Guidance for Industry

M4S: The CTD — Safety Appendices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2001
ICH

Guidance for Industry

M4S: The CTD — Safety Appendices

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
Mail: the Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2001
ICH

APPENDIX A: EXAMPLES OF TABLES AND FIGURES FOR WRITTEN SUMMARIES

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

Study references should be included in the table or text.

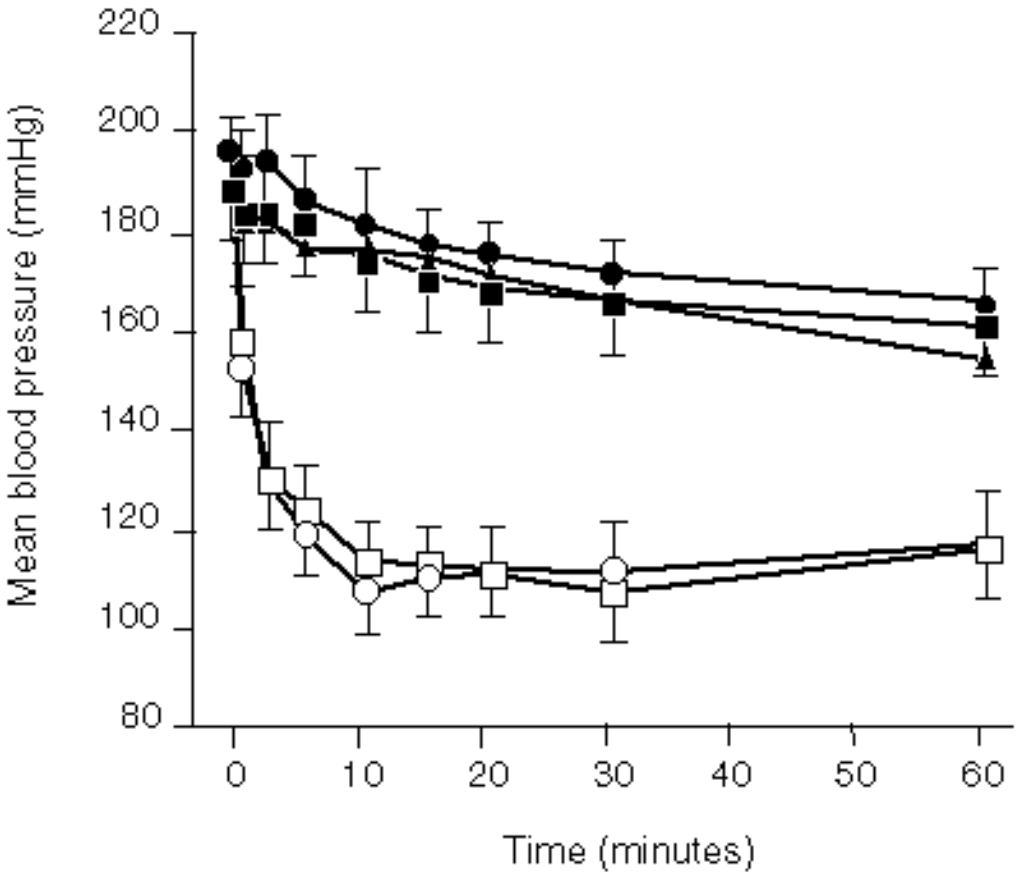
Tables should include statistics, if appropriate.

Table X: Binding of X and Its Major Metabolites and Comparators to Human X_2 and X_3 Receptors

Compound	X_2 K_i1(nM)	X_2 K_i2(nM)	X_3 K_i1(nM)	X_3 K_i2(nM)
1	538	2730	691	4550
2	2699	1050	2.0	181
3	578	14.4	141	10400
4	20	100	10.7	7.9
5	2100	3.1	281	28
6	7.5	8.4	44	2.8
7	3.11	3.76	1.94	1.93

K_i1 and K_i2 represent the high and low affinity binding sites, respectively (Data from Study Number).

Figure X: Blood Pressure Following Chronic Dosing With X to SHR[a]



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

Table X: Model Independent Pharmacokinetic Parameters for X in Mice Following Single Oral Doses at 2, 10 and 30 mg/kg [ref]

Parameter (units)	**Parameter value**					
Sex	**Males**			**Females**		
Dose (mg/kg)	2	10	30	2	10	30
C_{max} (ng/mL)	4.9	20.4	30.7	5.5	12.9	28.6
T_{max} (h)	0.8	0.4	0.3	0.4	0.5	0.3
$AUC_{0\text{-}t}$ (ng.h/mL)	21.6	80.5	267	33.3	80	298
$AUC_{0\text{-}inf}$ (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*	**Feces**	**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	**Feces**	**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 normalized 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 normalized $AUC_{0-\tau}$ x 24 in man.

$ - calculated from the total daily dose assuming a body weight of 50 kg for man.

* - Numbers in parentheses represent ratios of exposure in animals to those in patients.

Table X: Incidence of Proliferative Interstitial (Leydig) Cell Lesions in Rats [ref]

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

* Adenoma and/or Hyperplasia.

APPENDIX B: THE NONCLINICAL TABULATED SUMMARIES TEMPLATES

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

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

2.6.7 Toxicology
- 2.6.7.1 Toxicology: Overview
- 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies
- 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data
- 2.6.7.4 Toxicology: Drug Substance
- 2.6.7.5 Single-Dose Toxicity
- 2.6.7.6 Repeat-Dose Toxicity: Nonpivotal Studies
- 2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies
- 2.6.7.8 Genotoxicity: In Vitro
- 2.6.7.9 Genotoxicity: In Vivo
- 2.6.7.10 Carcinogenicity
- 2.6.7.11 Reproductive and Developmental Toxicity: Nonpivotal Studies
- 2.6.7.12 Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)
- 2.6.7.13 Reproductive and Developmental Toxicity: Effects on Embryofetal Development (Pivotal)
- 2.6.7.14 Reproductive and Developmental Toxicity: Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotol)

2.6.7.15 Studies in Juvenile Animals[a] (template not provided; see footnote a)
2.6.7.16 Local Tolerance
2.6.7.17 Other Toxicity Studies

* : Tabulated summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.
[a] : When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 2.6.7.15.

