	26	73	99	29	72	101
0 - 96 hr	31	67	98	29	70	99	26	74	100	29	73	102

Study number	95102	95156
Location in CTD	Volume 20, Section	Volume 20, Section

Additional Information:

a - Total radioactivity; percent recovery, ^{14}C

EXAMPLE

2.6.5.14 Pharmacokinetics: Excretion into Bile **Test Article:** Curitol Sodium

Species	**Rat**			**Rat**		
Gender (M/F) / Number of animals	4M			4M		
Feeding condition	Fasted			Fasted		
Vehicle/Formulation	Solution Water			Solution Saline		
Method of Administration	Oral			Intravenous		
Dose (mg/kg)	10			5		
Analyte	TRA[a]			TRA[a]		
Assay	LSC			LSC		
Excretion route	**Bile**	**Urine**	**Total**	**Bile**	**Urine**	**Total**
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, ^{14}C

EXAMPLE

2.6.7.1 Toxicology **Overview** **Test Article:** Curitol Sodium

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

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

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
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

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Study Number	Location Vol.	Location Section
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

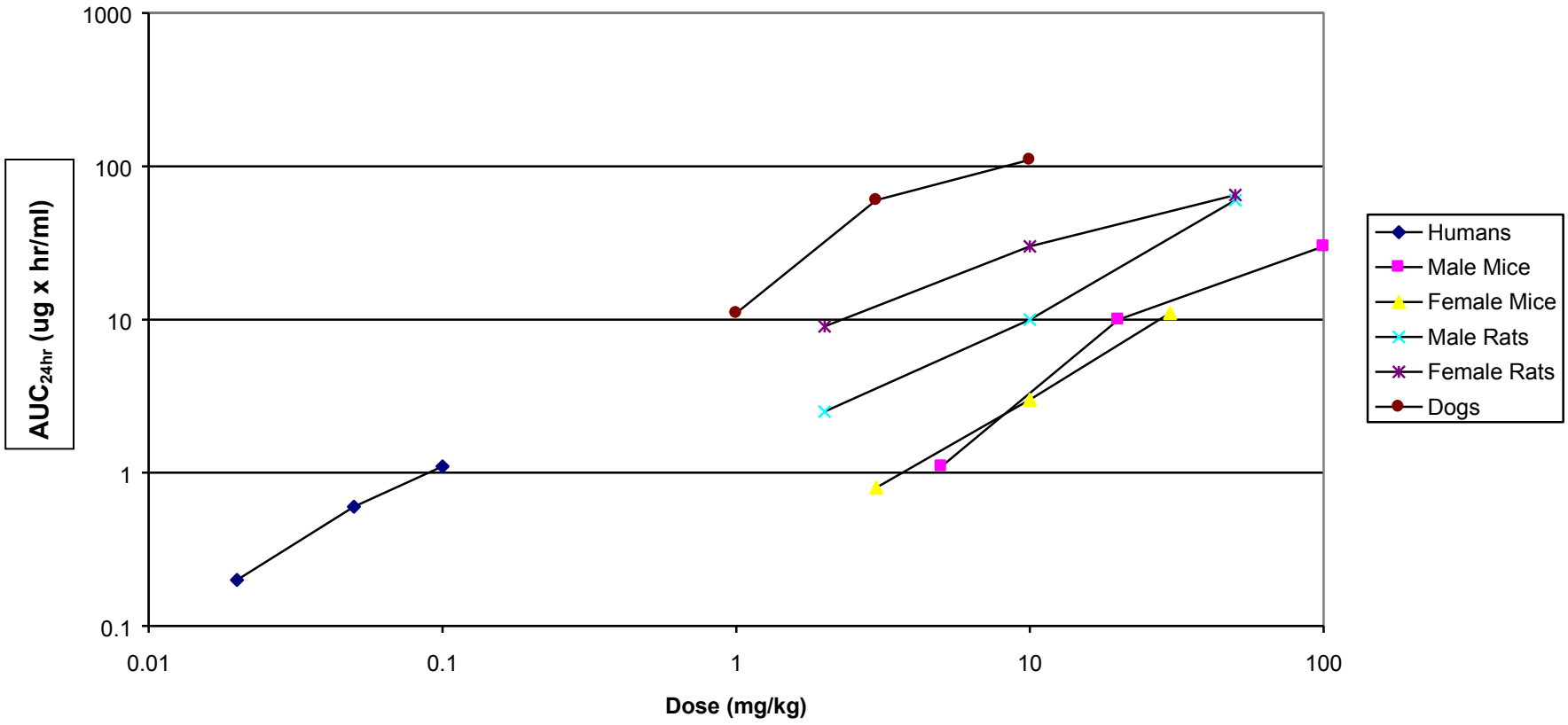
2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** Curitol Sodium

