

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

ORGANIZATION OF THE DOSSIER

PREAMBLE

This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the future, will ease the preparation of electronic documental submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.

This guideline merely demonstrates an appropriate write-up format for acquired data. However, applicants can modify, if needed, to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results upon pharmaceutical registration.

Throughout the ACTD, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on either A4 or 8.5 x 11 paper. The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font and size, (Times New Roman, 12-point font), for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Every page should be numbered, with the first page of each part designated as page 1. For a paper, Common Technical Acronyms and abbreviations should be defined the first time they are used in each part. References should be cited in accordance with the 1979 Vancouver Declaration on Uniform requirements for Manuscripts Submitted to Biomedical Journals.

The Common Technical Document is organized into four parts as follows:

Part I. Table of Contents, Administrative Data and Product Information.

Part I contains initially the overall Table of Contents of the whole ACTD to provide basically the informations that could be looked through respectively. Secondly, the next content is the Administrative Data where required specific documentation in details is put together such as application forms, label, package insert etc. The last section of this part is Product Information where necessary information includes prescribed information, mode of action, side effects etc.

A general introduction to the pharmaceutical, including its pharmacologic class and mode of action should be included.

Part II. Quality Document

Part II should provide the Overall Summary followed by the Study Reports. The quality control document should be described in details as much as possible.

Part III. Nonclinical¹ Document

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

¹ The word “Nonclinical” replaces “Pre-clinical”

may not be required for NCE, Biotechnological Products 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 specific Study Reports should ask for the necessary documents.

Part IV Clinical Document

Part IV should provide the Clinical Overview and the Clinical Summary. 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, Biotechnological Products 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 specific Study Reports should ask for the necessary documents.

The overall organisation of the Common Technical Dossier is presented on the following in Parts:

Part I : Table of Content Administrative Information and Prescribing Information

Section A:	Introduction
Section B:	Overall ASEAN Common Technical Dossier Table of Contents
Section C:	Documents required for registration (for example, application forms, labelling, Product Data Sheet, prescribing information)

Part II : Quality Document

Section A:	Table of Contents
Section B:	Quality Overall Summary
Section C:	Body of Data

Part III : Nonclinical Document

Section A:	Table of Contents
Section B:	Nonclinical Overview
Section C:	Nonclinical Written and Tabulated Summaries
	1. Table of Contents
	2. Pharmacology
	3. Pharmacokinetics
	4. Toxicology

Section D: Nonclinical Study Reports

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Part IV : Clinical Document

Section A:	Table of Contents
Section B:	Clinical Overview
Section C:	Clinical Summary
	1. Summary of Biopharmaceutics and Associated Analytical Methods
	2. Summary of Clinical Pharmacology Studies
	3. Summary of Clinical Efficacy
	4. Summary of Clinical Safety
	5. Synopses of Individual Studies
Section D:	Tabular Listing of All Clinical Studies
Section E:	Clinical Study Reports
Section F:	List of Key Literature References

SEPTEMBER 2002

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

PART I : ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Section A: Introduction

This section contains the Administrative Data and Product Information which is the Part I of the ASEAN Common Technical Document (ACTD) for application to the Drug Regulatory Authority

Section B:
Table of Contents

1. Application Form
2. Letter of Authorisation (**where applicable**)
3. Certifications
4. Labelling
5. Product Information

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

PART I : ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Section C: Guidance on the Administrative Data and Product Information

1. Application Form
(Model of Application Form - Appendix I)
English and/or official native language shall be used.
2. Letter of Authorisation (**where applicable**)
(Model of Letter of Authorisation - Appendix II)
3. Certifications:
 - For contract manufacturing:
 - a. Licence of pharmaceutical industries and contract manufacturer
 - b. Contract manufacturing agreement
 - c. GMP certificate of contract manufacturer
 - For manufacturing "under-licence" (country specific) :
 - a. Licence of pharmaceutical industries
 - b. GMP certificate of the manufacturer
 - c. Copy of "under-licence" agreement.
 - For locally manufactured products (excluding the above):
 - a. Licence of pharmaceutical industries
 - b. GMP certificate (country specific)
 - For imported products:
 - a. Licence of pharmaceutical industries/importer/wholesaler (country specific)
 - b. Certificate of Pharmaceutical Product issued by the competent authority in the country of origin according to the current WHO format (Appendix III)
 - c. Site master file of manufacturer (unless previously submitted within the last 2 years)
(country specific)
4. Labelling
(Appendix IV)
English and/or official native language shall be used.
5. Product Information
 - 5.1 Package Insert (Appendix V)
English and/or official native language shall be used.
Package Insert is required for generic products
 - 5.2 Summary of Product Characteristics (Product Data Sheet) (Appendix VI)
English and/or official native language shall be used.
Summary of Product Characteristics is required for NCE and Biotechnology products.
 - 5.3. Patient Information Leaflet (PIL) (Appendix VII)
English and/or official native language shall be used.
PIL is required for Over-the-Counter Products

NOTE:

Language of dossier:
English and/or official native language shall be used
For generic product either SPC or package insert is acceptable

APPENDIX I

MODEL OF APPLICATION FORM

A. DETAILS OF APPLICANT AND MANUFACTURER

1. Applicant's (Marketing Authorisation Holder) Name
2. Applicant's (Marketing Authorisation Holder) Address
3. Manufacturer's* Name
4. Manufacturer's Address

* = *Manufacturer responsible for final batch release.*

Other manufacturers

Name & address	Role**

** = e.g. "prepares semi-finished product", "packaging", "granulation", "manufactures bulk finished dosage form", "contract research organization", etc.