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

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

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

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

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

Notes: (1) All safety pharmacology studies should be summarized.
(2) International Nonproprietary Name (INN).
(3) Or Report Number (on all tables).

a - Single dose unless specified otherwise.

2.6.5.1 Pharmacokinetics **Overview** **Test Article:** *(1)*

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Page
Absorption ***(2)***					*(3)*	
Distribution						
Metabolism						
Excretion						
Pharmacokinetic Drug Interactions						
Other						

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

2.6.5.3 Pharmacokinetics: Absorption After a Single Dose

Test Article: *(1)*

Location in CTD: Vol. Page
Study No.

Species	_____	_____	_____	_____	_____
Gender (M/F)/Number of animals	***(4)***				
Feeding condition					
Vehicle/Formulation					
Method of Administration					
Dose (mg/kg)					
Sample (e.g., whole blood, plasma, serum)					
Analyte					
Assay ***(2)***					
PK parameters:					

Additional Information: ***(3)***

Notes: (1) International Nonproprietary Name (INN).
(2) For example, HPLC, LSC with ^{14}C-labeled compound.
(3) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
(4) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included.

2.6.5.4 Pharmacokinetics: Absorption after Repeated Doses **Test Article:**

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

Format A
2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. 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 (unit)					
Tissues/organs	**T(1)**	**T(2)**	**T(3)**	**T(4)**	**T(5)**	**$t_{1/2}$?**

Additional information:

Alternate Format B

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. Page
Study No.

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

	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]

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

Study system:
Target entity, Test system and method:

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

Additional Information:

2.6.5.7 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 2.6.5.7

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

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

2.6.5.8 Pharmacokinetics: Other Distribution Study **Test Article:**

2.6.5.9 Pharmacokinetics: Metabolism In Vivo **Test Article:**

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

				% of Compound in Sample				Location in CTD	
Species	**Sample**	**Sampling Time or Period**	**% of Dose in Sample**	**Parent**	**M1**	**M2**	**Study No.**	**Vol**	**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.*

2.6.5.10 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.

2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways **Test Article:**

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

2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes

Test Article:

Location in CTD: Vol. Page
Study No.

Note: Nonclinical studies only.

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.5.13 Pharmacokinetics: Excretion **Test Article:** *(1)*

Species	_____	_____	_____	_____
Gender (M/F)/Number of animals	*(3)*			
Feeding condition				
Vehicle/Formulation				
Method of Administration				
Dose (mg/kg)				
Analyte				
Assay				

Excretion route *(4)*	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**
Time												
0 - T hr												

Study number
Location in CTD

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

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

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

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

2.6.5.15 Pharmacokinetics: Drug-Drug Interactions

Test Article:

Location in CTD: Vol. Page
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.5.16 Pharmacokinetics: Other

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

Type of study:

Method:

Tabulated results:

Additional Information:

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

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg[a])	GLP Compliance	Testing Facility	Study Number	Location Vol. Page
Single-Dose Toxicity	*(2)*							*(3)*
Repeat-Dose Toxicity								
Genotoxicity								
Carcinogenicity								
Reproductive and Developmental Toxicity								
Local Tolerance								
Other Toxicity Studies								

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

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

2.6.7.2 Toxicokinetics **Overview of Toxicokinetics Studies** **Test Article:** ***(1)***

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

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

(2)

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

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

Batch No.	**Purity (%)**	**Specified Impurities ( )**	**Study Number**	**Type of Study**
PROPOSED SPECIFICATION:				
(2)				*(3)*

Notes: *(1) International Nonproprietary Name (INN).*
(2) All batches used in the Toxicology studies should be listed in approximate chronological order.
(3) The Toxicology studies in which each batch was used should be identified.

2.6.7.5 Single-Dose Toxicity *(1)* **Test Article:** *(2)*

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

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

2.6.7.6 Repeat-Dose Toxicity **Nonpivotal Studies** ***(1)*** **Test Article:** *(2)*

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

Notes: *(1) All repeat-dose toxicity studies (including all range-finding toxicity studies), other than the definitive GLP studies specified by ICH Guidance* M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmacaeuticals *(November 1997), should be summarized in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual age of test subjects.*

(2) International Nonproprietary Name (INN).

a - No Observed Adverse Effect Level.

2.6.7.7 *(1)* Repeat-Dose Toxicity *(2)* **Report Title:** **Test Article:** (*3)*

Species/Strain: **Duration of Dosing:** **Study No.**
Initial Age: **Duration of Postdose:** **Location in CTD:** Vol. Page
Date of First Dose: **Method of Administration:**
Vehicle/Formulation: **GLP Compliance:**
Special Features:
No Observed Adverse Effect Level:

Daily Dose (mg/kg)	0 (Control)							
Number of Animals	M:	F:	M:	F:	M:	F:	M:	F:
Toxicokinetics: AUC ( ) ***(4)***	*(5)*							
Noteworthy Findings								
Died or Sacrificed Moribund								
Body Weight (%[a])								
Food Consumption (%[a])	*(5)*							
Water Consumption ( )	*(5)*							
Clinical Observations								
Ophthalmoscopy								
Electrocardiography								

\- No noteworthy findings. + Mild ++ Moderate +++ Marked *(6)*
(7) * - p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

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

Daily Dose (mg/kg)	0 (Control)							
Number of Animals	M:	F:	M:	F:	M:	F:	M:	F:
Hematology								
Serum Chemistry								
Urinalysis								
Organ Weights[a] (%)								
Gross Pathology								
Histopathology								
Additional Examinations								
Postdose Evaluation: **Number Evaluated** ***(8) (9)***								

\- No noteworthy findings.

