THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Version: Revision 1

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PART III: NONCLINICAL DOCUMENT

PREAMBLE

Part III should provide the Nonclinical Overview*, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biologics, Vaccine, and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who requires Study Reports should ask for the necessary documents.

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A list of references used, stated in accordance with 1979 “Vancouver Declaration” on “Uniform Requirements for Manuscripts Submitted to Biomedical Journals”, or the system used in “Chemical Abstracts”, should be provided. Copies of important references cited in the Nonclinical Overview should be provided in this section. All references that have not been provided should be available upon request.

THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PART III: NONCLINICAL DOCUMENT

SECTION A. TABLE OF CONTENTS

GUIDE ON NONCLINICAL OVERVIEW AND SUMMARIES:

This guide provides recommendations for the harmonization of the Nonclinical Overview, Nonclinical Written and Tabulated Summaries.

The primary purpose of nonclinical written and tabulated summaries should be to provide a comprehensive, factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e. as applicable to labeling) should be addressed in the nonclinical overview.

SECTION B: NONCLINICAL OVERVIEW

The nonclinical overview should provide an integrated, overall analysis of the information in the Common Technical Document.

1. GENERAL ASPECTS

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

Except for Biologics and Vaccine, an assessment of the impurities and degradants present in the drug substance and product should be included, along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For Biologics and Vaccine, comparability of material used in nonclinical and clinical studies and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding the excipient’s safety should be provided.

Relevant, scientific literature and the properties of related products should be taken into account. If details references to published, scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidances. In addition, the availability of information on the quality of batches of drug substances used in these referenced studies should be discussed.

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

2. CONTENT AND STRUCTURAL FORMAT

The Nonclinical Overview should be presented in the following sequence:

NONCLINICAL OVERVIEW
1. Overview of the Nonclinical Testing Strategy
2. Pharmacology
3. Pharmacokinetics
4. Toxicology
5. Integrated Overview and Conclusions
6. 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, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g., impact of the disease states, changes in physiology, antiproduct antibodies, cross-pieces consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

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

- Pharmacodynamics
- Toxic signs
- Causes of death
- Pathologic findings
- Genotoxic activity ---- the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- The carcinogenic risk to humans – if epidemiologic data are available, they should be taken into account
- Fertility, embryofetal development, pre- and postnatal toxicity
- Studies in juvenile animals
- The consequences of use before and during pregnancy, during lactation, and during pediatric development
- Local tolerance
- Other toxicity studies and / or studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect and/or 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 summarizing this information are recommended
- The effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

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

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

SECTION C: NONCLINICAL WRITTEN AND TABULATED SUMMARIES

1. GUIDANCE ON NONCLINICAL WRITTEN SUMMARIES

1.1 Introduction

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

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

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

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

1.2 General Presentation Issues

Order of Presentation of Information Within Sections

When available, in vitro studies should precede in vivo studies. Where multiple studies of the same type are summarized within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Nonhuman primate
- Other nonrodent mammal
- Nonmammals

Routes of administration should be ordered as follows:

- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

Use of Tables and Figures

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

To allow authors flexibility in defining the optimal structure for the written summaries, tables and figures should preferably be included within the text. Alternately, they could be grouped together at the end of each of the Nonclinical Written Summaries.

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

Length of Nonclinical Written Summaries

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

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

- Introduction
- Pharmacology written summary

- Pharamcology tabulated summary
- Pharmacokinetics written summary
- Pharmacokinetics tabulated summary
- Toxicology written summary
- Toxicology tabulated summary

2. CONTENT OF NONCLINICAL WRITTEN AND TABULATED SUMMARIES

INTRODUCTION

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

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

2.1 PHARMACOLOGY

2.1.1 WRITTEN SUMMARY

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

- Brief summary
- Primary pharmacodynamics / Immunogenicity Study
- Secondary pharmacodynamics
- Safety pharmacology
- Pharmacodynamics drug interactions
- Discussion and conclusions
- Tables and figures (either here or included in text)

Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately two to three 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 and / or exclusion of particular data (e.g. lack of an animal model).