	Steady-State AUC (mcg-hr/ml)						
Daily Dose	**Mice**[a]		**Rats**[b]			**Female**	
(mg/kg)	**M**	**F**	**M**	**F**	**Dogs**[c]	**Rabbits**[b]	**Humans**[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
		A	B	C		
PROPOSED SPECIFICATION:	>95	≤ 0.1	≤ 0.2	≤ 0.3	-	-
LN125	98.2	0.1	0.1	0.2	94007	Two-Week Oral Range-Finding Study in Rats
					94008	Five-Day Oral Range-Finding Study in Monkeys
					96718	Ames Test
94NA103	99.1	0.2	0.1	0.2	96046	Single-Dose Oral Study in Mice
					96050	Single-Dose Oral Study in Rats
					94214	Three-Month Oral Study in Rats
					94020	One-Month Oral Study in Dogs
					97634	Human Lymphocytes Assay In Vitro
95NA215	97.3	0.1	0.3	0.1	96047	Single-Dose Intravenous Study in Mice
					96051	Single-Dose Intravenous Study in Rats
					96037	Micronucleus Test in Rats
					94211	Embryo-Fetal Development Study in Rats
					97028	Embryo-Fetal Development Study in Rabbits
95NB003	94.6	0.2	0.3	0.4	94019	Two-Week Palatability Study in Rats
					97012	Antigenicity Study in Hamsters
96NB101	99.0	0.4	0.1	0.0	94018	Three-Month Dietary Range-Finding Study in Mice
					95001	Six-Month Oral Study in Rats
					95002	One-Year Oral Study in Dogs
					95012	Dietary Carcinogenicity Study in Mice
					95013	Oral Carcinogenicity Study in Rats
					96208	Fertility and Early Embryonic Development Study in Rats
					95015	Dermal Irritation Study in Rabbits

a - Area percent.

EXAMPLE

2.6.7.5 Single-Dose Toxicity **Test Article:** Curitol Sodium

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

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	NOAEL[a] (mg/kg)	Noteworthy Findings	Study Number
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	
Number of Animals	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
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	-	-	-	-	-	+	-	++
Chromorhinorrhea, reddish-stained coat, white feces	-	-	-	-	-	-	++	++
Emaciated, piloerection, stilted gait	-	-	-	-	-	-	-	++
Ophthalmoscopy	-	-	-	-	-	-	-	-

- No noteworthy findings. + Mild ++ Moderate +++ Marked
Dunnett's Test: *- p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance 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	
Number of Animals	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
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)	260	49	102	34	123	54	126*	22*
pH	7.5	-	7.5	-	7.2	-	6.3**	-
Glucose (mg/dl)	-	0	-	0	-	20	-	98**
Urine Volume (ml)	-	18	-	18	-	16	-	12*

- No noteworthy findings.
Dunnett's Test: *- p<0.05 **- p<0.01

(Continued)

EXAMPLE #1

2.6.7.7A Repeat-Dose Toxicity **Study No. 94214 (Continued)**

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
Number of Animals	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
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
Initial Age: 5-6 Months
Date of First Dose: 2 Feb 94

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

Study No. 94020
Location in CTD: Vol. 6, Section

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	
Number of Animals	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
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	
Number of Animals	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
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
	MM-180801	312.5	24 ± 6	128 ± 11	12 ± 4	4 ± 2	14 ± 2
		625	32 ± 9	153 ± 9	9 ± 2	8 ± 2	17 ± 5
		1250	30 ± 4	152 ± 12	9 ± 3	9 ± 2	18 ± 4
		2500	27 ± 5	140 ± 6	9 ± 3	5 ± 1	19 ± 1
		5000[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
	MM-180801	312.5	31 ± 4	142 ± 8	12 ± 5	4 ± 2	17 ± 3
		625	30 ± 1	156 ± 15	17 ± 2	9 ± 5	23 3
		1250	33 ± 2	153 ± 13	13 ± 3	8 ± 2	18 ± 3
		2500	35 ± 8	160 ± 4	10 ± 2	8 ± 2	19 ± 5
		5000[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.

Metabolic Activation	Test Article	Concentration (mcg/ml)	Cytotoxicity[a] (% of control)	Aberrant Cells Mean %	Abs/Cell	*Total polyploid cells*
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.