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

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

Notes for Table 2.6.7.7

(1) The tables should be numbered consecutively (e.g., 2.6.7.7A, 2.6.7.7B, 2.6.7.7C).

(2) There should be one table for each of the repeat-dose toxicity studies specified by ICH Guidance M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmacaeuticals *(November 1997), as well as any other repeat-dose toxicity studies that could be considered pivotal.*

(3) International Nonproprietary Name (INN).

(4) Steady state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If from a separate study, the study number should be given in a footnote.

(5) ONLY NOTEWORTHY FINDINGS SHOULD BE PRESENTED. If additional parameters (other than those in the template) showed noteworthy changes, these should be added to the tables. In general, data at end of dosing period can be shown; however, if there were additional noteworthy findings at earlier timepoints, these should be included. Footnotes should be used as needed to provide additional information about the tests or the results.

(6) Or other scale, as appropriate.

(7) Methods of statistical analyses should be indicated.

(8) All parameters that still show drug-related changes should be listed. This section should be deleted if the study does not include a postdose evaluation.

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

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

Test for Induction of: **No. of Independent Assays:** **Study No.**
Strains: **No. of Replicate Cultures:** **Location in CTD:** Vol. Page
Metabolizing System: **No. of Cells Analyzed/Culture:**
Vehicles: **For Test Article:** **For Positive Controls:** **GLP Compliance:**
Treatment: **Date of Treatment:**
Cytotoxic Effects:
Genotoxic Effects:

Metabolic Activation	Test Article	Concentration or Dose Level (*(3)*)					
Without Activation							
		(4)					
With Activation							

Notes: *(1) The tables should be numbered consecutively (e.g.,2.6.7.8A, 2.6.7.8B). 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 indicated in a footnote.
(5) Methods of statistical analyses should be indicated.

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

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

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

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

Study No.
Location in CTD: Vol. Page

GLP Compliance:
Date of Dosing:

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

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

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

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

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

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

Daily Dose (mg/kg)	0 (Control)							
Gender	M	F	M	F	M	F	M	F
Toxicokinetics: AUC ( ) *(4)*								
Number of Animals								
At Start								
Died/Sacrificed Moribund								
Terminal Sacrifice								
Survival (%)	*(5)*							
Body Weight (%[a])								
Food Consumption (%[a])								

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

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

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

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

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

Notes for Table 2.6.7.10

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

(2) International Nonproprietary Name (INN).

(3) From ICH Guidance S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals *(March 1995).*

(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 and/or tissues.

2.6.7.11 Reproductive and Developmental Toxicity **Nonpivotal Studies** ***(1)*** **Test Article:** *(2)*

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

Notes: (1) All reproduction toxicity studies (including all relevant range-finding studies), other than the definitive GLP studies specified by M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, *November 1997, should be summarized in the same order as the CTD. However, investigative studies should be summarized using a more detailed template.*

(2) International Nonproprietary Name (INN).

2.6.7.12 ***(1)*** **Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation** ***(3)*** **Report Title:** **Test Article:** *(2)*

Design similar to ICH 4.1.1? **Duration of Dosing:**M: **Study No.**
Species/Strain: **Day of Mating:** ***(8)***F: **Location in CTD:** Vol. Page
Initial Age: **Day of C-Section:**
Date of First Dose: **Method of Administration:** **GLP Compliance:**
Special Features: **Vehicle/Formulation:**
No Observed Adverse Effect Level:
F_0 Males:
F_0 Females:
F_1 Litters:

Daily Dose (mg/kg) **0 (Control)**

Males Toxicokinetics: AUC ( ) *(4)*

No. Evaluated
No. Died or Sacrificed Moribund
Clinical Observations
Necropsy Observations
Body Weight (%[a])
Food Consumption (%[a])
Mean No. Days Prior to Mating
No. of Males that Mated
No. of Fertile Males *(5)*

-No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
(7) *- $p<0.05$ ** - $p<0.01$
a - After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

2.6.7.12 *(1)* Reproductive and Developmental Toxicity **Study No. (Continued)**

Daily Dose (mg/kg)	**0 (Control)**
Females Toxicokinetics: AUC ( ) *(4)*	
No. Evaluated	
No. Died or Sacrificed Moribund	
Clinical Observations	
Necropsy Observations	
Premating Body Weight (%[a])	
Gestation Body Weight (%[a])	
Premating Food Consumption (%[a])	
Gestation Food Consumption (%[a])	
Mean No. Estrous Cycles/14 days	
Mean No. Days Prior to Mating	
No. of Females Sperm Positive	
No. of Pregnant Females	
No. Aborted or with Total Resorption of Litter	
Mean No. Corpora Lutea	
Mean No. Implantations	
Mean % Preimplantation Loss	
Mean No. Live Conceptuses	
Mean No. Resorptions	
No. Dead Conceptuses	
Mean % Postimplantation Loss	

-No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$
a - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

Notes for Tables 2.6.7.12, 2.6.7.13, and 2.6.7.14

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

(2) International Nonproprietary Name (INN).

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

(4) Steady state AUC, Cmax, or other toxicokinetic information supporting the study. If the information is from a separate study, the study number should be given in a footnote.

(5) POSSIBLE PRESENTATIONS OF THE RESULTS ARE SHOWN IN THESE TEMPLATES. DATA PRESENTATION SHOULD BE FLEXIBLE AND APPROPRIATE ACCORDING TO OPTIMAL STATISTICAL ANALYSIS AND THE DESIGN OF THE STUDY. If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.

(6) Or other scale as appropriate.

(7) Methods of statistical analysis should be indicated.

