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

M4: COMMON TECHNICAL DOCUMENT

MODULES IIA, IIB NONCLINICAL
MODULE III, QUALITY
MODULES IV, NONCLINICAL
MODULE V, EFFICACY

8 NOVEMBER 1999

Preamble: The ICH Common Technical Document for the Registration of Pharmaceuticals for Human Use

Background

The ICH process has achieved significant harmonisation of the technical requirements for the registration of pharmaceuticals for human use in the three ICH regions. However, the regulatory submission documentation had not been examined, and there are currently significantly different requirements in each region for the composition and organisation of the registration documents. The ICH M4 topic, The Common Technical Document, addresses this issue. Three Expert Working Groups for Quality, Safety and Efficacy are developing guidelines for the Common Technical Document.

The ICH Steering Committee is controlling the work on this topic by the use of milestones to reflect the stages of completion that this work is moving through, and wish to ensure that this process is transparent. As part of this transparency it is considered important that as these milestones are achieved the document be disseminated widely for consultation. The document is hence being published for consultation as scientific consensus of the ICH parties on the component parts is reached, with these documents providing the framework and basis for the development of the final complete Guideline on the Common Technical Document.

Objective

The ICH M4 guideline will describe an acceptable format and content for a Common Technical Document suitable for submission to the Regulatory Authorities in the three ICH regions once supplemented with regional administration particulars.

Organisation of the Common Technical Document

The Common Technical Document represents the common part of any submission, presented in a modular fashion, with summaries and tables as appropriate (see also Diagram 1). One of the modules will not form part of the Common Technical Document, but is regional.

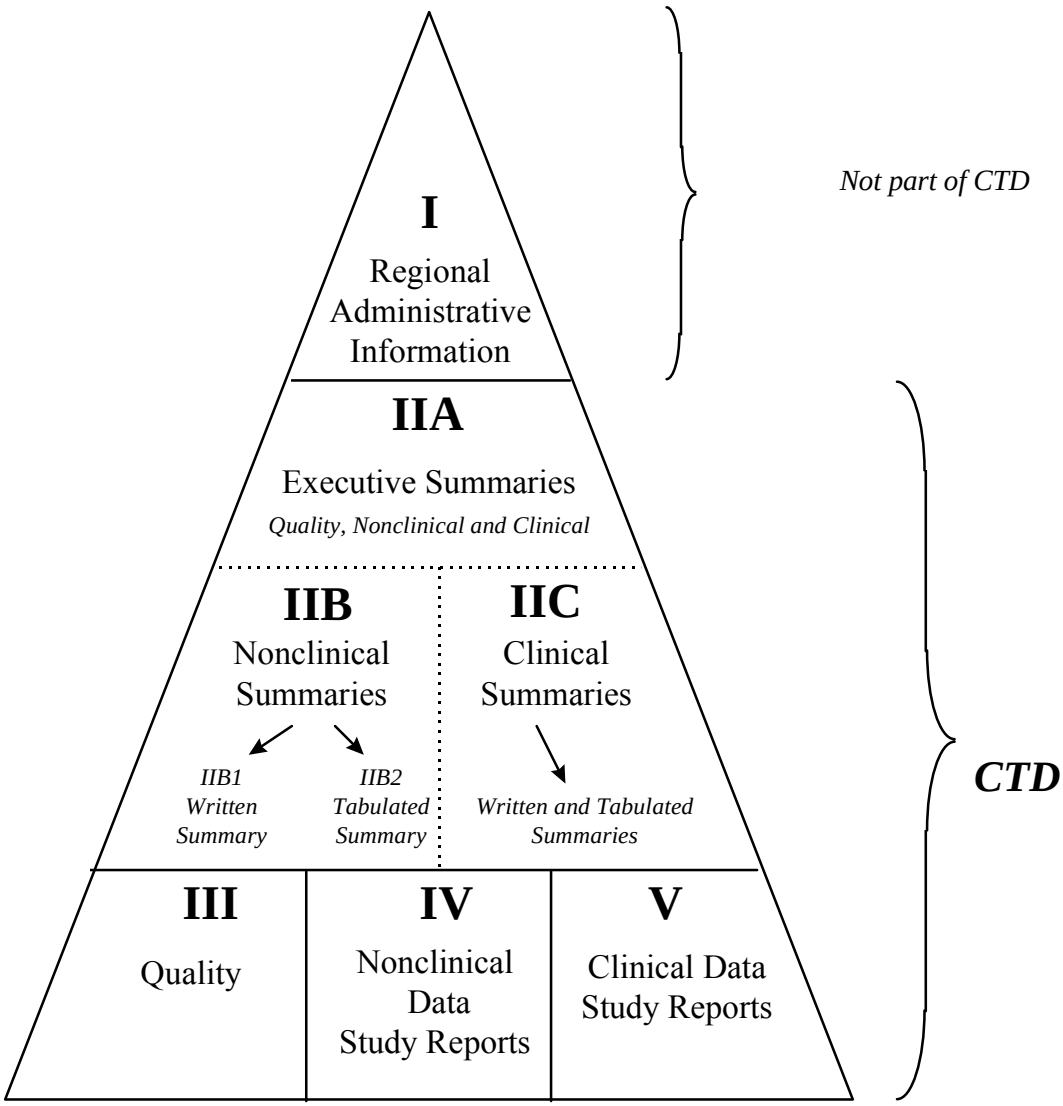
The Common Technical Document modular structure is as follows:

Module I	Regional Administrative Information	*(not part of Common Technical Document)*
Module II	IIA Executive Summaries	Quality (pending) Nonclinical (provided) Clinical (pending)
	IIB Nonclinical Summaries	IIB1 Written Summary (provided) IIB2 Tabulated Summary (provided)
	IIC Clinical Summaries, comprising written and tabulated summaries (pending)	
Module III	Quality	(provided - 9 attachments pending)
Module IV	Nonclinical Data Study Reports	(provided)
Module V	Clinical Data Study Reports	(provided)

The document published herein details the Tables of Contents for Modules III, IV and V accompanied by explanatory notes. Module III will be further supplemented by a series of nine detailed attachments, which it is intended will be made available in July 2000. (It should be noted that the exact content of Module III may evolve as the EWG's discussions progress). Modules IIA Clinical and Quality and IIC should also be released for consultation in July 2000, whereas Module IIA/B Nonclinical is also contained within this document.

The ICH Steering Committee and Expert Working Groups are requesting comments on the portions of the guideline contained in this document, which represent the scientific consensus of the Expert Working Groups, and have been approved by the ICH Steering Committee for release for further consultation. Once all the sections of the Guidelines for the Common Technical Document are available a compiled text will be released to complete Step 2 of the ICH process. It is anticipated that this will occur in July 2000.

Diagram 1: Diagrammatic Representation of the ICH Common Technical Document



MODULES IIA and IIB – NONCLINICAL

Guideline on the Nonclinical Executive Summary (Module IIA) and Nonclinical Summaries (Module IIB) in Module II of The Common Technical Document (CTD)

October 7, 1999

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

General Principles

Throughout the Common Technical Document, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. The overall organisation of summaries and tables should follow a logical order, reflecting the sequential pathway of drug development.

Text and tables should be prepared using margins that allow the document to be printed on either A4 paper (EU and Japan) or 8.5 x 11" paper (US). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying.

Guideline on the Nonclinical Executive Summary (Module IIA) of The Common Technical Document (CTD)

October 7, 1999

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

General Aspects

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

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

Relevant scientific literature should be taken into account in this Executive Summary. The list of references should be stated in accordance with internationally accepted standards or the system used in Chemical Abstracts. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification which 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 Executive Summary should contain appropriate cross-references to the relevant Written summaries, Tabular summaries, and Study Reports.

Content and Structural Format

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

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature citations

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

The assessment of the pharmacokinetic and metabolism data should consider the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It may 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 of the animal studies for prediction of potential adverse effects in humans highlighted.

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

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

The evaluation of toxicologic 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 validity should be discussed.

The Integrated Overview and Conclusions should clearly define the beneficial and advantageous aspects 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 pharmacologic, pharmacokinetic, and toxicologic results and the properties of related products into account, recommendations should be made for the product label.

Guideline on the Nonclinical Written and Tabulated Summaries (Module IIB) of The Common Technical Document (CTD)

October 7, 1999

Nonclinical Written Summaries

1. Introduction

This guideline is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format.

The sequence and content of the Nonclinical Written Summary sections are described below. It must be emphasised that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, authors should deviate from the guideline when necessary to facilitate a logical presentation of the information.