2.1.1.1 Primary Pharmacodynamics / Immunogenicity Study

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

A pharmacodynamic study for a vaccine product is generally conducted to evaluate the immunogenicity. However, a pharmacodynamics study may also extend to include the pharmacology of an adjuvant. Immunization studies in animal models should be conducted because they may provide valuable "proof of concept" information to support a clinical development plan. In addition, immunogenicity data derived from appropriate animal models are useful in establishing the immunological characteristics of the product and may guide selection of the doses, schedules and routes of administration to be evaluated in clinical trials.

Nonclinical immunogenicity studies should assess the relevant immune response, e.g. humoral and/or cell-mediated immune response, induced in the vaccinated animals.

2.1.1.2 Secondary Pharmacodynamics

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

2.1.1.3 Safety Pharmacology

Safety pharmacology studies should be summarized and evaluated in this section. In some cases, secondary pharmacodynamics studies can contribute to the safety evaluation when they predict or assess potential adverse effects in humans. In such cases, these secondary pharmacodynamics studies should be considered, along with safety pharmacology studies.

2.1.1.4 Pharmacodynamics Drug Interactions

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

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

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

2.1.2 PHARMACOLOGY TABULTED SUMMARY (SEE APPENDIX A)

2.2 PHARMACOKINETICS

2.2.1 WRITTEN SUMMARY

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

- Brief Summary
- Method of analysis
- Absorption
- Distribution
- Metabolism (Inter-species Comparison)
- Excretion
- Pharmacokinetic drug interactions
- Other pharmacokinetic studies
- Discussion and conclusions
- Tables and figures (either here or included in text)

Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately two or three pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasizing, for example, whether the species and strains

examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

Method of Analysis

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

2.2.1.1 Absorption

The following data should be summarized in this section:

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

2.2.1.2 Distribution

The following data should be summarized in this section

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

2.2.1.3 Metabolism (inter-species comparison)

The following data should be summarized in this section:

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

2.2.1.4 Excretion

The following data should be summarized in this section:

- Routes and extent of excretion
- Excretion in milk

2.2.1.5 Pharmacokinetic Drug Interaction

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

2.2.1.6 Other Pharmacokinetic Studies

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

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

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

2.2.2 PHARMACOKINETICS TABULATED SUMMARY (SEE APPENDIX A)

2.3 TOXICOLOGY

2.3.1 WRITTEN SUMMARY

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

- Brief summary
- Single-dose toxicity
- Repeat-dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Studies in juvenile animals
- Local Tolerance
- Other toxicity studies
- Discussion and conclusions
- Tables and figures (either here or included in text)

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

Toxicology Program

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

*This column should be included only if metabolites are investigated.

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

2.3.1.1 Single-dose Toxicity

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

2.3.1.2 Repeat-Dose Toxicity

Studies should be summarized 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) and / or response relationships, no observed adverse effect levels). Nonpivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH guidance M3).

2.3.1.3 Genotoxicity

Studies should briefly summarized in the following order:

- In vitro nonmammalian cell system
- In vitro mammalian cell system
- In vivo mammalian system (including supportive toxicokinetics evaluation)
- Other systems

2.3.1.4 Carcinogenicity (Including supportive toxicokinetics evaluation)

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

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

2.3.1.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations)

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

- Fertility and early embryonic development
- Embryofetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and / or further evaluated if such studies have been conducted

If modified study designs are used, the subheadings should be modified accordingly.

2.3.1.6 Local tolerance

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

2.3.1.7 Other Toxicity Studies (if available)

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

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

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

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

2.3.2 TOXICOLOGY TABULATED SUMMARY (SEE APPENDIX A)

GUIDANCE ON NONCLINICAL TABULATED SUMMARIES

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

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

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

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

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

SECTION D: NONCLINICAL STUDY REPORTS

For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biologics, Vaccine, and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. This guidance presents an agreed upon format for the organization of the nonclinical reports in the Common Technical Document for applications that will be submitted to regulatory authorities. This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual animal data is in the study report or as an appendix to the study report.

1. 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.