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

2.6.7.13 ***(1)*** **Reproductive and Developmental Toxicity - Effects on Embryofetal Development** ***(3)*** **Report Title:** **Test Article:** *(2)*

Design similar to ICH 4.1.3?
Duration of Dosing:
Day of Mating: ***(8)***
Study No.

Species/Strain:
Day of C-Section:
Location in CTD: Vol. Page

Initial Age:
Method of Administration:

Date of First Dose:
Vehicle/Formulation:
GLP Compliance:

Special Features:

No Observed Adverse Effect Level:

F_0 Females:

F_1 Litters:

Daily Dose (mg/kg)	**0 (Control)**
Dams/Does: Toxicokinetics: AUC **()** *(4)*	
No. Pregnant	
No. Died or Sacrificed Moribund	*(5)*
No. Aborted or with Total Resorption of Litter	
Clinical Observations	
Necropsy Observations	
Body Weight (%[a])	
Food Consumption (%[a])	
Mean No. Corpora Lutea	
Mean No. Implantations	
Mean % Preimplantation Loss	

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

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

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

2.6.7.13 *(1)* Reproductive and Developmental Toxicity **Study No. (Continued)**

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

- No noteworthy findings.

* - $p<0.05$ ** - $p<0.01$

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

Design similar to ICH 4.1.2? **Duration of Dosing:** **Study No.**
Day of Mating: ***(8)***
Species/Strain: **Method of Administration:** **Location in CTD:** Vol. Page
Initial Age **Vehicle/Formulation:**
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	
Gestation Body Weight (%[a])	*(5)*
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 L = Lactation day
(7) * - $p<0.05$ ** - $p<0.01$)
a -At end of gestation or lactation. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

2.6.7.14 *(1)* Reproductive and Developmental Toxicity **Study No. (Continued)**

Daily Dose (mg/kg)		**0 (Control)**
F_1 Litters:	No. Litters Evaluated	
(Preweaning)	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 Observations	
	No. Evaluated Postweaning	
F_1 Males:	Per Litter	
(Postweaning)	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Body Weight Change[b] (g)	
	Food Consumption (%[c])	
	Preputial Separation	
	Sensory Function	
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Males that Mated	
	No. of Fertile Males	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - p<0.05 ** - p<0.01
a - From birth to weaning.
b - From weaning to mating.
c - At end of postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.14 *(1)* Reproductive and Developmental Toxicity **Study No. (Continued)**

Daily Dose (mg/kg)		**0 (Control)**
F_1 Females:	No. Evaluated Postweaning	
(Postweaning)	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Premating Body Weight Change[a] (g)	
	Gestation Body Weight Change (g)	
	Premating Food Consumption (%[b])	
	Gestation Food Consumption (%[b])	
	Mean Age of Vaginal Patency (days)	
	Sensory Function	
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Females Sperm-Positive	
	No. of Pregnant Females	
	Mean No. Corpora Lutea	
	Mean No. Implantations	
	Mean % Preimplantation Loss	
F_2 Litters:	Mean No. Live Conceptuses/Litter	
	Mean No. Resorptions	
	No. of Litter with Dead Conceptuses	
	No. Dead Conceptuses	
	Mean % Postimplantation Loss	
	Fetal Body Weights (g)	
	Fetal Sex Ratios (% males)	
	Fetal Anomalies	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$
a - From weaning to mating
b - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.14 *(1)* Reproductive and Developmental Toxicity Study No. (Continued)

Daily Dose (mg/kg)		**0 (Control)**
F_1 Females:	No. Evaluated Postweaning	
(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 Format for Natural Parturition.*
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Females Sperm Positive	
	No. of Pregnant Females	
	Mean Duration of Gestation	
	Abnormal Parturition	
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 Observations	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$

a - From birth to mating.

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

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

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

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

2.6.7.17 Other Toxicity Studies ***(1)*** **Test Article:** *(2)*

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

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

APPENDIX C: THE NONCLINICAL TABULALTED SUMMARIES — EXAMPLES

(The following examples correspond to the templates in Appendix B; examples are not provided for the templates Studies in Juvenile Animals or Local Tolerance)

EXAMPLE

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

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

a - Report contains a GLP Compliance Statement.

EXAMPLE

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

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

a - Single dose unless specified otherwise.

EXAMPLE

2.6.5.1 Pharmacokinetics **Overview** **Test Article:** Curitol Sodium

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

a - Report contains a GLP Compliance Statement.

EXAMPLE

2.6.5.3 Pharmacokinetics: Absorption After a Single Dose

Test Article: Curitol Sodium

Location in CTD Volume 1, Page 258

Study number 95104

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

Additional Information:

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

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

a - Total radioactivity, ^{14}C

EXAMPLE

Format A

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: Curitol Sodium
Location in CTD: Vol.21 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 (mcg/mL)					
Tissues/organs	**0.25**	**0.5**	**2**	**6**	**24**	**$t_{1/2}$**
Blood	9.2	3.7	1.8	0.9	0.1	
Plasma	16.5	7.1	3.2	1.6	0.2	
Brain	0.3	0.3	0.2	0.1	nd	
Lung	9.6	14.1	7.3	2.9	0.1	
Liver	73.0	54.5	19.9	12.4	3.2	
Kidney	9.6	13.2	4.9	3.8	0.6	
Testis	0.3	0.5	0.6	0.5	0.1	
Muscle	1.0	1.2	0.8	0.3	nd	

Additional information:

Tissues and organs such as the heart, thymus, adrenal, spleen, stomach, intestine…..are examined but not shown.

nd = Not detected.