Whenever appropriate, information should be summarized across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses. Whenever appropriate, age- and gender-related effects should be discussed.

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. Applicants are encouraged to modify the format as needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

2. General Presentation Issues

2.1 Order of Presentation of Information Within Sections

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

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

Species should be ordered as follows:

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

Routes of administration should be ordered as follows:

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

Suggested order of dose groups as follows:

1. Untreated control
2. Vehicle control
3. Low dose
4. Middle dose(s)
5. High dose
6. Positive or comparative controls

2.2 Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them may 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 Annex A.

In order to allow authors' flexibility in defining the optimal structure for the Written Summaries, tables and figures can either be included within the text or be grouped together at the end of each of the nonclinical summaries.

The scope, format, and content of the Nonclinical Tabulated Summaries recommended to be included in applications are given below. The Tabulated Summaries should be placed together after all of the Written Summaries.

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

2.3 Length of Nonclinical Written Summaries

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

2.4 Relationship Between the Nonclinical Written Summaries and Other Sections of the Application

It is important that authors consider the overall structure of the application when writing Nonclinical Written Summaries.

The primary purpose of the summaries is to provide a comprehensive narrative review of the nonclinical studies. The level of detail should be less than that in the study report summaries. The clinical relevance of the findings, cross-linking with chemistry/pharmacy, and discussion relating to the proposed prescribing information are primarily addressed in the Nonclinical Executive Summary.

Where appropriate (e.g., to indicate the rationale for performing or omitting a particular study), the Nonclinical Written Summaries may cross-refer to data contained in other sections of the application.

2.5 Sequence of Written Summaries

The sequence for the Nonclinical Written Summaries generally follows the following organisation.

1. Introduction
2. Written Summary of Pharmacology
3. Written Summary of Pharmacokinetics
4. Written Summary of Toxicology

Guideline for preparing each of these sections follows.

3. Content of Nonclinical Written Summary

3.1 Introduction

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

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

3.2 The Pharmacology Written Summary

Within the Pharmacology Written Summary, the data are 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)

Guideline on the content of each of these sections is given below.

3.2.1 Brief Summary

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

3.2.2 Primary Pharmacodynamics

Studies on pharmacodynamic properties of a substance and its mode of action related to the proposed therapeutic indication should be summarised and evaluated. Where possible, it is helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

Relevant findings with stereoisomers and/or metabolites should be summarised, as appropriate.

3.2.3 Secondary Pharmacodynamics

Studies on the pharmacodynamic properties of a substance other than those related to the proposed therapeutic indication are defined as secondary pharmacodynamic studies. These are sometimes referred to as general pharmacology studies. The studies should be summarised by organ system, where appropriate, and evaluated in this section.

Relevant findings with stereoisomers and/or metabolites should be summarised, as appropriate.

3.2.4 Safety Pharmacology

Safety pharmacology studies are designed to assess undesirable pharmacodynamic effects of drugs on specific physiological systems. In some cases, secondary pharmacodynamic studies may 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. These studies should be summarised and evaluated in this section.

3.2.5 Pharmacodynamic Drug Interactions

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

3.2.6 Discussion and Conclusions

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

3.2.7 Tables and Figures (Annex A)

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

3.3 The Pharmacokinetics Written Summary

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

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

Guidance on the content of each of these sections is given below.

3.3.1 Brief Summary

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

3.3.2 Methods of Analysis

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

3.3.3 Kinetics (of parent drug and/or metabolite(s))

There is no set structure for this section, but the data could be summarised under the following subsections:

Pharmacokinetics After a Single Dose:

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

Pharmacokinetics after Repeated Administration:

- Plasma/serum and urine concentrations (data from multiple-dose studies)
- Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies)
- Excretion (routes and extent of excretion)

3.3.4 Tissue Distribution

The following data should be summarised in this section:

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

3.3.5 Metabolism (inter-species comparison)

The following data are summarised in this section:

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

3.3.6 Pharmacokinetic Drug Interactions

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

3.3.7 Other Pharmacokinetic Studies

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

3.3.8 Discussion and Conclusions

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

3.3.9 Tables and Figures (Annex A)

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

3.4 The Toxicology Written Summary

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

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

Each major section should conclude with a synthesis of the findings. Guidance on the content of each of these sections is given below.

3.4.1 Brief Summary

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

Study type and duration	Route of administration	Species	Compound (if parent drug and metabolite(s) investigated)
Single-dose toxicity	po and iv	Rat and mouse	Parent and metabolite X
Repeat-dose toxicity			
1 month	po	Rat and dog	Parent compound
6 months	po	Rat	" "
9 months, etc.	po	Dog	" "

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

3.4.2 Single-Dose Toxicity

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

3.4.3 Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)

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

3.4.4 Genotoxicity

Studies should be briefly summarised in the following order.

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

3.4.5 Carcinogenicity (including supportive toxicokinetics evaluations)

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

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

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

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

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

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

3.4.7 Local Tolerance

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

3.4.8 Other Toxicity Studies (if available)

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

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Metabolites
- Impurities
- Other

3.4.9 Discussion and Conclusions

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

3.5 Tables and Figures (Annex A)

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.

ANNEX A

3.6 Examples of Tables and Figures for Written Summaries

The following tables and figures 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

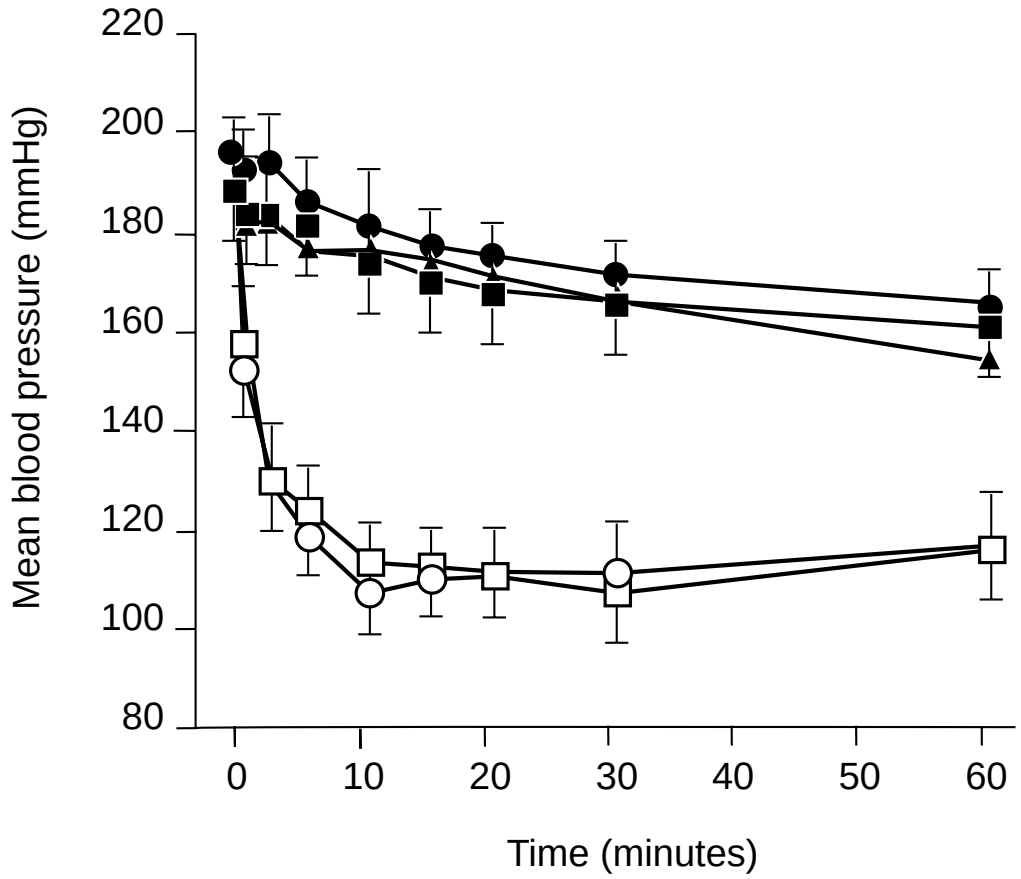
Binding of X and its Major Metabolites and Comparators to Human X_2, and X_3 Receptors [ref]

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 F1# and F2##).**D**D

Figure X

Blood pressure following chronic dosing with X to anaesthetised SHR[a][ref]



Blood pressure following chronic dosing with X to anaesthetised SHR[a][ref]. Hypotensive effect of saline i.v. infusion over 5 min (▲) compared to X, 3 mg/kg i.v. infusion to anaesthetised SHR pretreated twice daily with saline, 1 mL/kg p.o., for 7 (❍) or 14 (❒) days or X, 25 mg/kg p.o., for 7 (●) or 14 (■) days. Saline pretreated statistical significances: $p<0.05$, all other points after challenge $p<0.01$. Values represent mean ± s.e.m.
[a]SHR= spontaneous hypertensive rat (n=5 per group)

Table X

üModel-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

üüüTable X

üIncidence 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

Nonclinical Tabulated Summaries

Summary tables for the nonclinical information in the Common Technical Document should be provided in the format outlined in this Guideline.