B. DETAILS OF PRODUCT

1. Product Name, Dosage Form and Strength
2. Product Description
3. Generic Name and Quantity of active ingredients and excipients

C. TECHNICAL DOCUMENTS

1. Part II : ACTD-Quality
2. Part III : ACTD-Safety
3. Part IV : ACTD- Efficacy (Clinical Data)

Note : The documents (Part II or/and III or/and IV) required for submission are determined by the product category/classification

D. PATENT/TRADemark EVIDENCE, WHERE APPLICABLE

E. REFERENCE PRODUCT, WHERE APPLICABLE

F. APPLICANT DECLARATION (country specific)

APPENDIX II

MODEL OF LETTER OF AUTHORISATION

Company's Letterhead

LETTER OF AUTHORISATION

We, _____
Product Owner's Name and Address

Hereby appoint _____
Applicant's Name and Address

To apply for registration of our pharmaceutical product

Product Name,
Dosage Form and Strength

With the Drug Regulatory Authority in (state country) on our behalf . They will be the marketing authorisation holder of the registration certificate and be responsible for all matters pertaining to the regulation of this product.

Signature : _____

Date :

APPENDIX III

MODEL CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Certificate of a Pharmaceutical Product¹

This certificate conforms to the format recommended by the WHO (general instructions and explanatory notes attached)

Certificate No : _____

Exporting (Certifying) country: _____

Importing (Requesting) country: _____

1. Name and dosage form of product:

1.1 Active ingredient(s)² and amount(s)³ per unit dose:

For complete qualitative composition including excipients, see attached⁴.

1.2 Is this product licensed to be placed on the market for use in the exporting country?⁵
 Yes No

1.3 Is the product actually on the market in the exporting country?
 Yes No Unknown

If the answer to 1.2 is yes, continue with section 2A and omit section 2B.

If the answer to 1.2 is no, omit section 2A and continue with section 2B⁶.

2A.1 Number of product licence⁷ and date of issue:

2A.2 Product licence holder (name and address):

Name : _____

Address : _____

2A.3 Status of product-licence holder:⁸

a b c

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are:⁹

Name : _____

Address : _____

2A.4 Is Summary Basis of Approval appended?¹⁰

Yes No

2A.5 Is the attached, officially approved product information complete and consonant with the licence?¹¹

Yes No Not provided

2A.6 Applicant for the certificate (name and address):¹²

Name : _____

Address : _____

2B.1 Applicant for certificate (name and address):

Name : _____

Address : _____

2B.2 Status of applicant:⁸

a b c

2B.2.1 For categories b and c, the name and address of the manufacturer producing the dosage form is:⁹

Name : _____

Address : _____

- 2B.3 Why is marketing authorization lacking?
 not required under consideration
 not requested refused

2B.4 Remarks:¹³

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?¹⁴
 Yes No N/A

If no or not applicable proceed to question 4.

3.1 Periodicity of routine inspection (years): _____

- 3.2 Has the manufacture of this type of dosage form been inspected?
 Yes No

- 3.3 Does the facilities and operations conform to GMP as recommended by the WHO?¹⁵
 Yes No N/A

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product?¹⁶

If no explain: _____

Address of the certifying authority:

Telephone number: _____

Fax number: _____

Name of authorized person:

Signature of authorized person:

Stamp and date:

Explanatory notes

1. This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
2. Use whenever possible, international Non-proprietary Names (INNs) or national non-proprietary names.
3. The formula (complete composition) of dosage form should be given on the certificate or be appended.
4. Details of quantitative composition are preferred, but their provision is subject to the agreement of the product licence holder.
5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.
6. Sections 2A and 2B are mutually exclusive.
7. Indicate when applicable, if the licence is provisional, or the product has not yet been approved.
8. Specify whether the person responsible for placing the product on the market:
 - (a) manufactures the dosage form;
 - (b) packages and/or labels a dosage form manufactured by an independent company; or
 - (c) is involved in non of the above
9. This information can be provided only with the consent of the product licence holder or, in the case of non registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.
It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence must be updated or it will cease to be valid.
10. This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
11. This refers to the product information approved by the competent national regulatory authority, such as a Summary of Product Characteristics (SmPC).
12. In this circumstance, permission for issuing the certificate is required from the product licence holder. This permission must be provided to the authority by the applicant.
13. Please indicate the reason that the applicant has provided for not requesting registration:
 - (a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases – not endemic in the country of export;
 - (b) the product has been reformulated with a view to improving its stability under tropical conditions;
 - (c) the product has been reformulated to exclude excipients not approved for used in pharmaceutical products in the country of import;
 - (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
 - (e) any reason, please specify.

14. Not applicable means that the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.
15. The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No. 823, 1992 Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992 Annex 1)
16. This section is to be completed when the product licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

APPENDIX IV

LABELLING

A Labelling Parameters required for **UNIT CARTON**

1. Product Name
2. Dosage Form
3. Name of Active Ingredient(s)
4. Strength of Active Ingredient(s)
5. Batch Number
6. Manufacturing Date
7. Expiration Date
8. Route of Administration
9. Storage Condition
10. Country's Registration Number
11. Name and Address of Marketing Authorisation Holder
12. Name and Address of Manufacturer
13. Special Labelling (if applicable) eg. Sterile, External Use, Cytotoxic, Alcohol Content, Animal Origin (Bovine, porcine)
14. Recommended Daily Allowance (For Vitamins and Minerals)
15. Warning (if applicable)
16. Pack sizes (Unit/Volume)