2. PHARMACOLOGY

2.1 Written Study Reports

The study reports should be presented in the following order:

2.1.1 Primary Pharmacodynamics / Immunogenicity Study

2.1.2 Secondary Pharmacodynamics
2.1.3 Safety Pharmacology
2.1.4 Pharmacodynamic Drug Interactions

3. PHARMACOKINETICS

3.1 Written Study Reports

The study reports should be presented in the following order:

3.1.1 Analytical Methods and Validation Reports (if separate reports are available)
3.1.2 Absorption
3.1.3 Distribution
3.1.4 Metabolism (Inter-species comparison)

3.1.5 Excretion
3.1.6 Pharmacokinetic Drug Interactions (nonclinical)
3.1.7 Other Pharmacokinetic Studies

4. TOXICOLOGY

4.1 Written Study Reports

The study reports should be presented in the following order:

4.1.1 Single-Dose Toxicity (in order by species, by route)

4.1.2 Repeat-Dose Toxicity (in order by species, by route, by duration, including supportive toxicokinetics evaluations)

4.1.3 Genotoxicity

4.1.3.1 In vitro

4.1.3.2 In vivo (including supportive toxicokinetics evaluations)

4.1.4 Carcinogenicity (including supportive toxicokinetics evaluations)

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

4.1.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.1.4.3 Other studies

4.1.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly).

4.1.5.1 Fertility and early embryonic development

4.1.5.2 Embryofetal development

4.1.5.3 Prenatal and postnatal development, including maternal function

4.1.5.4 Studies in which offspring (juvenile animals) are dosed and / or further evaluated

4.1.6 Local Tolerance

4.1.7 Other Toxicity Studies (if available)

4.1.7.1 Antigenicity

4.1.7.2 Immunotoxicity

4.1.7.3 Mechanistic studies (if not included elsewhere)

4.1.7.4 Dependence

4.1.7.5 Metabolites

4.1.7.6 Impurities

4.1.7.7 Other

SECTION E: LIST OF KEY LITERATURE REFERENCES

APPENDIX A: THE NONCLINICAL TABULATED SUMMARIES TEMPLATE

2.1.2 Pharmacology

2.1.2.1 Pharmacology: Overview
2.1.2.2 Primary Pharmacodynamics / Immunogenicity Study*
2.1.2.3 Secondary Pharmacodynamics*
2.1.2.4 Safety Pharmacology
2.1.2.5 Pharmacodynamic Drug Interaction*

2.2.2 Pharmacokinetics

2.2.2.1 Pharmacokinetics: Overview
2.2.2.2 Analytical Methods and Validation Reports*
2.2.2.3 Pharmacokinetics: Absorption After a Single Dose
2.2.2.4 Pharmacokinetics: Absorption After Repeated Doses
2.2.2.5 Pharmacokinetics: Organ Distribution
2.2.2.6 Pharmacokinetics: Plasma Protein Binding
2.2.2.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
2.2.2.8 Pharmacokinetics: Other Distribution Study
2.2.2.9 Pharmacokinetics: Metabolism In Vivo
2.2.2.10 Pharmacokinetics: Metabolism In Vitro
2.2.2.11 Pharmacokinetics: Possible Metabolic Pathways
2.2.2.12 Pharmacokinetics: Induction / Inhibition of Drug Metabolizing Enzymes
2.2.2.13 Pharmacokinetics: Excretion
2.2.2.14 Pharmacokinetics: Excretion into Bile
2.2.2.15 Pharmacokinetics: Drug-Drug Interactions
2.2.2.16 Pharmacokinetics: Other

2.3.2 Toxicology

2.3.2.1 Toxicology: Overview
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2.3.2.3 Toxicokinetics: Overview of Toxicokinetics Data
2.3.2.4 Toxicology: Drug Substance
2.3.2.5 Single-Dose Toxicity
2.3.2.6 Repeat-Dose Toxicity: Nonpivotal Studies
2.3.2.7 Repeat-Dose Toxicity: Pivotal Studies
2.3.2.8 Genotoxicity: In Vitro
2.3.2.9 Genotoxicity: In Vivo
2.3.2.10 Carcinogenicity
2.3.2.11 Reproductive and Developmental Toxicity: Nonpivotal Studies
2.3.2.12 Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)
2.3.2.13 Reproductive and Developmental Toxicity: Effects on Embryofetal Development (Pivotal)

2.3.2.14 Reproductive and Developmental Toxicity: Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)
2.3.2.15 Tolerance
2.3.2.16 Other Toxicity Studies

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

2.1.2 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).