This Guideline is not intended to indicate what studies are requested, but solely instructs how to describe study results if the study was performed. Applicants may need to add or delete some items to or from the cited format where appropriate. One tabular format may contain results from several studies. Alternatively, the data resulting from one study may have to be cited in several tabular formats. Flexibility on where tabulated information is included can be retained. Applicants should decide the best presentation of their data.

The formats for the tables in the Nonclinical Tabulated Summaries are provided in two sections, which follow. The first section contains Templates to be used 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.) The second section 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 will ensure that a sufficient level of detail is available to the reviewer and will provide concise overviews of related information.

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

Tabulated Nonclinical Summaries - Templates

I. Pharmacology

1. Pharmacology

1.3 Safety Pharmacology

II. Pharmacokinetics

2A Pharmacokinetics

2.1.1 Pharmacokinetics: Absorption after a Single Dose

2.1.2 Pharmacokinetics: Absorption after Repeated Doses

2.2.1 Pharmacokinetics: Cumulative Excretion

2.2.2 Pharmacokinetics: Excretion into Bile

2.3.1 Pharmacokinetics: Organ Distribution

2.3.2 Pharmacokinetics: Plasma Protein Binding

2.3.3 Pharmacokinetics: Study in Pregnant or Nursing Animals

2.3.4 Pharmacokinetics: Other Distribution Study

2.4.1 Pharmacokinetics: Metabolism *In Vivo*

2.4.2 Pharmacokinetics: Metabolism *In Vitro*

2.4.3 Pharmacokinetics: Possible Metabolic Pathways

2.4.4 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes

2.4.5 Pharmacokinetics: Drug-Drug Interactions

2.5 Pharmacokinetics: Other

2B Toxicokinetics: Overview of Toxicokinetics Studies

2C Toxicokinetics: Overview of Toxicokinetics Data

III. Toxicology

3A Toxicology: Overview

3B Toxicology: Drug Substance

3.1 Single-Dose Toxicity

3.2A Repeat-Dose Toxicity: Non-Pivotal Studies

3.2 Repeat-Dose Toxicity

3.3.1 Genotoxicity *In Vitro*

3.3.2 Genotoxicity *In Vivo*

3.4 Carcinogenicity

3.5 Reproduction Toxicity: Non-Pivotal Studies

3.5.1 Reproduction Toxicity – Fertility and Early Embryonic Development to Implantation

3.5.2 Reproduction Toxicity – Effects on Embryo-Fetal Development

3.5.3 Reproduction Toxicity – Effects on Pre- and Postnatal Development, Including Maternal Function

3.6 Local Tolerance

3.7 Other Toxicity Studies

1 Pharmacology **Overview** **Test Article**: *(1)*

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

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

1.3 Safety Pharmacology*(1)* **Test Article:** *(2)*

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

2A Pharmacokinetics **Overview** **Test Article:** *(1)*

Type of Study	Test System	Method of Administration	Study Number	Location Vol.	Location Page
2.1 Kinetics ***(2)***				*(3)*	
2.2 Tissue Distribution					
2.3 Metabolism					
2.4 Pharmacokinetic Drug Interactions					

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

2.1.1 Pharmacokinetics: Absorption after a Single Dose Test Article: *(1)*

Species	_____	_____	_____	_____	_____
Gender (M/F) / Number of animals	***(4)***				
Feeding condition					
Vehicle/Formulation					
Method of Administration					
Dose (mg/kg)					
Sample (Whole blood, plasma, serum etc.)					
Analyte					
Assay *(2)*					
PK parameters:					
Study number					
Location in CTD					
Additional Information: *(3)*					

Notes: *(1) International Nonproprietary Name (INN).*
(2) For example, HPLC, LSC with ^{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.

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

2.2.1 Pharmacokinetics: Cumulative 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.

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

Format A

2.3.1 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. Page
Study No.

Species:
Gender (M/F)/Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Radionuclide:
Specific Activity:
Sampling time:

	Concentration					
Tissues/organs	**T(1)**	**T(2)**	**T(3)**	**T(4)**	**T(5)**	**$t_{1/2}$?**

Additional information:

Alternate Format B

2.3.1 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. Page
Study No.

Species:
Gender (M/F) / Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Radionuclide:
Specific Activity:
Sampling time:

	C_t		Last time-point				
Tissues/organs	**conc.**	**T/P[1)]**	**conc.**	**T/P[1)]**	**Time**	**AUC**	**$t_{1/2?}$**

Additional information:

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

2.3.2 Pharmacokinetics: Plasma Protein Binding Test Article:

Study system:
Target entity, Test system and method:

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

Additional Information:

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

Test Article: *(2)*

Location in CTD: Vol. Page

Placental transfer

Study No.

Species:
Gestation day / Number of animals:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Analyte:
Assay:

Time (hr)					
Concentration / Amount (% of dose)					
Dam *(3)*:					
Fetus *(3)*:					

Additional Information:

Location in CTD: Vol. Page

Excretion into milk

Study No.

Species:
Lactating date / Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Analyte:
Assay:

Time [hr]					
Concentration:					
Milk:					
Plasma:					
Milk / plasma:					
Neonates:					

Additional Information:

Notes for Table 2.3.3

(1) Even if the data are obtained in reproduction toxicology studies, they should be presented in this table.

(2) International Nonproprietary Name (INN).

(3) The tissue sampled should be described; e.g., plasma for dams, fetal concentrations.

2.3.4 Pharmacokinetics: Other Distribution Study

Test Article:

Gender(M/F) / Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Radionuclide:
Specific Activity:

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

Additional Information:

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

2.4.2 Pharmacokinetics: Metabolism *In Vitro*

Test Article:

Location in CTD: Vol. Page
Study No.

Study system:

Time	_____	_____	_____	_____	_____
Concentration:					
Compounds					
Parent					
M-1					
M-2					

Additional Information:

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

2.4.3 Pharmacokinetics: Possible Metabolic Pathways

Test Article:

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

2.4.4 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes

Test Article:

Location in CTD: Vol. Page
Study No.

Note: Nonclinical studies only.

Type of study:

Method:

Tabulated results:

Additional Information:

2.4.5 Pharmacokinetics: Drug-Drug Interactions

Test Article:

Location in CTD: Vol. Page
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2.5 Pharmacokinetics: Other

Test Article:

Location in CTD: Vol. Page
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2B 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.	Page
(2)						*(3)*	

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

(2)

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

3A 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. Page
3.1 Single-Dose Toxicity	*(2)*							*(3)*
3.2 Repeat-Dose Toxicity								
3.3 Genotoxicity								
3.4 Carcinogenicity								
3.5 Reproduction Toxicity								
3.6 Local Tolerance								
3.7 Other Toxicity Studies								

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

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

3B 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.

3.1 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	Testing Facility	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).

3.2A 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	Testing Facility	Study Number

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

(2) International Nonproprietary Name (INN).

_____

a - No Observed Adverse-Effect Level.

3.2 *(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. Page
Date of First Dose: **Method of Administration:** **Testing Facility:**
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 should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).

(Continued)

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[b]	*(11)*							
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 should indicate percent difference for the absolute organ weights.

b - Meets or exceeds Guideline of: CPMP*(9)* Japan*(10)*

Notes for Table 3.2

(1) The tables should be numbered consecutively: 3.2B, 3.2C, 3.2D etc.

(2) There should be one table for each of the repeat-dose toxicity studies required 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, 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 showed drug-related 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) CPMP Note for Guidance on Repeat Dose Toxicity Testing.

(10) Notification No. 24 of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, September 11, 1989, Section [2] Repeated Dose Toxicity Study.

(11) When appropriate, information on animals that were necropsied early should be presented separately.