B Labelling Parameters required for **INNER LABEL**

1. Product Name
2. Dosage Form*
3. Name of Active Ingredient(s)
4. Strength of Active Ingredient(s)
5. Batch Number
6. Manufacturing Date*
7. Expiration Date
8. Route of Administration
9. Storage Condition*
10. Country's Registration Number*
11. Name and Address of Marketing Authorisation Holder*
12. Name and Address of Manufacturer*
13. Special Labelling (if applicable) eg. Sterile, External Use, Cytotoxic, Alcohol Content, Animal Origin (Bovine, porcine)*
14. Recommended Daily Allowance (For Vitamins and Minerals)*
15. Warning (if applicable)*
16. Pack sizes (unit/Volume)

Note: * (exempted for small ampoule and vial)

C Labelling Parameters required for **BLISTER/STRIPS**

1. Product Name
2. Name of Active Ingredient(s)#
3. Strength of Active Ingredient(s)#
4. Batch Number
5. Expiration Date
6. Name/Logo of Manufacturer/Product Owner/Marketing Authorisation Holder (country specific)
7. Country's registration number (country specific)

Note: # (exempted for multi-ingredients product with more than 3 ingredients. For example multivitamins and multiminerals it is suggested to label as multivitamins and multiminerals.)

APPENDIX V
PACKAGE INSERT

1. Product Name
2. Name and Strength of Active Ingredient (s)
3. Product Description
4. Pharmacodynamics / Pharmacokinetics
5. Indication
6. Recommended Dose
7. Mode of Administration
8. Contraindication
9. Warnings and Precautions
10. Interactions With Other Medicaments
11. Pregnancy and Lactation
12. Undesirable Effects
13. Overdose and treatment
14. Storage Condition
15. Dosage Forms and packaging available
16. Name and Address of Manufacturer/Marketing Authorization Holder
17. Date of Revision of Package Insert

APPENDIX VI

**SUMMARY OF PRODUCT CHARACTERISTICS
(PRODUCT DATA SHEET)**

1. Name of the Medicinal Product
 - 1.1 Product Name
 - 1.2 Strength
 - 1.3 Pharmaceutical Dosage Form

2. Quality and Quantitative Composition
 - 2.1 Qualitative Declaration
The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant
 - 2.2 Quantitative Declaration
The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per puff) per unit volume or per unit of weight).

3. Pharmaceutical Form
Visual description of the appearance of the product (colour, markings, etc) e.g.:
"Tablet White, circular flat beveled edge tablets marked '100' on one side

4. Clinical Particulars
 - 4.1 Therapeutic indications
 - 4.2 Posology and method of administration
 - 4.3 Contraindications
 - 4.4 Special warning and precautions for use
 - 4.5 Interaction with other medicinal products and other forms of interactions
 - 4.6 Pregnancy and lactation
 - 4.7 Effects on ability to drive and use machine
 - 4.8 Undesirable effects
 - 4.9 Overdose

5. Pharmacological Properties
 - 5.1 Pharmacodynamic Properties
 - 5.2 Pharmacokinetic Properties
 - 5.3 Preclinical safety Data

6. Pharmaceutical Particulars
 - 6.1 List of excipients
 - 6.2 Incompatibilities
 - 6.3 Shelf life
Shelf life of the medicinal product as packages for sale. Shelf life after dilution or reconstitution according to directions. Shelf-life after first opening the container
 - 6.4 Special precautions for storage
 - 6.5 Nature and contents of container

7. Marketing Authorization Holder

8. Marketing Authorization Numbers

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text

APPENDIX VII
PATIENT INFORMATION LEAFLET (PIL)

- 1 Name of Product
- 2 Description of Product
- 3 What is in the medicine?
- 4 Strength of the medicine
- 5 What is this medicine used for?
- 6 How much and how often should you use this medicine?
- 7 When should you not take this medicine?
- 8 Undesirable effects
- 9 What other medicine or food should be avoided whilst taking this medicine?
- 10 What should you do if you miss a dose?
- 11 How should you keep this medicine?
- 12 Signs & Symptoms of over dosage
- 13 What to do when you have taken more than the recommended dosage?
- 14 Name/logo of manufacturer/importer/Marketing Authorisation Holder
- 15 Care that should be taken when taking this medicine?
- 16 When should you consult your doctor?
17. Date of Revision of PIL

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

PART IV: CLINICAL DOCUMENT

SECTION A. TABLE OF CONTENTS

A table of contents for the filed application should be provided.

SECTION B. CLINICAL OVERVIEW

3 5 (\$ 0 % (

The Clinical Overview is intended to provide a critical analysis of the clinical data in the ASEAN Common Technical Dossier (ACTD). The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should:

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.
- provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage risks.
- address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved.
- explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them.
- explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or Clinical Study Reports are encouraged.

TABLE OF CONTENTS FOR THE CLINICAL OVERVIEW

1.	Product Development Rationale.....	2
2.	Overview of Biopharmaceutics.....	2
3.	Overview of Clinical Pharmacology.....	2
4.	Overview of Efficacy.....	2
5.	Overview of Safety.....	3
6.	Benefits and Risks Conclusions	4

DETAILED DISCUSSION OF CONTENT OF THE CLINICAL OVERVIEW SECTION

1. Product Development Rationale

The discussion of the rationale for the development of the medicinal product should:

- identify the pharmacological class of the medicinal product.
- describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication).
- briefly summarise the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied.
- briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme.
- note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced

2. Overview of Biopharmaceutics

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

3. Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the pharmacokinetic (PK), pharmacodynamic (PD), and related *in vitro* data in the ACTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasise unusual results and known or potential problems, or note the lack thereof. This section should address:

- pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.
- pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the

proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.

- interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies.

4. Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be considered:

- relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed.
- implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.
- for non-inferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).
- statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints).
- similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.
- observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).
- for products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
- data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.
- the clinical relevance of the magnitude of the observed effects.
- if surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
- efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

5. Overview of Safety

The purpose of this section is to provide a concise critical analysis of the safety data, noting how results support and justify proposed prescribing information. A critical analysis of safety should consider:

- adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
- special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
- relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
- the nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.
- common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.
- serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.
- similarities and differences in results among studies, and their effect upon the interpretation of the safety data.
- any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
- relation of adverse events to dose, dose regimen, and treatment duration.
- long-term safety (E1a).
- methods to prevent, mitigate, or manage adverse events.
- reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
- world-wide marketing experience. The following should be briefly discussed:
 - the extent of the world-wide experience,
 - any new or different safety issues identified,
 - any regulatory actions related to safety.

6. Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option; and should clarify the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of

emergence of drug -resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

- the efficacy of the medicinal product for each proposed indication.
- significant safety findings and any measures that may enhance safety.
- dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
- efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.
- data in children in different age groups, if applicable, and any plans for a development programme in children.
- any risks to the patient of known and potential interactions, including food-drug and drug-drug interactions, and recommendations for product use.
- any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery.

Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include:

- the drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro -arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.
- the proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.
- safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

SECTION C: CLINICAL SUMMARY

PREAMBLE

The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Clinical Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who wishes to obtain such Clinical Study Reports should request for additional documentation.

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the ASEAN Common Technical Dossier. This includes information provided in Clinical Study Reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Clinical Study Reports and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the ACTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

TABLE OF CONTENTS FOR THE CLINICAL SUMMARY

1.	SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS	8
	1.1 Background and Overview	8
	1.2 Summary of Results of Individual Studies	8
	1.3 Comparison and Analyses of Results Across Studies	8
	Appendix 1	9
2.	SUMMARY OF CLINICAL PHARMACOLOGY STUDIES	9
	2.1 Background and Overview	9
	2.2 Summary of Results of Individual Studies	9
	2.3 Comparison and Analyses of Results Across Studies	10
	2.4 Special Studies	10
	Example 1: Immunogenicity.....	10
	Example 2: Clinical microbiology.....	11
	Appendix 2	11
3.	SUMMARY OF CLINICAL EFFICACY.....	11
	3.1 Background and Overview of Clinical Efficacy	12
	3.2 Summary of Results of Individual Studies	12
	3.3 Comparison and Analyses of Results Across Studies	12
	3.4 Analysis of Clinical Information Relevant to Dosing Recommendations.....	14
	3.5 Persistence of Efficacy and/or Tolerance Effects.....	14
	Appendix 3	14
4.	SUMMARY OF CLINICAL SAFETY.....	15
	4.1 Exposure to the Drug.....	15
	4.2 Adverse Events	17
	4.3 Clinical Laboratory Evaluations.....	20
	4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety	21
	4.5 Safety in Special Groups and Situations.....	21
	4.6 Post-marketing Data.....	22
	Appendix 4	22
5.	SYNOPSIS OF INDIVIDUAL STUDIES	22

DETAILED GUIDANCE ON ITEMS OF THE CLINICAL SUMMARY

1. SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and *in vitro* dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

1.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutic studies should generally be provided (see Appendix 1), together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important *in vitro* or *in vivo* data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

1.3 Comparison and Analyses of Results across Studies

This section should provide a factual summary of all *in vitro* dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarise the findings in text and tables (see Appendix 1) and should consider the following:

- evidence of the effects of formulation and manufacturing changes on *in vitro* dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, pharmacodynamic (PD) studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.
- evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).
- evidence of correlations between *in vitro* dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.
- comparative bioavailability, including BE conclusions, for different dosage form strengths.
- comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- the source and magnitude of observed inter- and intra-subject variability for each formulation in a comparative BA study.

Appendix 1

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

Tables 1.1 and 1.2 are provided as examples of tabular formats for reporting information and results related to bioavailability and *in vitro* dissolution studies respectively. These examples give results as well as identifying the type and design of the study. Tables prepared for reporting the results of BE studies could also include the mean ratios (test/reference) for C_{max} and AUC and their 90% confidence interval, or the currently recommended metrics for BE assessments.

These tables are not intended to be templates, but only to illustrate the type of information that should be considered by an applicant in designing the tables for biopharmaceutical studies. Applicants should also decide whether information and results from these studies are best presented in tables, text or figures in order to aid clarity. If, for example, results are best presented in text and figures, tables might be used simply to list the studies.

2. SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.1 Background and Overview

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human pharmacokinetics (PK), and pharmacodynamics (PD), and *in vitro* studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarised in Items 1, 3 and 4 of Section C can also be referenced to provide a comprehensive view of the approach and rationale for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human biomaterial database. This section should not include detailed information about individual studies.

This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug-drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterise PK and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects and patients. Critical aspects of study design and data analysis should be noted, e.g., the choice of the single or multiple doses used, the study population, the choice of PD endpoints, and whether a traditional approach or a population approach was used to collect and analyse data to assess PK or PD.

2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided (see Appendix 2), together with a narrative description of the relevant features and outcomes of each of the critical individual studies that provided *in vitro* or *in vivo* data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References or electronic links to the full report of each study should be included in the narratives.

Summaries of dose-response or concentration response (PK/PD) studies with pharmacodynamic endpoints should generally be included in this section. In some cases, however, when well-controlled dose-response PD or PK/PD studies provide important

evidence of efficacy or safety, they should be placed in Item 3 or 4 as appropriate and referenced, but not summarised, here.