EXAMPLE

Alternate Format B

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: Curitol Sodium
Location in CTD: Vol. 21 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: Nonlabeled compound
Specific Activity: -
Analyte/Assay: Unchanged compound (mcg/mL)/HPLC
Sampling time: 10 min, 1, 4, 8, 24, 48, 96, and 168 hr

Tissues/organs	C_{1hr} conc.	C_{1hr} T/P[1)]	Last time point conc.	Last time point T/P[1)]	Time	AUC	$t_{1/2}$
Heart	1.4	0.08	0.44	22	48	57.3	37.3
Liver	4.5	6	1.85	92.5	48	290	51.7
Kidney	2.8	0.20	1.07	53.5	48	126	36.3
Spleen	6.5	8.6	3.5	175	48	410	46.9

Additional information:

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

EXAMPLE

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

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

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

EXAMPLE

2.6.5.7 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, ^{14}C
Assay: LSC

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

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

Location in CTD: Vol. 22 Page 102

Excretion into milk **Study No.** 95703
Species: Rat
Lactating date/Number of animals: day 7/3
Feeding condition: Fed
Vehicle/Formulation: Solution/Water
Method of Administration: Oral gavage
Dose (mg/kg): 5
Analyte: Total radioactivity, ^{14}C
Assay: LSC

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

Additional Information:

EXAMPLE

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

Gender (M/F)/Number of animals: **Rats:** 4M **Dogs:** 3F **Humans:** 8M
Feeding condition: Fed
Vehicle/Formulation: **Rats:** Solution/water **Dogs:** Capsules **Humans:** 75 mg tablets
Method of Administration: **Rats:** Gavage* **Dogs:** Oral Capsule* **Humans:** Oral Tablet
Dose (mg/kg): **Rats:** 5 mg/kg **Dogs:** 5 mg/kg **Humans:** 75 mg
Radionuclide: ^{14}C
Specific Activity: 2×10^5 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.

EXAMPLE

2.6.5.13 Pharmacokinetics: Excretion **Test Article:** Curitol Sodium

Species	Rat			Rat			Dog			Dog		
Gender (M/F)/Number of animals	4M			4M			3M			3M		
Feeding condition	Fasted			Fasted			Fasted			Fasted		
Vehicle/Formulation	Solution Water			Solution Saline			Capsule			Solution Saline		
Method of Administration	Oral			Intravenous			Oral			Intravenous		
Dose (mg/kg)	10			5			10			5		
Analyte	TRA[a]			TRA[a]			TRA[a]			TRA[a]		
Assay	LSC			LSC			LSC			LSC		
Excretion route	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**
Time												
0 - 24 hr	26	57	83	22	63	85	20	29	49	23	42	65
0 - 48 hr	30	65	95	27	69	96	25	65	90	28	78	96
0 - 72 hr	31	65	97	28	70	98	26	73	99	29	72	101
0 - 96 hr	31	67	98	29	70	99	26	74	100	29	73	102
Study number	95102						95156					
Location in CTD	Volume 20, Page 75						Volume 20, Page 150					

Additional Information:

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

EXAMPLE

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

Species	**Rat**			**Rat**		
Gender (M/F) / Number of animals	4M			4M		
Feeding condition	Fasted			Fasted		
Vehicle/Formulation	Solution			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, ^{14}C

EXAMPLE

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

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg[a])	GLP Compliance	Testing Facility	Study Number	Location Vol.	Location Page
Single-Dose Toxicity	CD-1 Mice	Gavage	-	0, 1000, 2000, 5000	Yes	Sponsor Inc.	96046	1	1
		Intravenous	-	0, 100, 250, 500	Yes	CRO Co.	96047	1	100
	Wistar Rats	Gavage	-	0, 1000, 2000, 5000	Yes	Sponsor Inc.	96050	1	200
		Intravenous	-	0, 100, 250, 500	Yes	CRO Co.	96051	1	300
Repeat-Dose Toxicity	CD-1 Mice	Diet	3 Months	0, 62.5, 250, 1000, 4000, 7000	Yes	CRO Co.	94018	2	1
	Wistar Rats	Diet	2 Weeks	0, 1000, 2000, 4000	No	Sponsor Inc.	94019	3	1
		Gavage	2 Weeks	0, 500, 1000, 2000	No	Sponsor Inc.	94007	3	200
		Gavage	3 Months	0, 200, 600, 1800	Yes	Sponsor Inc.	94214	4	1
		Gavage	6 Months	0, 100, 300, 900	Yes	Sponsor Inc.	95001	5	1
	Beagle Dogs	Capsules	1 Month	0, 10, 40, 100	Yes	Sponsor Inc.	94020	6	1
		Capsules	9 Months	0, 5, 20, 50	Yes	Sponsor Inc.	96041	7	1
	Cynomolgus Monkeys	Gavage	5 Days	0, 500, 1000	No	CRO Co.	94008	8	1
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 No Observed Adverse Effect Level (NOAEL) is underlined.

(Continued)

EXAMPLE

2.6.7.1 Toxicology **Overview (Continued)** **Test Article:** Curitol Sodium

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number	Location Vol.	Location Page
Carcinogenicity	CD-1 Mice	Diet	21 Months	0, 0, 25, 100, 400	Yes	CRO Co.	95012	10	1
	Wistar Rats	Gavage	24 Months	0, 0, 25, 100, 400	Yes	Sponsor Inc.	95013	12	1
Reproduction Toxicity	Wistar Rats	Gavage	a	0, 5, 30, 180	Yes	CRO Co.	96208	14	1
	Wistar 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
Local Tolerance	NZW Rabbits	Dermal	1 Hour	0, 15 mg	No	Sponsor Inc.	95015	18	1
Other Toxicity Studies									
Antigenicity	Guinea Pigs	Subcutaneous	Weekly for 3 weeks	0, 5 mg	No	CRO Co.	97012	18	20
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