3.3.1 *(1)* Genotoxicity In Vitro **Report Title:** **Test Article:** *(2)*

Test for Induction of: **No. of Independent Assays:** **Study No.**
Strains: **No. of Replicate Cultures:** **Location in CTD:** Vol. Page
Metabolizing System: **No. of Cells Analyzed/Culture:** **Testing Facility:**
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: 3.3.1A, 3.3.1B, etc. Results of replicate assays should be shown on subsequent pages.*
(2) International Nonproprietary Name (INN).
(3) Units should be inserted.
(4) If precipitation is observed, this should be inserted in a footnote.
(5) Methods of statistical analyses should be indicated.

(5) * - $p<0.05$ ** - $p<0.01$

3.3.2 *(1)* Genotoxicity In Vivo **Report Title:** **Test Article:** *(2)*

Test for Induction of:
Species/Strain:
Age:
Cells Evaluated:
No. of Cells Analyzed/Animal:
Special Features:
Toxic/Cytotoxic Effects:
Genotoxic Effects:
Evidence of Exposure:

Treatment Schedule:
Sampling Time:
Method of Administration:
Vehicle/Formulation:

Study No.
Location in CTD: Vol. Page
Testing Facility:
GLP Compliance:
Date of Dosing:

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

Notes: *(1) The tables should be numbered consecutively: 3.3.2A, 3.3.2B, etc.*
(2) International Nonproprietary Name (INN).
(3) Methods of statistical analysis should be indicated.

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

3.4 *(1)*Carcinogenicity **Report Title:** **Test Article:** *(2)*

Species/Strain: **Duration of Dosing:** **Study No.**
Initial Age: **Method of Administration:** **Location in CTD:** Vol. Page
Date of First Dose: **Vehicle/Formulation:** **Testing Facility:**
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 (%)								
Body Weight (%[a])	*(5)*							
Food Consumption (%[a])								

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

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

(Continued)

3.4 *(1)* Carcinogenicity **Study No. (Continued)**

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

\- No noteworthy findings.
* - p<0.05 ** - p<0.01
a - Meets or exceeds Guidelines of: CPMP *(8)* Japan *(9)*

(a) Notes for Table 3.4

(1) Tables should be numbered consecutively: 3.4A, 3.4B, etc. There should be one table for each carcinogenicity study.

(2) International Nonproprietary Name (INN).

(3) From ICH Guideline S1C.

(4) Steady-state AUC, 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.

(8) CPMP Note for Guidance on Carcinogenicity Testing [currently being revised].

(9) Notification No. 24 of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, September 11, 1989. Section [5] Carcinogenicity Test Study, Note 11.

3.5 Reproduction 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	Testing Facility	Study Number

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

(2) International Nonproprietary Name (INN).

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

Report Title:

Test Article: *(2)*

Design similar to ICH 4.1.1?
Species/Strain:
Initial Age:
Date of First Dose:
Special Features:
No Observed Adverse-Effect Level:
F_0 Males:
F_0 Females:
F_1 Litters:

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

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

Daily Dose (mg/kg)	**0 (Control)**
Males Toxicokinetics: AUC ( ) *(4)*	
No. Evaluated	
No. Died or Sacrificed Moribund	
Clinical Observations	
Necropsy Observations	
Body Weight (%[a])	
Food Consumption (%[a])	
Mean No. Days Prior to Mating	
No. of Males that Mated	
No. of Fertile Males	*(5)*

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

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

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

(Continued)

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

Notes for Tables 3.5.1, 3.5.2, and 3.5.3

(1) If there are multiple studies of this type, the tables should be numbered consecutively: 3.5.1A, 3.5.1B, 3.5.2A, 3.5.2B, 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

3.5.2 ***(1)*** **Reproduction 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:
Initial Age:
Date of First Dose:
Special Features:
No Observed Adverse-Effect Level:
F_0 Females:
F_1 Litters:

Day of C-Section:
Method of Administration:
Vehicle/Formulation:

Location in CTD: Vol. Page
Testing Facility:
GLP Compliance:

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

(Continued)

Daily Dose (mg/kg)	**0 (Control)**
Litters: No. Litters Evaluated	
No. Live Fetuses	
Mean No. Resorptions	
No. of Litters with Dead Fetuses	
Mean % Postimplantation Loss	
Mean Fetal Body Weight (g)	
Fetal Sex Ratios	
Fetal Anomalies:	
Gross External	
Visceral Anomalies	
Skeletal Anomalies	
Total Affected Fetuses (Litters)	

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

3.5.3 ***(1)*** **Reproduction Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function** ***(3)*** **Report Title:** **Test Article:** *(2)*

Design similar to ICH 4.1.2? **Duration of Dosing:** **Study No.**
Day of Mating: ***(8)***
Species/Strain: **Method of Administration:** **Location in CTD:** Vol. Page
Initial Age **Vehicle/Formulation:** **Testing Facility:**
Date of First Dose: **Litters Culled/Not Culled:** **GLP Compliance:**
Special Features:
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 should be shown. For treated groups, percent differences from controls should be shown. Statistical significance should be based on actual data (not on the percent differences).
(Continued)

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 - During postweaning period.

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

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 birth to mating.

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

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	*Note: Alternate*
	Motor Activity	*Format for*
	Learning and Memory	*Natural Parturition.*
	Mean No. Days Prior to Mating	
	No. of Females Sperm-Positive	
	No. of Pregnant Females	
	Mean Duration of Gestation	
	Abnormal 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 should be shown. For treated groups, percent differences from controls should be shown. Statistical significance based on actual data (not on the percent differences).

3.6 Local Tolerance *(1)* **Test Article:** *(2)*

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

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

3.7 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	Testing Facility	Study Number

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

Module IIB (Nonclinical): Common Technical Document Summaries

Tabulated Nonclinical Summaries

EXAMPLES

EXAMPLE

1 Pharmacology **Overview** **Test Article:** Curitol Sodium

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

a - Report contains a GLP Compliance Statement.

1.3 Safety Pharmacology **Test Article:** Curitol Sodium

Species/ Strain	Method of Admin.	Organ Systems Evaluated	Doses[a] (mg/kg)	Gender and No. per Group	Noteworthy Findings	Testing Facility	Study Number
CD-1 Mice	Gavage	CNS	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.	Sponsor Inc.	92201
CD-1 Mice	Gavage	Renal, GI, CNS, and Hemostasis	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.	Sponsor Inc.	92205
Mongrel Dogs	Intravenous	Cardiovascular	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.	Sponsor Inc.	92210

a - Single dose unless specified otherwise.

2A Pharmacokinetics **Overview** **Test Article:** Curitol Sodium

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

a - Report contains a GLP Compliance Statement.

EXAMPLE

2.1.1 Pharmacokinetics: Absorption after a Single Dose

Test Article: **Curitol Sodium**

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)

Study number 95104

Location in CTD Volume 1, Page 258

Additional Information:

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

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

a - Total radioactivity

EXAMPLE

2.2.1 Pharmacokinetics: Cumulative 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, Page 75	Volume 20, Page 150

Additional Information:

a - Total radioactivity; percent recovery.

2.2.2 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			Solution		
	Water			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, Page 150

a - Total radioactivity; percent recovery.

EXAMPLE

Format A

2.3.1 Pharmacokinetics: Organ Distribution

Test Article: **Curitol Sodium**

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

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

	Concentration					
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.

Alternate Format B

2.3.1 Pharmacokinetics: Organ Distribution

Test Article: **Curitol Sodium**

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

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

Tissues/organs	C_t		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]**

2.3.2 Pharmacokinetics: Plasma Protein Binding Test Article: **Curitol Sodium**

Study system: In vitro
Target entity, Test system and method: Ultrafiltration

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

Additional Information:

2.3.3 Pharmacokinetics: Study in Pregnant or Nursing Animals

Test Article: **Curitol Sodium**

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

Placental transfer
Species: Rat
Gestation day / Number of animals: 14 and 19 days gestation/3 animals at each time point
Vehicle/Formulation: Solution/Water
Method of Administration: Oral gavage
Dose (mg/kg): 5
Analyte: Total radioactivity
Assay: LSC

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

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

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

Excretion into milk
Species: Rat
Lactating date / Number of animals: day 7/3
Feeding condition: Fed
Vehicle/Formulation: Solution/Water
Method of Administration: Oral gavage
Dose (mg/kg): 5
Analyte: Total radioactivity
Assay: LSC

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

Additional Information:

2.4.1 Pharmacokinetics: Metabolism *In Vivo* **Test Article: Curitol Sodium**

Gender (M/F) / Number of animals: **Rats:** 4M **Dogs:** 3F **Humans:** 8M
Feeding condition: Fed
EXAMPLE
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.	Page
Rats	Plasma	0.5 hr	-	87.2	6.1	3.4	95076	26	101
	Urine	0-24 hr	2.1	0.6	n.d.	0.2			
	Bile	0-4 hr	28.0	15.5	7.2	5.1			
	Feces	-	-	-	-	-			
Dogs	Plasma	0.5 hr	-	92.8	n.d.	7.2	95082	26	301
	Urine	0-24 hr	6.6	6.4	n.d.	n.d.			
	Bile	0-4 hr	32.0	28.5	2.8	n.d.			
	Feces	-	-	-	-	-			
Humans	Plasma	1 hr	-	87.5	trace	12.5	CD-102	42	1
	Urine	0-24 hr	5.5	2.4	2.9	n.d.			
	Bile	-	-	-	-	-			
	Feces	-	-	-	-	-			

Additional Information

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

2B 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 Page
Three-month range-finding study	Mice	Diet	62.5, 250, 1000, 4000, 7000	Yes	94018	2	1
Two-week toxicity study	Rats	Gavage	500, 1000, 2000	No	94007	3	200
Six-month toxicity study	Rats	Gavage	100, 300, 900	Yes	95001	5	1
One-month toxicity study	Dogs	Capsules	10, 40, 100	Yes	94020	6	1
Nine-month toxicity study	Dogs	Capsules	5, 20, 50	Yes	96041	7	1
Carcinogenicity study	Mice	Diet	25, 100, 400	Yes	95012	10	1
Carcinogenicity study	Rats	Gavage	25, 100, 400	Yes	95013	12	1
Toxicokinetics study	Rabbits	Gavage	1, 5, 25	No	97231	16	1

2C 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

2C 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

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

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

Continued)

3A 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.	Location Page
3.4 Carcinogenicity	CD-1 Mice	Diet	21 Months	0, 0, 25, 100, 400	Yes	CRO Co.	95012	10	1
	Wsitar Rats	Gavage	24 Months	0, 0, 25, 100, 400	Yes	Sponsor Inc.	95013	12	1
3.5 Reproduction Toxicity	Wistar Rats	Gavage	a	0, 5, 30, 180	Yes	CRO Co.	96208	14	1
	Wisar Rats	Gavage	F: G6 - G15[b]	0, 10, 100, 1000	Yes	Sponsor Inc.	94211	15	1
	NZW Rabbits	Gavage	F: G6 - G18[b]	0, 1, 5, 25	Yes	CRO Co.	97028	16	1
	Wistar Rats	Gavage	F: G6 - L21[b]	0, 7.5, 75, 750	Yes	Sponsor Inc.	95201	17	1
3.6 Local Tolerance	NZW Rabbits	Dermal	1 Hour	0, 15 mg	No	Sponsor Inc.	95015	18	1
3.7 Other Toxicity Studies									
3.7.1 Antigenicity	Guinea Pigs	Subcutaneous	Weekly for 3 weeks	0, 5 mg	No	CRO Co.	97012	18	20
3.7.2 Impurities	Wistar Rats	Gavage	2 Weeks	0, 1000, 2000	Yes	Sponsor Inc.	97025	18	200

_____

a - Males: 4 weeks prior to mating. Females - 2 weeks prior to mating through Gestation Day 7.
b - G = Gestation Day L = Lactation Day

3B Toxicology **Batches Used** **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	Study of Embryo-Fetal Development in Rats
					97028	Study of Embryo-Fetal Development 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	Study of Fertility and Early Embryonic Development in Rats
					95015	Dermal Irritation in Rabbits

a - Area percent.

3.1 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	Testing Facility	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.	Sponsor Inc.	96046
	Intravenous (Saline)	0, 100, 250, 500	10M 10F	250 250	>250 <500	—250: Body-weight losses. 500: 3M and 2F died.	CRO Co.	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.	Sponsor Inc.	96050
	Intravenous (5% Dextrose)	0, 100, 250, 500	5M 5F	250 —500	>250 <500	—250: Body-weight losses in males. 500: 3M died.	CRO Co.	96051

EXAMPLE

3.2A 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	Testing Facility	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.	CRO Co.	94018
Wistar Rats	Diet	2 Weeks	0, 1000, 2000, and 4000	5M, 5F	1000	—2000: Lower body weights. 4000: 2M and 1F sacrificed moribund.	Sponsor Inc.	94019
	Gavage (Water)	2 Weeks	0, 500, 1000, and 2000	5M, 5F	1000	2000: Lower body weights; single-cell necrosis in liver.	Sponsor Inc.	94007
Beagle Dogs	Gavage (CMC Suspension)	5 Days	0, 500, and 1000	1M, 1F	<500	—500: Weight losses, inappetence.	Sponsor Inc.	94008

a - No Observed Adverse-Effect Level.

3.2B Repeat-Dose Toxicity **Report Title:** MM-180801: Three-Month Oral Toxicity Study in Rats **Test Article:** Curitol Sodium

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

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

Study No. 94214
Location in CTD: Vol. 4 Page 1
Testing Facility: Sponsor Inc.
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 based on actual data (not on the percent differences).

(Continued)

3.2B 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	15.8	15.0	15.7	14.9	15.8	14.6	14.0*	13.1*
Erythrocyte Count	8.1	-	7.9	-	8.1	-	7.4*	-
MCH	-	22	-	21	-	22	-	19*
MCHC	-	34	-	34	-	34	-	30*
Platelet Count	846	799	825	814	914	856	931*	911*
Serum Chemistry								
Creatinine	0.7	0.7	0.7	0.7	0.7	0.7	1.1*	1.1*
Proteins	-	6.7	-	6.6	-	6.6	-	5.0***
Cholesterol	96	-	86	-	90	-	105*	-
ALT	67	56	60*	52	55*	47*	53*	58
AST	88	92	96	90	87*	84*	85*	93
Bilirubin	0.18	0.20	0.17	0.20	0.18	0.20	0.22**	0.26**
Calcium	-	10.7	-	10.8	-	10.8	-	9.8**
Phosphorus	9.3	-	9.3	-	9.3	-	8.2*	-
Urinalysis								
Protein Conc.	260	49	102	34	123	54	126*	22*
pH	7.5	-	7.5	-	7.2	-	6.3**	-
Glucose	-	0	-	0	-	20	-	98**
Urine Volume	-	18	-	18	-	16	-	12*

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

(Continued)

3.2B 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[c]								
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 period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

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

c - Meets or exceeds Guideline of: EEC? Yes Japan? Yes

3.2C Repeat-Dose Toxicity **Report Title:** MM-180801: One-Month Oral Toxicity Study in Dogs **Test Article:** Curitol Sodium

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

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

Study No. 94020
Location in CTD: Vol. 6 Page 1
Testing Facility: Sponsor Inc.
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: Week 2	22	25	24	27	21	24	48*	69**
Week 4	25	27	26	25	23	25	54*	84**

- No noteworthy findings. + Mild ++ Moderate +++ Marked
Dunnett's Test: * - p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

(Continued)

3.2C 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[b]								
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.

b - Meets or exceeds Guidelines of: EEC? Yes Japan? Yes

3.3.1A 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 Page 211
Metabolizing System: Arochlor-induced rat liver S9**,** 7.1% **No. of Cells Analyzed/Culture:** - **Testing Facility:** Sponsor Inc.
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.

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

Test for Induction of: Chromosome aberrations **No. of Independent Assays:** 1 **Study No.** 96668
Strains: Primary human lymphocytes **No. of Replicate Cultures:** 2 **Location in CTD:** Vol. 10 Page 245
Metabolizing System: Arochlor-induced rat liver S9**,** 5% **No. of Cells Analyzed/Culture:** 100 **Testing Facility:** CRO Co.
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.

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

Test for Induction of: Bone-marrow micronuclei
Species/Strain: Wistar Rats
Age: 5 Weeks
Cells Evaluated: Polychromatic erythrocytes
No. of Cells Analyzed/Animal: 2000
Special Features: None.

Treatment Schedule: Three daily doses.
Sampling Time: 24 hr after last dose.
Method of Administration: Gavage.
Vehicle/Formulation: Aqueous solution.

Study No: 96683
Location in CTD: Vol. 10 Page 502
Testing Facility: Sponsor Inc.
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: * - $p<0.05$ ** - $p<0.01$

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

Test for Induction of: Unscheduled DNA synthesis
Species/Strain: Wistar Rats
Age: 5 Weeks
Cells Evaluated: Hepatocytes.
No. of Cells Analyzed/Animal: 100
Special Features: None.
Toxic/Cytotoxic Effects: None.
Genotoxic Effects: None.
Evidence of Exposure: Toxicokinetics - See Study No. 94007, Two-Week Oral Toxicity Study in Rats.