2.3 Comparison and Analyses of Results across Studies

This section should use the results of all *in vitro* human biomaterial studies and PK, PD and PK/PD studies to characterise the PK, PD and PK/PD relationships of the drug. Results related to the inter- and intra-individual variability in these data affecting these pharmacokinetic relationships should be discussed.

This section (typically with the use of text and tables) should provide a factual presentation of all data across studies pertinent to the following:

- *in vitro* drug metabolism and *in vitro* drug-drug interaction studies and their clinical implications.
- human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualisation in the target patient population and in special populations, e.g., pediatric or geriatric patients, or patients with renal or hepatic impairment.
- comparison between single and repeated-dose PK
- population PK analyses, such as results based on sparse sampling across studies that address inter-individual variations in the PK or PD of the active drug substances.
- dose-response or concentration-response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labelling should be discussed in Item 3.4.
- major inconsistencies in the human biomaterial, PK, or PD database.

2.4 Special Studies

This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarised here. Any observed or potential effects on PK, PD, safety and/or efficacy should be considered in other appropriate sections of the Clinical Summary as well, with cross-referencing to this section. Human studies that address a specific safety issue should not be reported here, but instead should be reported in Item 4, Summary of Clinical Safety.

Example 1: Immunogenicity

For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarised in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data should be described in the efficacy section. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarised; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre (titer), timing of onset and duration of antibody responses should be summarised for each type of antibody assay used (e.g., IgG by ELISA, neutralisation). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarised.

For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analysed and summarised.

It is particularly important to summarise analyses of potential clinically relevant correlates of immunogenicity, e.g., to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events. Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug.

Example 2: Clinical microbiology

For antimicrobial or antiviral medicinal products, *in vitro* studies to characterise the spectrum of activity are an important part of the programme of studies relevant to clinical efficacy. Clinical efficacy studies that include characterisation of the susceptibility of the clinical isolates as a part of the efficacy determination should be included in Item 3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of *in vitro* susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

Appendix 2

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

Table 2.1 is provided as an example of a tabular format for reporting information and results related to pharmacokinetic drug-drug interaction studies. Similar tables could be prepared for PK/PD studies, dose-response studies, studies of effects on human biomaterials, and population PK studies. This table is not intended to be a template, but only to illustrate the type of information that should be considered by sponsors in designing their own tables.

Applicants should also decide whether information and results from clinical pharmacology studies are best presented in tables, text or figures in order to aid clarity. If, for example, results are best presented in text and figures, the tables might simply list the studies.

In designing tables, if any, for various types of other clinical pharmacology studies such as those listed below, applicants should consider including the following types of information. These examples are for illustrative purposes only and the sponsor should decide which information needs to be presented.

- metabolism studies using human biomaterials: biomaterials used (e.g., microsomes, hepatocytes), probe drugs, enzymatic pathways and % contribution and relevant kinetic parameters (e.g., V_{max} , K_m).
- *in vitro* studies of drug-drug interactions using human biomaterials: for studies of other drugs inhibiting the new drug, the metabolite(s) inhibited, enzymatic pathways affected, range of inhibitor concentrations used, IC_{50} and K_i values and proposed mechanism of inhibition should be included. For studies of the new drug inhibiting other drugs, the drugs and metabolites inhibited should be included, along with the information mentioned above.
- population PK studies: co-variates studied, number and type of subjects or patients studied, summary statistical parameters and final estimates of mean (\pm standard deviation) PK parameters.

3. SUMMARY OF CLINICAL EFFICACY

There might be time when a product may be effective for more than one indication, then a separate Section 3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 3 is submitted, the sections should be labelled 3A, 3B, 3C, etc.

3.1 Background and Overview of Clinical Efficacy

This section should describe the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought. Any results of these studies that are pertinent to evaluation of safety should be discussed in Item 4, Summary of Clinical Safety.

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of ACTD clinical final

study design should be discussed, e.g., randomisation, blinding, choices of control treatment, choice of patient population, unusual design features such as crossover or randomised withdrawal designs, use of run-in periods, other methods of “enrichment”, study endpoints, study duration, and prespecified plans for analysis of the study results. Although this section is intended to focus on clinical investigations, nonclinical data and clinical pharmacology data may also be referenced as appropriate to provide a comprehensive summary of human experience related to efficacy. This section should not include detailed information about individual studies.

3.2 Summary of Results of Individual Studies

A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided (see Appendix 3), together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. For studies that also contributed significantly to the safety analysis, study narratives should include information about the extent of exposure of study subjects to the test drug or control agent, and how safety data were collected. These narratives can be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

3.3 Comparison and Analyses of Results across Studies

Using text, figures, and tables as appropriate (see Appendix 3), the Item of 3.3 should summarise all available data that characterise the efficacy of the drug. This summary should include analyses of all data, irrespective of their support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilise two kinds of analyses: comparison of results of individual studies, and analysis of data combined from various studies. Details of analyses that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Clinical Study Reports.

This section should also cross-reference important evidence from Item 2, such as data that support the dosage and administration section of the labelling. These data include dosage and dose interval recommended, evidence pertinent to individualisation of dosage and need for modifications of dosage for specific subgroups (e.g., pediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships.

3.3.1 Study Populations

The demographic and other baseline characteristics of patients across all efficacy studies should be described. The following should be included:

- the characteristics of the disease (e.g., severity, duration) and prior treatment in the study subjects, and study inclusion/exclusion criteria
- differences in baseline characteristics of the study populations in different studies or groups of studies.
- any differences between populations included in critical efficacy analyses and the overall patient population that would be expected to receive the drug when it is marketed should be noted.
- assessment of the number of patients who dropped out of the studies, time of withdrawal (a defined study day or visit during treatment or follow up period), and reasons for discontinuation.