EXAMPLE

2.6.7.2 Toxicokinetics **Overview of Toxicokinetics Studies** **Test Article:** Curitol Sodium

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

EXAMPLE

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

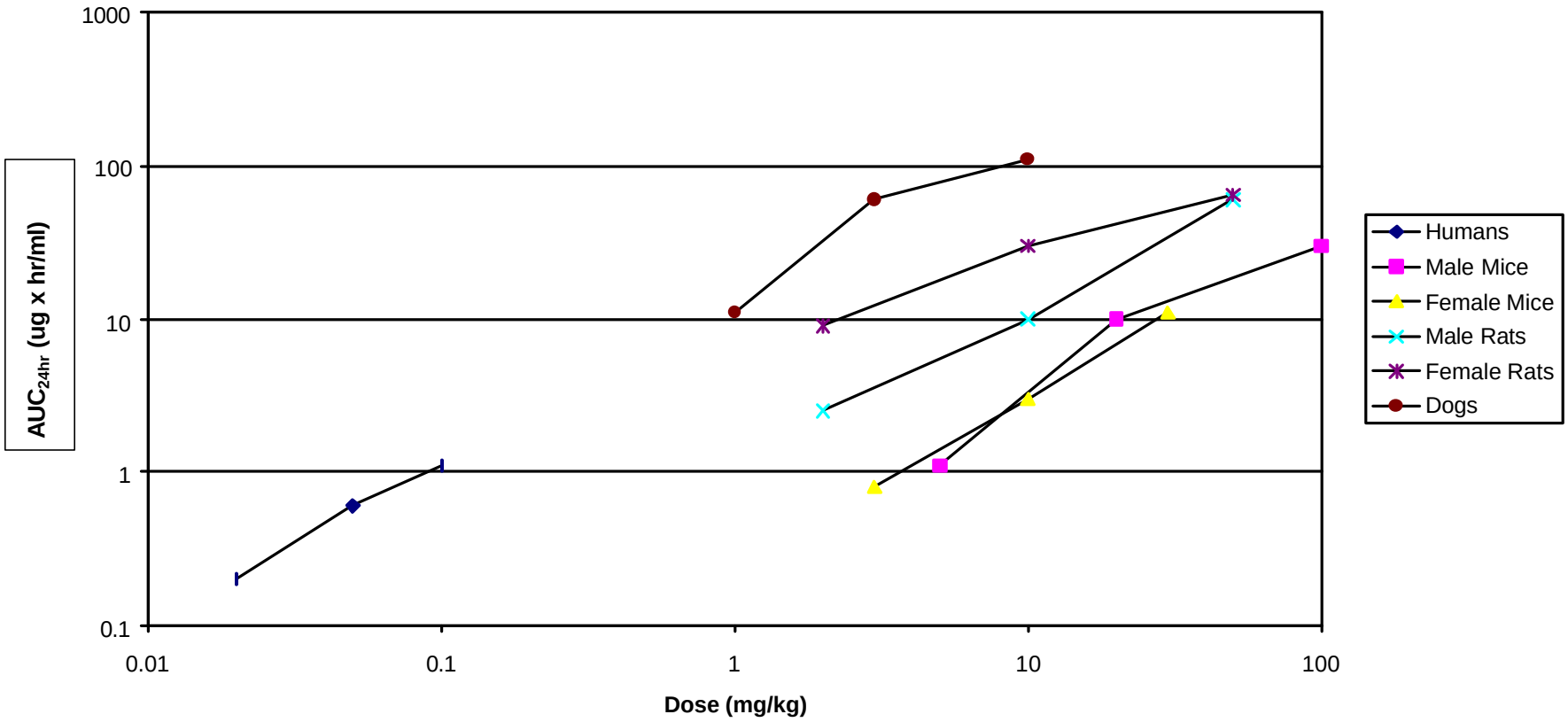
	Steady State AUC (mcg-hr/ml)						
Daily Dose	**Mice[a]**		**Rats[b]**			**Female**	
(mg/kg)	**M**	**F**	**M**	**F**	**Dogs[c]**	**Rabbits[b]**	**Humans[f]**
1						9	3
5					3	25	
10					4		
20					10		
25	10	12	6	8		273	
40					10		
50					12		
62.5	35	40					
100	40	48	25[d], 20[e]	27[d], 22[e]	40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

_____

a - In diet.
b - By gavage.
c - In capsules. Males and females combined.
d - Six-month toxicity study.
e - Carcinogenicity study.
f - Protocol 147-007.

EXAMPLE

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



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

EXAMPLE

2.6.7.4 Toxicology **Drug Substance** **Test Article:** Curitol Sodium

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

a - Area percent.

EXAMPLE

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

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

EXAMPLE

2.6.7.6 Repeat-Dose Toxicity **Nonpivotal Studies** **Test Article:** Curitol Sodium

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

a - No Observed Adverse Effect Level.

EXAMPLE #1

2.6.7.7A Repeat-Dose Toxicity **Report Title:** MM-180801: Three--Month Oral Toxicity Study in Rats **Test Article:** Curitol Sodium

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

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

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

GLP Compliance: Yes

Special Features: None
No Observed Adverse Effect Level: 200 mg/kg

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

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

(Continued)

EXAMPLE #1

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

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

- No noteworthy findings.

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

(Continued)

EXAMPLE #1

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

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

\- No noteworthy findings.