Treatment Schedule: Single dose.
Sampling Time: 2 and 16 hr.
Method of Administration: Gavage.
Vehicle/Formulation: Aqueous solution.

Study No: 51970
Location in CTD: Vol. 11 Page 2
Testing Facility: CRO Co.
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.

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

Species/Strain: CD-1 Mice
Initial Age: 6 Weeks
Date of First Dose: 20 Sep 95
Duration of Dosing: 21 months
Method of Administration: Diet
Vehicle/Formulation: In Diet
Treatment of Controls: Drug-Free Diet
Study No. 95012
Location in CTD: Vol. 4 Page 1
Testing Facility: CRO Co.
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. Statistical significance based on actual data (not on the percent differences)
c - One missing mouse could not be evaluated.

(Continued)

3.4A 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)

3.4A 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[a] - 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
a - Meets or exceeds Guidelines of: EEC? Yes Japan? Yes

EXAMPLE

3.5 Reproduction 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	Testing Facility	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.	Sponsor Inc.	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.	Sponsor Inc.	97020

3.5.1 Reproduction 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

Duration of Dosing: M: 4 weeks prior to mating
F: 2 weeks prior to mating, through day 7 of gestation
Day of Mating: Day 0
Day of C-Section: Day 16 of gestation
Method of Administration: Gavage
Vehicle/Formulation: Aqueous solution.

Study No. 97072
Location in CTD: Vol. 6 Page 1
Testing Facility: CRO Co.

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

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 based on actual data (not on the percent differences).
b - From Study No. 94220.

(Continued)

3.5.1 Reproduction 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 based on actual data (not on the percent differences).

b - From Study No. 94220.

3.5.2B Reproduction Toxicity - Effects on Embryo-Fetal Development

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

Test Article: Curitol Sodium

Design similar to ICH 4.1.3? Yes

Duration of Dosing: G6-G18
Day of Mating: Day 0
Day of C-Section: G29
Method of Administration: Gavage
Vehicle/Formulation: Aqueous Solution

Study No. 97028

Species/Strain: NZW Rabbits
Initial Age: 5 months
Date of First Dose: 7 Aug 97
Special Features: None.
No Observed Adverse-Effect Level:
F_0 Females: 1 mg/kg
F_1 Litters: 5 mg/kg

Location in CTD: Vol. 6 Page 200
Testing Facility: Sponsor Inc.
GLP Compliance: Yes

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 based on actual data (not on the percent differences).
b - From Study No. 97231.

(Continued)

3.5.2B Reproduction 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)

- No noteworthy findings.

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

3.5.3 Reproduction 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 Page 1
Testing Facility: CRO Co.
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 based on actual data (not on the percent differences).
b - From Study No. 97227.

(Continued)

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

(Continued)

3.5.3 Reproduction Toxicity **Study No. 95201 (Continued)**

Daily Dose (mg/kg)		0 (Control)	7.5	75	750
F_1 Females:	No. Evaluated Postweaning	23	21	22	23
(Postweaning)	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 birth to mating.
b - During postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance based on actual data (not on the percent differences).

(Continued)

EXAMPLE

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

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Testing Facility	Study Number
3.7.1 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.	CRO Co.	97012
3.7.2 Impurities							
WISTA R 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.	Sponsor Inc.	97025

MODULE III – QUALITY

Table of Contents (Version 10.1)

Preamble

The draft guidance, "Table of Contents", was developed for the purpose of defining the technical framework for the submission of chemistry, manufacturing, and controls data in support of registration in the three regions and is the product of the M4: Quality Expert Working Group (EWG) of the ICH.

This document currently consists of a "Table of Contents", addressing new chemical entities and biotech products with brief explanatory notes and illustrative examples. For biotech products, specifically, additional information should be placed in the appendices. The format for summaries and additional information will be developed. Currently, the EWG is considering the development of attachments in nine (9) distinct topic areas. These are, with reference to the section of the "Table of Contents" listed below.

Section Referenced	Proposed Attachment Topic
S2.2	Description of Manufacturing Process and Process Controls for (a) New Chemical Entities and (b) Biotech Products
S2.3	Control of Materials For Biotech
S2.5	Process Validation or Evaluation
S6	Container Closure System
P2	Pharmaceutical Development Report
P3.3	Description of Manufacturing Process and Process Controls
P6	Container Closure System
A1	Description of Biotech Facilities and Equipment
A2	Viral Safety Evaluation

The EWG now seeks input from its constituencies regarding the organisation and completeness of the "Table of Contents". The reader should note that this is a framework document and comments should be focused on the organisation of the individual sections listed and not the detailed contents of those sections.

Common Technical Document (CTD) – Module III (Quality)
Table of Contents, Version 10.1
October 7, 1999

Contents

Scope

This document is intended to provide guidance on the format of a registration dossier for new drug substances and their corresponding drug products as defined in the scope of the ICH Guidelines Q 6 A ("NCE") and ICH Guideline Q 6 B ("Biotech"). This format may also be appropriate for certain other categories of products; to determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities. The timing for the submission of specific supporting data has not been addressed in this document and may depend upon regional requirements.

Notes:

1. The text following the section titles is explanatory only and is not all- inclusive. Additional requirements may apply.
2. In “Part O: Other Information” all relevant section titles may not be included. Additional “Part O: Other Information” or section titles may be required by the regional authorities.
3. Further explanatory information may be added in subsequent versions as Attachments.

Common Technical Document (CTD) – Module III (Quality)
Table of Contents - Format, Version 10.1
October 7, 1999

Part	Data Module	Reference
S	**Drug Substance**	
S 1	**General Information**	
S 1.1	**Nomenclature** Recommended INN, compendial name, (if relevant), chemical name(s), other name(s), company or laboratory code, the regional name, national name, e.g., BAN, USAN, JAN, and the Chemical Abstracts Service (CAS) registry number	**---**
S 1.2	**Structure** NCE: The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass. Biotech: Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass as appropriate.	**---**
S 1.3	**General Properties** Brief description of the physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.	**Q6A, Q6B**
S 2	**Manufacture**	
S 2.1	**Manufacturer(s)** Name, address, and responsibility of each manufacturer, including contractors and each proposed production site or facility involved in manufacture and testing.	**---**
S 2.2	**Description of Manufacturing Process and Process Controls** NCE: Information on manufacturing route including a synthetic flow diagram and a description of the synthetic process, including process parameters and types of equipment, tests and measurements such as temperature, pressure, pH, and time, at the appropriate control points. See also Attachment. Biotech: Description of manufacturing process (including flow diagram) describing all steps in the process (e.g., cell culture, harvest, isolation, purification, modification, concentration, and filling) and process parameters. (See also Attachment and Appendix A1 for "Facilities and Equipment'.) Description of shipping and storage conditions for intermediates and drug substance.	**Q5A, Q5B, Q6B**

Part	Data Module	Reference
S 2.3	**Control of Materials** Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drug substance indicating where each material is used in the process. Acceptance criteria and testing. Additionally for Biotech products produced from cell banks: Description of genetic construct for recombinant cell substrates, development and stability, and cell bank system (MCB and WCB) and materials used for cell banking, with information on their origin. For Biotech: see Attachment.	**Q5A, Q5B, Q5D, Q6A, Q6B**
S 2.4	**Controls of Critical Steps and Intermediates** Critical Steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled. Intermediates: Specifications and analytical procedures, if any, on intermediates including validation of analytical procedures, where appropriate. Additionally for Biotech: Stability data supporting storage conditions.	**Q6A, Q6B, Q5C**
S 2.5	**Process Validation or Evaluation** NCE: Process validation or evaluation studies for aseptic processing and sterilisation consistent with the requirements of the region. Biotech: Description, documentation, and results of the validation or evaluation studies, consistent with the requirements of the region, for critical steps or critical assays used in the manufacturing process, including aseptic processing and sterilisation. See also appendix for viral safety evaluation (A2) and Attachment.	
S 2.6	**Manufacturing Process Development** Description and discussion of significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing pre-clinical, clinical, scale-up, pilot, and, if available, production scale batches. If there are significant changes, provide data comparing the drug substance batches.	
S 3	**Characterisation**	
S 3.1	**Elucidation of Structure and/or Biological Characterisation** NCE: Confirmation of structure based on e.g., synthetic route and spectral analyses. Information on the potential for isomerism and the identification of stereochemistry. Biotech: Details on primary, secondary and higher- order structure and information on biological activity, purity, and immunochemical properties (when relevant).	**Q6B**
S 3.2	**Impurities**	**Q3A, Q3C, Q6B**
S 4	**Control of Drug Substance**	