Tabular presentations that combine and compare study populations across studies may be useful.

3.3.2 Comparison of Efficacy Results of all Studies

The results from all studies designed to evaluate the drug's efficacy should be summarised and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, control group, study duration, statistical methods, patient population, and dose should be identified.

Comparisons of results across studies should focus on pre-specified primary endpoints.

However, when the primary endpoints involved different variables or time points in different efficacy studies, it may be useful to provide cross-study comparisons of important data elements that were obtained in all studies. If results over time are important, results of studies may be displayed in a figure that illustrates the change over time in each study.

Confidence intervals for treatment effects should be given to aid in the interpretation of point estimates. If differences are shown between placebo and test drugs in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo and active controls (if used), should generally be presented in the table or in text accompanying a figure. If the objective of an active control trial was to show equivalence or non-inferiority, the difference or the ratio of outcomes between treatments should be given with the confidence interval. The results should be evaluated by using the predefined criteria for defining equivalence or non-inferiority and the rationale for the criteria and support for the determination that the study (studies) had assay sensitivity should be provided (see ICH E10).

Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross-study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (See ICH E9). A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (Clinical Study Reports).

3.3.3 Comparison of Results in Sub-populations

The results of individual studies or overview analyses of efficacy in specific populations should be summarised in this section. The purpose of these comparisons should be to show whether the claimed treatment effects are observed consistently across all relevant sub-populations, especially those where there are special reasons for concern. The comparisons may highlight apparent variations in efficacy that require further investigation and discussion. The limitations of such analyses, however, should be recognised (ICH E9), and it is important to note that their purpose is not to provide the basis for specific claims, nor to attempt to improve the evidence of efficacy in situations where the overall results are disappointing.

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) on efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the pediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive, detailed efficacy analyses are performed, they can be placed in Clinical Study Reports, with the results of those analyses reported here.

3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose-response or blood level-response relationships of effectiveness (including dose-blood level relationships), and thus have contributed to dose selection and choice of dose interval. Relevant data from nonclinical studies may be referenced, and relevant data from pharmacokinetic studies, other clinical pharmacology studies, and controlled and

uncontrolled clinical studies should be summarised to illustrate these dose-response or blood level-response relationships. For pharmacokinetic and pharmacodynamic studies from which data have been summarised in Item 2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in Item 2.2, without repeating those summaries.

While the interpretation of how these data support specific dosing recommendations should be supplied in the Clinical Overview document, the individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualisation of dosage) should be summarised here. Any identified deviations from relatively simple dose-response or blood-level response relationships due to non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be described.

Any evidence of differences in dose-response relationships that result from a patient's age, sex, race, disease, or other factors should be described. Any evidence of different pharmacokinetic or pharmacodynamic responses should also be discussed, or discussions in Item 2 can be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the test drug).

3.5 Persistence of Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarised. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted. Examination of any apparent relationships between dose changes over time and long-term efficacy may be useful.

The primary focus should be on controlled studies specifically designed to collect long-term efficacy data, and such studies should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see Item 4).

In long-term efficacy trials, the effect of premature discontinuation of therapy or switching to other therapies upon the assessment of the results should be considered. These issues might also be important for short term trials and should be addressed when discussing the results of these trials, if appropriate.

Appendix 3

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

Tables should identify all studies pertinent to the evaluation of efficacy (including studies that were terminated or are not yet completed, studies that failed to show effectiveness for any reason, studies available only as publications, studies reported in full technical reports (ICH E3), and studies described in abbreviated reports); and should provide the most important results of those studies. Note, however, that unplanned interim analyses on ongoing studies are generally not needed or encouraged. When more than one section 3 is provided for an application with more than one indication, usually each section should have its own appendix with tables.

Illustrative tables for an antihypertensive drug are provided, but these examples will not be relevant to every application. In general, applications will require tables and/or figures that are developed specifically for the particular drug class and the studies that were carried out.

Table 3.1 Description of Clinical Efficacy and Safety Studies

Table 3.2 Results of Efficacy Studies

4. SUMMARY OF CLINICAL SAFETY

This section should be a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports as well as other relevant reports, e.g., the integrated analyses of safety that are routinely submitted in some regions. The display of safety-related data can be considered at three levels (ICH E3):

- The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database.
- The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarised.
- Serious adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and their occurrence should be summarised. These events should be examined for frequency over time, particularly for drugs that may be used chronically.

The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

4.1 Exposure to the Drug

4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the nonclinical data, any relevant pharmacological class effects, and the sources of the safety data (controlled trials, open studies, etc). A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided (see Appendix 4). In addition to studies that evaluated efficacy and safety, and uncontrolled studies that generate safety information, this section includes studies that consider special safety issues. Examples would include studies to compare particular adverse event rates for two therapies, to assess safety in particular demographic subsets, to evaluate withdrawal or rebound phenomena, or to evaluate particular adverse events (e.g., sedation, sexual function, effects on driving, absence of a class adverse effect). Studies in indications for which approval is not being sought in the current application and ongoing studies would also be included here if they contribute to the safety analysis.

Narrative descriptions of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in Item 3.2 and cross-referenced here. The narratives should provide enough detail to allow the reviewer to understand the exposure of study subjects to the test drug or control agent, and how safety data were collected (including the methods used and the extent of safety monitoring of the subjects enrolled in the individual studies). If some studies are not analysed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.

4.1.2 Overall Extent of Exposure

A table (see example provided in Appendix 4) and appropriate text should be generated to summarise the overall extent of drug exposure from all phases of the clinical study development programme. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes, and durations. If a large number of different doses and/or durations of exposure were used, these can be grouped in a manner appropriate for the drug. Thus, for any dose or range of doses, duration of exposure can be summarised by the number of subjects exposed for specific periods of time, such as 1 day or less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3). In some applications it may be important to identify diagnostic subgroups and/or groups receiving specific concomitant therapies deemed particularly relevant to safety assessment in the intended use.