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

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

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

EXAMPLE #2

2.6.7.7B Repeat-Dose Toxicity **Report Title:** MM-180801: One-Month Oral Toxicity Study in Dogs **Test Article:** Curitol Sodium

Species/Strain: Beagle Dogs
Initial Age: 5-6 Months
Date of First Dose: 2 Feb 94
Duration of Dosing: 1 Month
Duration of Postdose: None
Method of Administration: Oral
Vehicle/Formulation: Gelatin Capsules
Study No. 94020
Location in CTD: Vol. 6 Page 1
GLP Compliance: Yes

Special Features: Hepatic enzyme induction evaluated at termination.
No Observed Adverse Effect Level: 10 mg/kg

Daily Dose (mg/kg)	0 (Control)		10		40		100	
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								
Body Weight (%[a])	0	0	0	0	0	0	0	0
Clinical Observations:	9.8 kg	9.2 kg	0	0	-1	-19**	0	-18**
Hypoactivity (after dosing)								
Ophthalmoscopy	-	-	-	-	-	-	+	++
Electrocardiography	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-
ALT (IU/L): Week 2								
Week 4	22	25	24	27	21	24	48*	69**
	25	27	26	25	23	25	54*	84**

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

EXAMPLE #2

2.6.7.7B Repeat-Dose Toxicity **Study No. 94020 (Continued)**

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

\- No noteworthy findings.

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

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

EXAMPLE #1

2.6.7.8A Genotoxicity: In Vitro **Report Title:** MM-180801: Ames Reverse Mutation Study in Salmonella and E. Coli **Test Article:** Curitol Sodium

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 2 **Study No.** 96669
Strains: S. typhimurium and E. coli **No. of Replicate Cultures:** 3 **Location in CTD:** Vol. 10 Page211
Metabolizing System: Aroclor-induced rat liver S9**,** 7.1% **No. of Cells Analyzed/Culture:** -
Vehicles: **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes
Treatment: Plate incorporation for 48 hr. **Date of Treatment:** Feb. 1996
Cytotoxic Effects: None.
Genotoxic Effects: None.

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

a - Precipitation.

EXAMPLE #2

2.6.7.8B Genotoxicity: In Vitro **Report Title:** MM-180801: Cytogenetics Study in Primary Human Lymphocytes **Test Article:** Curitol Sodium

Test for Induction of: Chromosome aberrations **No. of Independent Assays:** 1 **Study No.** 96668
Strains: Primary human lymphocytes **No. of Replicate Cultures:** 2 **Location in CTD:** Vol. 10 Page245
Metabolizing System: Aroclor-induced rat liver S9**,** 5% **No. of Cells Analyzed/Culture:** 100
Vehicles: **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes
Treatment: Continuous treatment for 24 hrs. without S9; pulse treatment 5 hrs. and recovery time 24 hrs. with and without S9. **Date of Treatment:** Aug. 1996
Cytotoxic Effects: Dose-related decreases in mitotic indices.
Genotoxic Effects: Chromosome aberrations without S9 at 10 and 20 µg/ml, and with S9 at 50 and 200 µg/ml.

Metabolic Activation	Test Article	Concentration (mcg/ml)	Cytotoxicity[a] (% of control)	Aberrant Cells Mean %	Abs/Cell	Total polyploid cells
Without Activation	DMSO	-	100	2.0	0.02	4
	MM-180801	2.5	78	3.0	0.03	3
		5	59	4.0	0.05	4
		10	36	16.5**	0.20	2
		20	32	35.0**	0.55	3
	Mitomycin	0.10	52	38.5**	0.64	5
With Activation	DMSO	-	100	4.0	0.04	3
	MM-180801	2.5	91	4.5	0.05	3
		10	88	4.5	0.05	2
		50	80	9.5*	0.10	4
		200	43	34.0**	0.66	3
	Cyclophosphamide	4	68	36.5**	0.63	6

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$
a - Based on mitotic indices.

EXAMPLE #1

2.6.7.9A Genotoxicity: In Vivo **Report Title:** MM-180801: Oral Micronucleus Study in Rats **Test Article:** Curitol Solution

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

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

Study No: 96683
Location in CTD: Vol. 10 Page502

GLP Compliance: Yes
Date of Dosing: July 1996

Toxic/Cytotoxic Effects: At 2000 mg/kg, clinical signs, two deaths, and decreases in bone marrow PCEs.
Genotoxic Effects: None.
Evidence of Exposure: Overt toxicity at 2000 mg/kg.

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

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

EXAMPLE #2

2.6.7.9B Genotoxicity: In Vivo **Report Title:** MM-180801: Oral DNA Repair Study in Rats **Test Article:** Curitol Solution

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

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

Study No: 51970
Location in CTD: Vol. 11 Page 2

GLP Compliance: Yes
Date of Dosing: Jan. 1997

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

Nuclear = Nuclear grain count; the number of grains over the nucleus.
Cytoplasm = Cytoplasmic grain count; the highest grain count from 2 nuclear-sized areas adjacent to the nucleus.
NG = Net grains/nucleus; the nuclear count minus the cytoplasmic count.
% IR = Percentage of cells with at least 5 NG.
NGIR = Average net grains/nucleus of cells in repair.

EXAMPLE

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

Species/Strain: CD-1 Mice
Initial Age: 6 Weeks
Date of First Dose: 20 Sep 95
Duration of Dosing: 21 months
Method of Administration: Diet
Vehicle/Formulation: In Diet
Treatment of Controls: Drug-Free Diet
Study No. 95012
Location in CTD: Vol. 4 Page 1
GLP Compliance: Yes

Basis for High-Dose Selection: Toxicity-based endpoint.
Special Features: 12 additional males and 12 additional females per drug-treated group bled at 6 months for toxicokinetic monitoring and then removed from the study.

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

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$
a - From Study No. 95013.
b - At 6 months. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
c - One missing mouse could not be evaluated.
(Continued)

EXAMPLE

2.6.7.10 Carcinogenicity **Study No. 95012 (Continued)**

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

a - Trend analysis, $p<0.005$
b - Trend analysis, $p<0.025$
(Continued)

EXAMPLE

2.6.7.10 Carcinogenicity **Study No. 95012 (Continued)**

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

- No noteworthy findings.
Fisher Exact Test: * - p<0.05 ** - p<0.01

EXAMPLE

2.6.7.11 Reproductive and Developmental Toxicity **Nonpivotal Studies** **Test Article:** Curitol Sodium

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

G – Gestation day

EXAMPLE

2.6.7.12 Reproductive and Developmental Toxicity Fertility and Early Embryonic Development to Implantation

Report Title: MM-180801: Oral Study of Effects on Fertility and Early Embryonic Development in Rats **Test Article:** Curitol Sodium

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

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

Study No. 97072
Location in CTD: Vol. 6 Page 1

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

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

GLP Compliance: Yes

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

\- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - $p<0.05$ ** - $p<0.01$
a -After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
b -From Study No. 94220.