2.1.2.4 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.

2.2.2 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.

2.2.2.3 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 indicated.

2.2.2.4 Pharmacokinetics: Absorption after Repeated Doses Test Article:

(Data can be tabulated as in the format of 2.2.2.3, if applicable)

Format A

Test Article:

2.2.2.5 Pharmacokinetics: Organ Distribution

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)					
	T(1)	T(2)	T(3)	T(4)	T(5)	T ½
Tissues/organs						

Additional Information:

[1)] [Tissue]/[Plasma]

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)] **[Tisssue]/[Plasma]**

2.2.2.6 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:

2.2.2.7 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

Exretion 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:
Nenonates:

Additional Information:

Notes for Table 2.2.2.7

(1)' Even if the data are obtained in reproduction toxicology studies, they should be presented in this table.
(2)' International Nonpropriety Nama (INN).
(3)' The tissue sampled should be described (e.g., plasma foe dams, fetal concentratios).

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

2.2.2.9 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 Samp			Location in CTD		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.*

2.2.2.10 Pharmacokinetics: Metabolism In Vitro

Test Article:

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

Study system:

Time					
Concentratoin:					
Compounds					
Parent					
M-1					
M-2					

Additional Information:

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

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

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

2.2.2.12 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:

2.2.2.13 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 Nonpropriety 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.

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

[Data can be tabulated as in the format of 2.2.2.13 if applicable.]

2.2.2.15 Pharmacokinetics: Drug-Drug Interactions

Test Article:

Location in CTD: Vol. Page
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2.2.2.16 Pharmacokinetics: Other

Test Article:

Location in CTD: Vol. Page
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2.3.2 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 Nonpropriety 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.

2.3.2.2 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.	Page
(2)						***(3)***	

Notes: '(1) International Nonpropriety 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.

2.3.2.3 Toxicokinetics	**Overview of Toxicokinetics Data**	**Test Article: '(1)**
	(2)	

Notes: '(1) International Nonpropriety 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.

2.3.2.4 Toxicology **Drug Substance** **Test Article:***'(1)*

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

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

2.3.2.5 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 Nonpropriety Name (INN).

2.3.2.6 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 Pharmaceuticals *(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 Nonpropriety Name (INN).

a - No Observed Adverse Effect Level.

2.3.2.7 *(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)

2.3.2.7 *(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 2.3.2.7

(1) The tables should be numbered consecutively (e.g., 2.3.2.7A, 2.3.2.7B, 2.3.2.7C).

(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 Pharmaceuticals (November 1997), as well as any other repeat-dose toxicity studies that could be considered pivotal.*

(3) International Nonpropriety 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.

2.3.2.8 *(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., 2.3.2.8A, 2.3.2.8B). Results of replicate assays should be shown on subsequent pages.
(2) International Nonpropriety 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

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

Test for Induction of: **Treatment Schedule:** **Study No.**
Species/Strain: **Sampling Time:** **Location in CTD: Vol.** **Page**
Age: **Method of Administration:**
Cells Evaluated: **Vehicle/Formulation:** **GLP Compliance:**
No. of Cells Analyzed/Animal: **Date of Dosing:**
Special Features:
Toxic/Cytotoxic Effects:
Genotoxic Effects:
Evidence of Exposure:

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

Notes: *(1) The tables should be numbered consecutively (e.g., 2.3.2.9A, 2.3.2.9B).*
(2) *International Nonpropriety Name (INN).*
(3) *Methods of statistical analyses should be indicated.*

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

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

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:**
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)

2.3.2.10 *(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										

###

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

Notes for Table 2.3.2.10

(1) Tables should be numbered consecutively(e.g., 2.3.2.10A), 2.3.2.10B). There should be ona table for each carcinogenicity study.