The dose levels used for each subject in this presentation could be the maximum dose received by that subject, the dose with longest exposure, and/or the mean daily dose, as

appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m² basis, as appropriate. If available, drug concentration data (e.g., concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables.

It is assumed that all subjects who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

4.1.3 Demographic and Other Characteristics of Study Population

A summary table should provide the reader with an overview of the demographic characteristics (Table 4.2) of the population that was exposed to the therapeutic agent during its development. Choice of age ranges used should take into account considerations discussed in ICH E7 [Studies in Support of Special Populations: Geriatrics] and ICH E11 [Clinical Investigation of Medicinal Products in the Paediatric Population]. If the relative exposure of demographic groups in the controlled trials differed from overall exposure, it may be useful to provide separate tables.

In addition, one or more tables should show the relevant characteristics of the study population, and the numbers of subjects with special characteristics. Such characteristics could include:

- Severity of disease
- Hospitalisation
- Impaired renal function
- Concomitant illnesses
- Concomitant use of particular medications
- Geographical location

If these characteristics are distributed differently in controlled trials versus the overall database, it will generally be useful to present tables on both groupings.

The text accompanying the table(s) should mention any imbalance(s) between the drug and placebo and/or comparator regarding any of the above demographic characteristics, particularly if they could lead to differences in safety outcomes.

If certain subjects were excluded from studies (concomitant illness, severity of illness, concomitant medications), this fact should be noted.

Separate demographic tables should be provided for every indication, although closely related indications can be considered together, if study subject characteristics are such that risks are believed to be the same.

4.2 Adverse Events

4.2.1 Analysis of Adverse Events

Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate Item 4.2.1 and the tables that are not embedded in the text should be placed in Appendix 4.

All adverse events occurring or worsening after treatment has begun ("treatment emergent signs and symptoms," those adverse events not seen at baseline and those that worsened even if present at baseline) should be summarised in tables listing each event, the number of subjects in whom the event occurred and the frequency of occurrence in subjects treated with the drug under investigation, with comparator drugs, and with placebo. Such tables could also present results for each dose and could be modified to show, e.g., adverse event rates by severity, by time from onset of therapy, or by assessment of causality.

When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping

the studies and pooling the results to improve precision of estimates and sensitivity to differences should generally be considered.

While often useful, pooling of safety data across studies should be approached with caution because in some cases interpretation can be difficult, and it can obscure real differences. In cases where differences are apparent, it is more appropriate to present the data by study. The following issues should be considered:

- it is most appropriate to combine data from studies that are of similar design, e.g., similar in dose, duration, methods of determining adverse events, and population.
- if the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- any study with an unusual adverse event pattern should be presented separately.
- the appropriate extent of analysis depends on the seriousness of the adverse event and the strength of evidence of drug causation. Differences in rates of drug-related, serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.
- examination of which subjects experience extreme laboratory value abnormalities ("outliers") may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

Groups of studies that could be used in pooled safety analyses include:

- all controlled studies or subsets of controlled studies, such as all placebo-controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- all studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- all studies using a particular dose route or regimen, or a particular concomitant therapy.
- studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are volunteered.
- pools of studies by region.

It is almost always useful to carry out the first two groupings; the others chosen would vary from drug to drug and should be influenced by inspection of individual study results.

Whatever methods are used, it should be recognised that, as for results of single studies, any numerical rate is often only a rough approximation of reality.

When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is common to combine the numerator events and the denominators for the selected studies. Other methods for pooling results across studies are available, e.g., weighting data from studies on the basis of study size or inversely to their variance.

If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose administration, or in methods of collecting adverse event data).

Adverse events should be described as shown in the individual study report (ICH E3). In combining data from many studies, it is important to use standardised terms to describe events and collect synonymous terms under a single preferred term. This can be done with international standard dictionary and terminology should be used and specified. Frequencies should be presented for preferred terms and for appropriately defined groupings. Examination

of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help in assessing the clinical importance of adverse events. These rates can be added to the adverse event rate tables, or can be presented in separate tables. Overall discontinuation rates by study may be useful but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.

4.2.1.1 Common Adverse Events

Tabular displays of adverse event rates (see Appendix 4) should be used to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. It should be noted that while causality categories may be reported, if used, the presentation of the data should include total adverse events (whether deemed related or unrelated to treatment); evaluations of causality are inherently subjective and may exclude unexpected adverse events that are in fact treatment related. Additionally, comparisons of rates of adverse events between treatment and control groups in individual trials should be summarised here. It is often useful to tabulate rates in selected trials (see example table 4.4, in Appendix 4).

It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to relevant factors, including:

- dosage;
- mg/kg or mg/m² dose;
- dose regimen;
- duration of treatment;
- total dose;
- demographic characteristics such as age, sex, race;
- concomitant medication use;
- other baseline features such as renal status;
- efficacy outcomes;
- drug concentration, where available.

It may also be useful to summarise the results of examination of time of onset and duration for these drug-related events.

Rigorous statistical evaluations of the possible relationship of specific adverse events to each of the above factors are often unnecessary. It may be apparent from initial display and inspection of the data that there is no evidence of a significant relationship to demographic or other baseline features. In that case, no further analysis of these particular factors is needed. Further, it is not necessary that all such analyses be presented in this report. When the safety analyses are too extensive to be presented in detail in this report, they may be presented in a separate report in Clinical Study Reports, and summarised here.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates.