Part	Data Module	Reference
S 4.1	**Specification**	**Q6A, Q6B**
S 4.2	**Analytical Procedures**	**Q2A, Q6B**
S 4.3	**Validation of Analytical Procedures**	**Q2A, Q2B, Q6B**
S 4.4	**Batch Analyses** Description (including size, origin, and use) and test results of all relevant batches (e.g., pre-clinical, clinical, pilot, scale-up, and, if available, production-scale batches) used to establish specifications and evaluate consistency in manufacturing.	**Q3A, Q3C, Q6A, Q6B**
S 4.5	**Justification of Specification**	**Q6A, Q6B**
S 5	**Reference Standards or Materials** Information on the reference standards or reference materials used for testing of the drug substance and drug product.	**Q6A, Q6B**
S 6	**Container Closure System** Description of the container closure system suitable for the storage and shipment of the drug substance, including components, composition, and specifications. See also Attachment.	
S 7	**Stability**	
S 7.1	**Stability Summary and Conclusions** Summary of the types of studies conducted, protocols used, and the results obtained. Conclusions with respect to storage conditions and retest date or expiry period.	**Q1A, Q1B, Q5C**
S 7.2	**Post-approval stability protocol and stability commitment**	**Q1A, Q5C**
S 7.3	**Stability Data** Results of the stability studies conducted in an appropriate format such as tabular, graphical, narrative. Information on analytical procedures used and their validation.	**Q1A, Q5C**
P	**Drug Product**	
P 1	**Description and Composition of the Drug Product** ·Description of the dosage form. · Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis, including overages, if any, the function of the components, and a reference to their quality standards, e.g., compendial monographs or manufacturer's specifications. ·——Type of container and closure used	**Q6A, Q6B**

Part	Data Module	Reference
P 2	**Pharmaceutical Development Report** Description, and, if necessary, justification of differences between clinical formulation(s) and the formulation described in "P1". A summary of bioequivalence and bioavailability data generated on clinical formulations. Preformulation studies on the drug substance, including compatibility studies with excipients used in the formulation described in "P1". Pharmaceutical development studies on key parameters, which might have an influence on the performance of the drug product. NCE: examples include physicochemical characteristics of the drug substance, which affect drug product dissolution, such as morphic form, particle size. Biotech: an example is the selection of a stabilising excipient. Identification and discussion of critical steps in the manufacturing process and justification of non-standard sterilisation process. Justification of overages, if any. Microbiological attributes. Suitability of container closure system. See Attachment.	**Q6A, Q6B**
P 3	**Manufacture**	
P 3.1	**Manufacturer(s)** Name, address, and responsibility for each manufacturer including contractors, and each proposed production site or facility involved in manufacture and testing.	**---**
P 3.2	**Batch Formula** List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis, including overages, and a reference to quality standards.	**---**
P 3.3	**Description of Manufacturing Process and Process Controls** Information on manufacturing process including a flow diagram and a description of the process, including process parameters, tests and measurements at the appropriate control points, and type of equipment. See Attachment. Additionally for Biotech: Scale of production and Appendix A1 for facilities.	**Q6B**
P 3.4	**Controls of Critical Steps and Intermediates** Critical Steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled. Intermediates: Specifications and analytical procedures, if any, for intermediates including validation of analytical procedures, where appropriate.	**Q6A, Q6B, Q2A, Q2B**

Part	Data Module	Reference
P 3.5	**Process Validation or Evaluation** Process evaluation or validation protocol, based on experimental data on pilot or production scale batches, or validation data for production scale batches, where appropriate. Validation of the sterilisation process or aseptic processing or filling, consistent with the requirements of the region. Additionally for Biotech: Description, documentation, and results of the validation or evaluation studies, consistent with the requirements of the region, for critical steps or critical assays used in the manufacturing process. See also appendix for viral safety evaluation (A2).	**Q6B**
P 4	**Control of Excipients**	
P 4.1	**Specifications**	**Q6B**
P 4.2	**Analytical Procedures**	**Q2A, Q6B**
P 4.3	**Validation of Analytical Procedures**	**Q2A, Q2B, Q6B**
P 4.4	**Justification of Specifications**	**Q3C, Q6B**
P 4.5	**Excipients of Human or Animal Origin** For excipients of human or animal source, provide information (e.g., specifications, viral safety data, description of the testing performed, letters of certification) regarding adventitious agents (e.g., TSE, viruses, mycoplasma).	**Q5A, Q5D, Q6B**
P 4.6	**Novel Excipients** Excipient used for the first time in a drug product or by a new route of administration. Full details of manufacture, characterisation, and controls as for new drug substances, with cross references to supporting safety (non-clinical and/or clinical) data.	**---**
P 5	**Control of Drug Product**	
P 5.1	**Specification**	**Q6A, Q6B**
P 5.2	**Analytical Procedures**	**Q2A**
P 5.3	**Validation of Analytical Procedures**	**Q2A, Q2B**
P 5.4	**Batch Analyses** Description (including size, origin, and use) and test results of all relevant batches (e.g., pre-clinical, clinical, pilot, scale-up, and, if available, production-scale batches) used to establish specifications and evaluate consistency in manufacturing.	**Q3B, Q3C, Q6A, Q6B**
P 5.5	**Justification of Specification**	**Q6A, Q6B**
P 6	**Container Closure System** Description of the container closure system suitable for the storage and shipment of the marketed drug product, including components, composition, and specifications. See also Attachment.	
P 7	**Stability**	

Part	Data Module	Reference
P 7.1	**Stability Summary and Conclusions** A summary discussing the types of studies conducted, protocols used and the results obtained. Conclusions with respect to storage conditions and expiry period, and, if applicable, in-use storage conditions and expiry period.	**Q1A, Q1B, Q5C**
P 7.2	**Post-approval Stability Protocol and Stability Commitment**	**Q1A, Q5C**
P 7.3	**Stability Data** Results of the stability studies conducted in an appropriate format such as tabular, graphical, narrative. Information on analytical procedures used and their validation.	**Q1A, Q5C**
O	**Other Information (Refer to regional guidelines)**	
O 1	**Executed Batch Records (USA only)**	**---**
O 2	**Method Validation Package (USA only)**	**---**
O 3	**Comparability Protocols (USA only)**	**---**
A	**Appendices**	
A 1	**Description of Biotech Facilities and Equipment** See Attachment.	**---**
A 2	**Viral Safety Evaluation** See Attachment.	**Q5A**

MODULE IV – NONCLINICAL

Table of Contents : Organisation of Nonclinical Data

October 7, 1999

This guideline presents an acceptable format for the organisation of the nonclinical reports in the Common Technical Document for applications that will be submitted to Regulatory Authorities. A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified.

Background

Through the ICH process, considerable harmonisation has been achieved among the three regions in the technical requirements for the registration of pharmaceuticals for human use. However, there is no harmonisation of the organisation of the registration documents. Each region has its own requirements for the organisation of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the GAIYO, which organises and presents a summary of the technical information. In Europe, an Expert Report and a Tabulated Summary are required, and a Written Summary of the nonclinical pharmacology is recommended. The US FDA has guidance regarding the format and content of the New Drug Application. To address these differences, this guideline describes a format for the Common Technical Document that will be acceptable in all three regions.

Scope of the Guideline

This guideline primarily addresses the organisation of the nonclinical information to be presented in Registration Applications for new molecular entities (including biologics) and associated drug products. With appropriate modifications, the guideline may also be applied to abbreviated or abridged applications and variations.