(2) International Nonpropriety Name (INN).

(3) From ICH Guidance SIC 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.

2.3.2.11 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 However, investigative studies should be summarized using a more detailed template.*

(2) *International Nonpropriety Name (INN).*

2.3.2.12 ***(1)*** **Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation** ***(3)***

Report Title:

Test Article: ***(2)***

Study Design :

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:

Fo Males:

Fo Females:

F1 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 Fertiles 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)

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

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

Females Toxicokinetics: AUC ( ) (*4*)

No. Evaluated
No. Died or Sacrified 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 2.3.2.11, 2.3.2.13 and 2.3.2.14

(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 SHOEN IN THESE TEMPLATES. DATA PRESENTATION SHOULD BE FLEXIBLE AND A PPROPRIATE ACCORDING TO OPTIMAL STATISTICAL ANALYSIS AND THE DESIGN OF THE STUDY. If additional parametes 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)

2.3.2.13 (*1*) Reproductive and Developmental Toxicity - Efects on Embryofetal Development (*3*) **Report Title:** **Test Article: (*2*)**

Study Design: **Duration of Dosing:** **Study No.**
Day of Mating: (*8*)
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:
Fo Females:
F1 Litters:

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

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

No. Pregnant
No. Died or Sacrificed Moribund (5)
No. Aborted or with Total Resorption of Litter
Clinical Observations
Necropsy Observations
Body Weight (%[a])
Food Consumption (%[a])
Mean No. Corpora Lutea
Mean No. Implantations
Mean % Preimplantation Loss

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

2.3.2.13 (*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

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

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

Study Design: **Duration of Dosing:** **Day of Mating : (8)** **Study No.**

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:

Fo Females:

F1 Males:

F1 Females:

Daily Dose (mg/kg)	**0 (Control)**
Fo Females: Toxicokinetics: AUC ( ) (*4*)	
No. Pregnant	
No. Died or Sacrified 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)

2.3.2.14 (*1*) Reproductive and Developmental Toxicity **Study No.** **(Continued)**

Daily Dose (mg/kg)		**0 (Control)**
F1 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	
F1 Males:	No. Evaluated Postweaning 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). (Continued)

2.3.2.14 (1) Reproductive and Developmental Toxicicty **Study No. (Continued)**

Daily dose (mg/kg)		**0 (Control)**
F1 Females:	No. evaluated Post eaning	
(Postweaning)	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Premating Body Weigth 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. Females Sperm-Positive	
	No. of Pregnant Females	
	Mean No. Corpora Lutea	
	Mean No. Implantations	
	Mean % Preimplantation Loss	
F2 Litters:	Mean No. Live Conceptuses/Litter	
	Mean No. Resorptions	
	No. of Litter with Dead Conceptuses	
	No. Dead Conceptuses	
	Mean % Postimplantation Loss	
	Fetal Body Weights (g)	
	Fetal Sex Ratios (% males)	
	Fetal Anomalies	

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

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

a - From weaning to mating

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

2.3.2.14 (1) Reproductive and Developmental Toxicicty **Study No. (Continued)**

Daily dose (mg/kg)		**0 (Control)**
F1 Females:	No. evaluated Post eaning	
(Postweaning)	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Premating Body Weigth Changea (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*
	Mean No. Days Prior to Mating	*Parturition*
	No. of Females Sperm-Positive	
	No. of Pregnant Females	
	Mean Duration of Gestation	
	Abnormal Parturition	
F2 Litters:	No. Litters Evaluated	
	Mean No. of Implantations	
	Mean No. Pups/Litter	
	Mean No. Liveborn Pups/Litter	
	Mean No. Stillborn Pups/Litter	
	Postnatal Survival to Day 4	
	Postnatal Survival to Weaning	
	Change in Pup Body Weightsa (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).

2.3.2.15 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).

2.3.2.16 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 local tolerance studies should be summarized.*
(2) International Nonproprietary Name (INN).