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

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.

Test Article	Dose (mg/kg)	No. of Animals	Mean % PCEs (±SD)	Mean % MN-PCEs (±SD)
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

Test Article	Dose (mg/kg)	No. of Animals	Time hr	Nuclear Mean ± SD	Cytoplasm Mean ± SD	NG Mean ± SD	% IR Mean ± SD	NGIR Mean ± SD
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	
Gender	M	F	M	F	M	F	M	F
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)	0 (Control)		25		100		400	
Number Evaluated	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	
Number Evaluated	M: 60	F: 60	M: 59	F: 60	M: 60	F: 60	M: 60	F: 60
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
Noteworthy Findings:								
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

Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Dosing Period**	**Doses mg/kg**	**No. per Group**	**Noteworthy Findings**	**Study Number**
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 - Fertility and Early Embryonic Development to Implantation

Report Title: MM-180801: Oral Study of Effects on Fertility and Early Embryonic Development in Rats

Test Article: Curitol Sodium

Design similar to ICH 4.1.1? Yes
Species/Strain: Wistar Rats
Initial Age: 10 Weeks
Day of Mating: Day 0
Date of First Dose: 3 Mar 97
Special Features: None
No Observed Adverse-Effect Level:
F_0 Males: 100 mg/kg
F_0 Females: 100 mg/kg
F_1 Litters: 1000 mg/kg

Duration of Dosing: M: 4 weeks prior to mating
F: 2 weeks prior to mating, through day 7 of gestation
Day of C-Section: Day 16 of gestation
Method of Administration: Gavage
Vehicle/Formulation: Aqueous solution.

Study No. 97072
Location in CTD: Vol. 6, Section

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	10	100	1000
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)**

Daily Dose (mg/kg)	**0 (Control)**	**10**	**100**	**1000**
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 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).
b - From Study No. 94220.

EXAMPLE

2.6.7.13 Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development

Report Title: MM-180801: Oral Study of Effects on Embryo-Fetal Development in Rabbits

Test Article: Curitol Sodium

Design similar to ICH 4.1.3? Yes

Duration of Dosing: G6-G18

Study No. 97028

Day of Mating: Day 0

Species/Strain: NZW Rabbits

Day of C-Section: G29

Location in CTD: Vol. 6, Section

Initial Age: 5 months

Method of Administration: Gavage

Date of First Dose: 7 Aug 97

Vehicle/Formulation: Aqueous Solution

GLP Compliance: Yes

Special Features: None.

No Observed Adverse-Effect Level:

F_0 Females: 1 mg/kg

F_1 Litters: 5 mg/kg

Daily Dose (mg/kg)	0 (Control)	1	5	25
Dams/Does: 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)**

Daily Dose (mg/kg)		**0 (Control)**	**1**	**5**	**25**
Litters:	No. Litters Evaluated	18	16	17	18
	No. Live Fetuses	140	126	148	86*
	Mean No. Resorptions	0.2	0.3	0.4	4.7**
	No. Dead Fetuses	1	0	0	0
	Mean % Postimplantation Loss	4.3	2.8	5.4	49.0**
	Mean Fetal Body Weight (g)	44.82	42.44	42.14	42.39
	Fetal Sex Ratios (% males)	46.3	57.7	57.4	52.8
	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 - Effects on Pre- and Postnatal Development, Including Maternal Function

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

Test Article: Curitol Sodium

Design similar to ICH 4.1.2? Yes

Duration of Dosing: G6 - L21
Day of Mating: Day 0

Study No. 95201

Species/Strain: Wistar Rats
Initial Age: 9-10 Weeks
Date of First Dose: 8 Oct 95
Special Features: None

Method of Administration: Gavage
Vehicle/Formulation: Water
Litters Culled/Not Culled: Culled to 4/sex/litter

Location in CTD: Vol. 10, Section

GLP Compliance: Yes

No Observed Adverse-Effect Level:
- **F_0 Females:** 7.5 mg/kg
- **F_1 Males:** 75 mg/kg
- **F_1 Females:** 75 mg/kg

Daily Dose (mg/kg)		0 (Control)	7.5	75	750
F_0 Females:	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)**

Daily Dose (mg/kg)		0 (Control)	7.5	75	750
F_1 Litters: (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.	-	-	-	-
F_1 Males: (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)

Daily Dose (mg/kg)		0 (Control)	7.5	75	750
F_1 Females: (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
F_2 Litters:	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)

2.6.7.17 Other Toxicity Studies **Test Article:** Curitol Sodium

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