(Continued)

EXAMPLE

2.6.7.12 Reproductive and Developmental Toxicity **Study No. 97072**

(Continued)

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

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - $p<0.05$ ** - $p<0.01$

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

b - From Study No. 94220.

EXAMPLE

2.6.7.13 Reproductive and Developmental Toxicity - Effects on Embryofetal Development

Report Title: MM-180801: Oral Study of Effects on Embryofetal 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

Location in CTD: Vol. 6 Page 200

GLP Compliance: Yes

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

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

- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day
Dunnett's Test * - $p<0.05$ ** - $p<0.01$
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
b - From Study No. 97231.

(Continued)

EXAMPLE

2.6.7.13 Reproductive and Developmental Toxicity **Study No. 97028**

(Continued)

Daily Dose (mg/kg)		**0 (Control)**	**1**	**5**	**25**
Litters:	No. Litters Evaluated	18	16	17	18
	No. Live Fetuses	140	126	148	86*
	Mean No. Resorptions	0.2	0.3	0.4	4.7**
	No. Dead Fetuses	1	0	0	0
	Mean % Postimplantation Loss	4.3	2.8	5.4	49.0**
	Mean Fetal Body Weight (g)	44.82	42.44	42.14	42.39
	Fetal Sex Ratios (% males)	46.3	57.7	57.4	52.8
	Fetal Anomalies:				
	Gross External				
	Lower jaw: Short				
	No. Fetuses (%)	0	0	0	7 (8.0)*
	No. Litters (%)	0	0	0	5 (27.8)**
	Visceral Anomalies				
	Tongue: Absent				
	No. Fetuses (%)	0	0	0	6 (6.9)*
	No. Litters (%)	0	0	0	6 (33.3)**
	Skeletal Anomalies				
	Mandible: Cleft				
	No. Fetuses (%)	0	0	0	10 (11.5)**
	No. Litters (%)	0	0	0	8 (44.4)**
	Ribs: Cervical				
	No. Fetuses (%)	2 (1.4)	0	1 (0.7)	0
	No. Litters (%)	1 (5.6)	0	1 (5.9)	0
	Sternebrae: Misshapen				
	No. Fetuses (%)	2 (1.4)	1 (0.8)	0	1 (1.2)
	No. Litters (%)	2 (11.1)	1 (6.3)	0	1 (5.6)
	Total Affected Fetuses (Litters)	2 (2)	1 (1)	0	15 (10)

- No noteworthy findings.

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

EXAMPLE

2.6.7.14 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function

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

Test Article: Curitol Sodium

Design similar to ICH 4.1.2? Yes

Duration of Dosing: G6 - L21

Day of Mating: Day 0

Study No. 95201

Species/Strain: Wistar Rats

Method of Administration: Gavage

Location in CTD: Vol. 10 Page 1

Initial Age: 9-10 Weeks

Vehicle/Formulation: Water

Date of First Dose: 8 Oct 95

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

GLP Compliance: Yes

Special Features: None

No Observed AdverseEffect Level:

F_0 Females: 7.5 mg/kg

F_1 Males: 75 mg/kg

F_1 Females: 75 mg/kg

Daily Dose (mg/kg)		**0 (Control)**	**7.5**	**75**	**750**
F_0 Females:	Toxicokinetics: AUC[b] (mcg-hr/ml)	-	2.4	21	150
	No. Pregnant	23	21	22	23
	No. Died or Sacrificed Moribund	0	0	0	8
	Clinical Observations	-	-	++	+++
	Necropsy Observations	-	-	-	-
	Gestation Body Weight (%[a])	225 g	0	0	-25**
	Lactation Body Weight (%[a])	210 g	0	0	0
	Gestation Food Consumption (%[a])	15 g	0	0	-12*
	Lactation Food Consumption (%[a])	16 g	0	0	0
	Mean Duration of Gestation (days)	22.1	22.2	22.1	23.5[+]
	Abnormal Parturition	-	-	-	-

\- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day
Dunnett's Test * - $p<0.05$ ** - $p<0.01$ L = Lactation day
Kruskal-Wallis with Dunn's procedure + - $p<0.05$

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

b -From Study No. 97227

(Continued)

EXAMPLE

2.6.7.14 Reproductive and Developmental Toxicity **Study No. 95201**

(Continued)

Daily Dose (mg/kg)		**0 (Control)**	**7.5**	**75**	**750**
F_1 Litters:	No. Litters Evaluated	23	21	22	15
(Preweaning)	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 Observations	-	-	-	-
F_1 Males:	No. Evaluated Postweaning	23	21	22	15
(Postweaning)	No. Died or Sacrificed Moribund	-	-	-	-
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Change[b] (g)	200	195	195	186*
	Food Consumption (%[b])	15 g	0	0	-11*
	Preputial Separation	-	-	-	-
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	2.4	3.3	2.9	3.5
	No. of Males that Mated	23	21	21	23
	No. of Fertile Males	23	21	19	20

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - p<0.05 ** - p<0.01
Kruskal-Wallis with Dunn's procedure + - p<0.05 ++ - p<0.01
a - From birth to weaning.
b - From weaning to mating. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences) (Continued)

EXAMPLE

2.6.7.14 Reproductive and Developmental Toxicity **Study No. 95201**

(Continued)

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

EXAMPLE

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

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