ACTD Check List for Product Classification
(ASEAN Common Technical Dossier on Nonclinical Data for Pharmaceutical Registration)

Part III: Document	NCE	BIOLOGICS	RT	S/P	IND	Vaccine				
						NV	NC	CV/ EV	IND	S/P
Section A. Table of Content	√	√	❖	❖	❖	√	√	❖	❖	❖
Section B. Nonclinical Overview	√	√	❖	❖	❖	√	√	❖	❖	❖
1. General Aspect	√	√	❖	❖	❖	√	√	❖	❖	❖
2. Content and structural format	√	√	❖	❖	❖	√	√	❖	❖	❖
Section C. Nonclinical Summary (Written and Tabulated)										
1. **Nonclinical Written Summaries**	√	√	❖	❖	❖	√	√	❖	❖	❖
1.1 Pharmacology										
1.1.1 Primary Pharmacodynamics / Immunogenicity Study	√	√	-	-	-	√	√	-	-	-
1.1.2 Secondary Pharmacodynamics	√	√	-	-	-	-	-	-	-	-
1.1.3 Safety Pharmacology	√	√	-	-	-	❖	-	-	-	-
1.1.4 Pharmacodynamics Drug Interactions	√	√	-	-	-	❖	❖	-	-	-
1.2 Pharmacokinetics										
1.2.1 Absorption	√	❖	❖	❖	-	-	-	-	-	-
1.2.2 Distribution	√	❖	❖	❖	-	❖	❖	❖	-	❖
1.2.3 Metabolism (Inter-species comparison)	√	❖	❖	❖	-	-	-	-	-	-
	√	❖	❖	❖	-	-	-	-	-	-
1.2.4 Excretion	√	-	-	-	-	-	-	-	-	-
1.2.5 Pharmacokinetics Drug Interaction (non-clinical)	√	-	❖	-	-	-	-	-	-	-
1.2.6 Other Pharmacokinetics Studies										
1.3 Toxicology										
1.3.1 Single dose toxicity	√	√	-	-	-	❖	❖	❖	-	-

Part III: Document	NCE	BIOLOGICS	RT	S/P	IND	Vaccine				
						NV	NC	CV/ EV	IND	S/P
1.3.2 Repeat dose toxicity	√	√	-	-	-	√	❖	❖ *)	-	-
1.3.3 Genotoxicity	√	-	-	-	-	❖	❖	❖	-	-
1.3.4 Carcinogenicity	√	♦	-	-	-	❖	❖	❖	-	-
1.3.5 Reproductive and developmental toxicity	√	√	-	-	-	❖	❖	❖	-	-
1.3.5.1 Fertility and early embryonic development	√	√	-	-	-	❖	❖	❖	-	-
1.3.5.2 Embryo-fetal development	√	√	-	-	-	❖	❖	❖	-	-
1.3.5.3 Prenatal and postnatal development including maternal function										
1.3.6 Local tolerance	❖	❖	❖	❖	❖	❖	❖	❖	-	❖
1.3.7 Other toxicity studies, if available	❖	❖	❖	❖	❖	❖	❖	❖	-	❖
2. Nonclinical Tabulated Summaries										
Section D. Nonclinical Study Report (As requested)										
1. **Table of Content**	√	√	❖	❖	❖	√	√	❖	❖	❖
2. **Pharmacology**										
2.1 Primary Pharmacodynamics / Immunogenicity Study	√	√	-	-	-	√	√	-	❖	-
2.2 Secondary Pharmacodynamics	√	√	-	-	-	-	-	-	-	-
2.3 Safety Pharmacology	√	√	-	-	-	❖	-	-	-	-
2.4 Pharmacodynamics Drug Interactions	√	√	-	-	-	❖	❖	-	-	-