This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the data that have been acquired. Applicants are encouraged to modify the format as needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Organisation of the Nonclinical Data

A. Table of Contents

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

B. Study Reports

The study reports should be presented in the following order:

1. Pharmacology
    - 1.1 Primary Pharmacodynamics
    - 1.2 Secondary Pharmacodynamics
    - 1.3 Safety Pharmacology
    - 1.4 Pharmacodynamic Drug Interactions

2. Pharmacokinetics
    - 2.1 Analytical Methods and Validation Reports (if separate reports are available)
    - 2.2 Kinetics (including *in vivo* studies of absorption and excretion, including excretion in milk, of parent drug and/or metabolite(s))
    - 2.3 Tissue Distribution
    - 2.4 Metabolism
    - 2.5 Pharmacokinetic Drug Interactions (nonclinical)
    - 2.6 Other Pharmacokinetic Studies

3. Toxicology
    - 3.1 Single-Dose Toxicity (in order by species, by route)
    - 3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluation)
    - 3.3 Genotoxicity
        - *3.3.1 In vitro*
        - *3.3.2 In vivo* (including supportive toxicokinetics evaluations)
    - 3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
        - 3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
        - 3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
        - 3.4.3 Other studies
    - 3.5 Reproduction Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

MODULE V – EFFICACY

Table of Contents: Organisation of Human Study Reports and Related Information

October 7, 1999

Preamble

Through the ICH process, a guideline has been published on the structure and content of clinical study reports (E3). The present document provides guidance on the organisation of these study reports and other clinical data within a Common Technical Document (CTD) for registration of a pharmaceutical product for human use. Future guidance will address clinical summary reports and the other elements needed for a comprehensive presentation of clinical information within a CTD. These elements should facilitate the preparation and review of a marketing application.

This guideline is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical data reports that are in the application.

The organization of clinical data within a CTD for the registration of a new active substance has been addressed here. With appropriate modifications, this organisation may also be applied to other types of applications presenting clinical data.

Organization of Human Study Reports and Related Information in Module V (Efficacy) of The Common Technical Document (CTD)

October 7, 1999

A. Table of Contents of Human Study Reports and Related Information

B. Tabular Listing of All Human Studies

C. Human Study Reports

1. Reports of Bioavailability (BA) and Bioequivalence (BE) Studies
   - 1.1 BA Study Reports
   - 1.2 BE Study Reports
   - 1.3 *In Vitro-In Vivo* Comparison Study Reports
   - 1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
2. Reports of Studies Using Human Biomaterials Pertinent to Absorption or Disposition
   - 2.1 Plasma Protein Binding Study Reports
   - 2.2 Reports of Hepatic Metabolism and Interaction Studies
   - 2.3 Reports of Studies Using Other Human Biomaterials
3. Reports of Human Pharmacokinetic (PK) Studies
   - 3.1 Healthy Subject PK and Initial Tolerability Study Reports
   - 3.2 Patient PK and Initial Tolerability Study Reports
   - 3.3 Intrinsic Factor PK Study Reports
   - 3.4 Extrinsic Factor PK Study Reports
   - 3.5 Population PK Study Reports
4. Reports of Human Pharmacodynamic (PD) Studies
   - 4.1 Healthy Subject PD and PK/PD Study Reports
   - 4.2 Patient PD and PK/PD Study Reports
5. Reports of Efficacy and Safety Studies
   - 5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
   - 5.2 Study Reports of Uncontrolled Clinical Studies
   - 5.3 Reports of Analyses of Data From More Than One Study
   - 5.4 Other Study Reports
6. Reports of Post-Marketing Experience
7. Case Report Forms and Individual Patient Listings

Guideline on Organisation of Human Study Reports and Related Information in Module V (Efficacy) of The Common Technical Document (CTD)

October 7, 1999

This guideline suggests a specific organization for the placement of human study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

A Table of Contents for Study Reports

A Table of Contents for the study reports should be provided.

B. Tabular Listing of All Human Studies

A tabular listing of all human studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information may be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section C below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

C. Human Study Reports

1. Reports of BA and BE Studies

BA and BE studies evaluate the rate and extent of release of the active substance from the medicinal product. BA/BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA or BE information, the study report should be submitted in Section 3, and referenced in Sections 1.1 and/or 1.2.

Section 1.1 BA Study Reports

BA studies in this section include 1) studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously (absolute BA study) or as an oral liquid dosage form (relative BA study), 2) dosage form proportionality studies, and 3) food-effect studies.

Section 1.2 BE Study Reports

BE studies in this section compare the rate and extent of release of the drug substance from drug products (e.g., tablet to tablet, tablet to capsule). BE studies may include comparisons between 1) the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, 2) the drug product used in clinical studies supporting effectiveness and the drug product used in

stability batches, and 3) similar drug products from different manufacturers.

Section 1.3 In Vitro – In Vivo Comparison Study Reports

In vitro dissolution studies that provide BA/BE information, including studies used in seeking to correlate *in vitro* data with *in vivo* comparisons, should be placed in Section 1.3. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD.

Section 1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for BA/BE or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Section 1.4 and referenced in the appropriate individual study reports.

2. Reports of Studies Using Human Biomaterials Pertinent to Absorption or Disposition

Human biomaterials is a term that refers to proteins, cells, and tissues derived from human sources that are used *in vitro* or *ex vivo* to assess absorption and disposition properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways relative to drug absorption and elimination and to assess bi-directional drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Human Study Reports Section.

Section 2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided in Section 2.1. Protein binding data from PK blood and/or plasma studies should be provided in Section 3.

Section 2.2 Reports of Hepatic Metabolism and Interaction Studies

Reports of metabolic/interaction studies with hepatic tissue should be placed in Section 2.2.

Section 2.3 Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in section 2.3.

3. Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments provide a description of the body's handling of a drug

over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s).

The PK studies in Sections 3.1 and 3.2 generally (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faeces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Section 3.1 to 3.2, as appropriate. These studies characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Sections 3.1 and/or 3.2. Apart from describing mean PK in normal and patient volunteers, PK studies also describe the range of individual variability. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors which may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organized in Sections 3.3 and 3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during efficacy and safety studies can also address questions about intrinsic and extrinsic factors contributing to the variability in the dose-exposure-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 3.5.

Section 3.1 Healthy Subject PK and Initial Tolerability Study Reports

Study reports of PK and initial tolerability in healthy subjects should be placed in Section 3.1.

Section 3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK studies and initial tolerability in patients should be placed in Section 3.2.

Section 3.3 Intrinsic Factor PK Study Reports

PK study reports to assess intrinsic factors, such as age, race and gender, should be placed in Section 3.3.

Section 3.4: Extrinsic Factor PK Study Reports

PK studies to assess extrinsic factors, such as other drugs, food, or smoking, should be placed in Section 3.4.

Section 3.5: Population PK Study Reports

Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 3.5.

4. Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the effects of a drug product in humans, as opposed to those studies whose primary objective is to establish efficacy or to accumulate safety data (see Section 5), should be placed in Section 4.

PD studies in Section 4 thus should include 1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers), 2) short-term studies of the main clinical effect, and 3) studies of other properties not related to the desired clinical effect, including studies to focus on specific safety concerns, e.g., QTc prolongation. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected together with drug concentration information (concentration-response or PK/PD studies). Relationships between PK and PD data may generally be evaluated using an appropriate model that can be used as a basis for interpolation and/or extrapolation of dose- and/or concentration-response information.

Dose-finding and/or PK-PD studies may be conducted in healthy subjects and/or patients, and may also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of PD, dose-finding, and/or PK/PD studies conducted in healthy subjects should be placed in Section 4.1, and the reports for those studies conducted in patients should be placed in Section 4.2.

In some cases, the PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). When these studies are part of the efficacy demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5, not in Section 4.

Section 4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in Section 4.1.

Section 4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in Section 4.2.

5. Reports of Efficacy and Safety Studies

Section 5 should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor or otherwise available, including both completed and ongoing studies of the drug in proposed and related indications, and, where appropriate, studies of indications other than those proposed. The study reports should provide the level of detail appropriate to the study. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see E3 and individual guidance by region).

Within Section 5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E-3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should come last.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section 5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it is included in the appropriate Section 5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5 and referenced as necessary in other Sections 5, e.g., Section 5A, Section 5B.

5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for the proposed use, should be included in Section 5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Section 5.1. The sequence in which studies were conducted is not pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Section 5.1. Controlled safety studies should also be reported in Section 5.1.

5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in Section 5.2.

5.3 Reports of Analyses of Data from More than One Study

Clinical issues in an application may be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Section 5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as

dose, demographics, and concomitant medications.

5.4 Other Study Reports

This section may include:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports not included in Section 5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Section 5.1
- Reports of ongoing studies

6. Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (incuding all significant safety observations) should be included in Section 6.

7. Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline. When these are submitted, they should be included in Section 7 and placed in the same order as the clinical study reports and indexed by study.

Table 1. Listing of Human Studies

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Number of Subjects**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	20	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	32	Cross-over	Two tablet formulations, 50 mg, oral	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	50	Cross-over	Tablet, 50mg single dose, oral	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	24	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	Patients with primary hypertension	2 weeks	Ongoing; Interim
Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	300	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	Patients with primary hypertension	48 weeks	Complete; Full