Part III: Document	NCE	BIOLOGICS	RT	S/P	IND	Vaccine				
						NV	NC	CV/ EV	IND	S/P
3. **Pharmacokinetics**										
3.1 Analytical Methods and Validation	√	❖	❖	❖	-	-	-	-	-	-
Reports	√	❖	❖	❖	-	-	-	-	-	-
3.2 Absorption	√	❖	❖	❖	-	❖	❖	❖	-	❖
3.3 Distribution	√	❖	❖	❖	-	-	-	-	-	-
3.4 Metabolism (Inter-species comparison)	√	❖	❖	❖	-	-	-	-	-	-
3.5 Excretion	√	-	-	-	-	-	-	-	-	-
3.6 Pharmacokinetics Drug Interaction (non-clinical)	√	-	❖	-	-	-	-	-	-	-
3.7 Other Pharmacokinetics studies										
4. Toxicology										
4.1 Single dose toxicity	√	√	-	-	-	❖	❖	❖	-	-
4.2 Repeat dose toxicity	√	√	-	-	-	√	❖	❖ *)	-	-
4.3 Genotoxicity	√	-	-	-	-	❖	❖	❖	-	-
4.3.1 In vitro	√	-	-	-	-	❖	❖	❖	-	-
4.3.2 In vivo	√	-	-	-	-	❖	❖	❖	-	-
4.4 Carcinogenicity	√	♦	-	-	-	❖	❖	❖	-	-
4.4.1 Long term studies	√	♦	-	-	-	❖	❖	❖	-	-
4.4.2 Short or medium term studies	√	♦	-	-	-	❖	❖	❖	-	-
4.4.3 Other studies	√	♦	-	-	-	❖	❖	❖	-	-

Part III: Document	NCE	BIOLOGICS	RT	S/P	IND	Vaccine				
						NV	NC	CV/ EV	IND	S/P
4.5 Reproductive and developmental toxicity	√	√	-	-	-	❖	❖	❖	-	-
4.5.1 Fertility and early embryonic development	√	√	-	-	-	❖	❖	❖	-	-
	√	√	-	-	-	❖	❖	❖	-	-
4.5.2 Embryo-fetal development	√	√	-	-	-	❖	❖	❖	-	-
4.5.3 Prenatal and postnatal development including maternal function	√	√	-	-	-	❖	❖	❖	-	-
4.5.4 Studies in which the offspring are dosed and/or further evaluated										
4.6 Local tolerance	❖	❖	❖	❖	❖	❖	❖	❖	-	❖
4.7 Other toxicity studies, if available	❖	❖	❖	❖	❖	❖	❖	❖	-	❖
4.7.1 Antigenicity										
4.7.2 Immunotoxicity										
4.7.3 Dependence										
4.7.4 Metabolites										
4.7.5 Impurities										
4.7.6 Other										
Section E. List of Key Literature References	√	√	❖	❖	❖	❖	❖	❖	-	❖

NCE - New chemical entity
RT - New Route of Administration
S/P - New Strength and Posology
IND - New Indication
NC - New Combination
NV - New/Novel Vaccine, including new adjuvanted vaccine
CV/EV - Conventional Vaccine / Established Vaccine

√ - Required

– - Not Required

❖ - Where applicable, i.e. change of route of administration due to change in formulation, change of formulation and posology such as immediate release to sustained released) and/or for product with narrow margin of safety or variable kinetics

♦ - Generally inappropriate for Biological products, however, product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (e.g. Growth factors, immunosuppressive agents, etc.)

*) - Repeated toxicity study may not be needed if no difference in formulation compared to the approved vaccine. Different manufacturer may have different formulation, process and/or composition although the antigen have been established. Hence, the toxicity profile and tolerance may differ with the approved vaccine

- Where Applicable (Note: Vaccine efficacy data is generally required, unless otherwise scientifically justified.)

Notes:

1. As references for requirement, the following WHO Guidelines or their relevant updates are used:
   a. Guidelines on procedures and data requirements for changes to approved vaccines (WHO TRS 993, Annex 4)
   b. Guidelines on procedures and data requirements for changes to approved biotherapeutic products (2017)
   c. WHO Guidelines on nonclinical evaluation of vaccines (WHO TRS 927, Annex 1)
   d. Guidelines on clinical evaluation of vaccines: regulatory expectations (WHO TRS 1004, Annex 9)
   e. Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (WHO TRS 987, Annex 2)
2. The term ‘Biologics’ used in this document does not include vaccines with the rationale that vaccines has different characteristics compared with other biological products so that in many cases the requirements are different.