4.2.1.2 Deaths

A table in Appendix 4 should list all deaths occurring while on study (including deaths that occurred shortly following treatment termination, e.g., within 30 days or as specified in the study protocol, as well as all other deaths that occurred later but may have resulted from a process that began during studies). Only deaths that are clearly disease-related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in

studies where mortality from disease is a primary study endpoint, should be excepted from this listing (it is assumed, however, that these deaths would still be reported in the individual ICH E3 study reports). Even these deaths should be examined for any unexpected patterns between study arms, and further analysed if unexplained differences are observed. Deaths should be examined individually and analysed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause-specific deaths. Potential relationships to the factors listed in Item 4.2.1.1 should also be considered. Although cause-specific mortality can be difficult to determine, some deaths are relatively easy to interpret. Thus deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not considered to be informative, but even one death due to a QT interval prolongation-associated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.

4.2.1.3 Other Serious Adverse Events

Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the drug use was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events using the ICH E2A definitions. Results of analyses or assessments of serious adverse events across studies should be presented. Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Potential relationships to the factors listed in Item 4.2.1.1 should also be considered.

4.2.1.4 Other Significant Adverse Events

Marked haematologic and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed.

Events that led to premature discontinuation of study drug represent an important safety concern and deserve particular attention in the analysis of drug safety for two reasons. First, even for expected events (based on pharmacologic activity), the need to discontinue (or otherwise alter) treatment reflects the severity and perceived importance of the event to patient and physician. Second, discontinuation may represent a drug-related event not yet recognised as drug related. Adverse events leading to treatment discontinuation should be considered possibly drug-related even if this was not recognised initially and even if the event was thought to represent intercurrent illness. Reasons for premature treatment discontinuations should be discussed and rates of discontinuations should be compared across studies and compared with those for placebo and/or active control treatment. In addition, the study data should be examined for any potential relationships to the factors listed in Item 4.2.1.1.

4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Assessment of the causality of, and risk factors for, deaths, other serious events, and other significant events is often complicated by the fact that they are uncommon. As a result, consideration of related events as a group, including less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. For example, the relationship to treatment of an isolated sudden death

may become much clearer when considered in the context of cases of syncope, palpitations, and asymptomatic arrhythmias.

It is thus generally useful to summarise adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities. Such presentations of adverse events by organ system should be placed in Item 4.2.1.5, labelled as 4.2.1.5.1, 4.2.1.5.2, etc., and titled by the organ system under consideration. The list of organ systems to be addressed and the approach to grouping certain events should be selected as appropriate to best present the adverse event data for the medicinal product. If some adverse events tend to occur in syndromes (e.g., influenza-like syndrome, cytokine release syndrome), the sponsor may choose to create some Item 4.2.1.5 for syndromes rather than organ systems.

The same data and summarisations should generally not be repeated in more than one subsection of Item 4.2.1. Instead, a summary presentation may be placed in one subsection and cross-referenced as needed in the other.

4.2.2 Narratives

The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance (as described in ICH E3 individual study reports) should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, if there is such a report. In cases where there is no individual study report (e.g., if many open studies are pooled as part of a safety analysis and are not individually described), narratives can be placed in Clinical Study Reports, Item 5.3. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug.

4.3 Clinical Laboratory Evaluations

This section should describe changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in Item 4.2.1.3 or 4.2.1.4. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The appropriate evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis (ICH E3). Where possible, laboratory values should be provided in standard international units.

A brief overview of the major changes in laboratory values across the clinical studies should be provided. Laboratory data should include haematology, clinical chemistry, urinalysis and other data as appropriate. Each parameter at each time over the course of the study (e.g., at each visit) should be described at the following three levels:

- the central tendency, i.e., the group mean and median values,
- the range of values, and the number of subjects with abnormal values or with abnormal values of a certain size (e.g. twice the upper limit of normal, 5 times the upper limit; choices should be explained). When data are pooled from centers with differences in normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual subject changes by treatment group can be shown with a variety of approaches (e.g., shift tables, see ICH E3 for examples).
- individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g., by analysis of such features as relationship to dose, relation to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy). Potential relationships to other factors listed in Item 4.2.1.1 should also be considered.

4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

The manner of presenting cross-study observations and comparisons of vital signs (e.g., heart rate, blood pressure, temperature, respiratory rate), weight and other data (e.g., electrocardiograms, X-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a drug effect, any dose-response or drug concentration-response relationship or relationship to individual variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events. Particular attention should be given to studies that were designed to evaluate specific safety issues, e.g., studies of QT interval prolongation.

4.5 Safety in Special Groups and Situations

4.5.1 Patient Groups

This section should summarise safety data pertinent to individualising therapy or patient management on the basis of demographic, age, sex, height, weight, lean body mass, genetic polymorphism, body composition, other illness and organ dysfunction. Safety in the pediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Analysis of the impact on safety outcomes should have been presented in other sections but should be summarised here, together with pertinent PK or other information, e.g., in patients with renal or hepatic disease, the medical environment, use of other drugs (see 4.5.2, Drug Interactions), use of tobacco, use of alcohol, and food habits. For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by post-marketing experience, or by information on similar drugs, information should be provided here. If a sufficiently large number of subjects with a given co-morbid condition such as hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to assess whether the co-morbid condition affected the safety of the drug under study. Cross reference should be made to the tables or description of adverse events when analyses of such sub-groups has been carried out.

4.5.2 Drug Interactions

Studies on potential drug-drug or drug-food interactions should be summarised in the Summary of Clinical Pharmacology Studies section of the ACTD. The potential impact on safety of such interactions should be summarised here, based on PK, PD, or clinical observations. Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.

4.5.3 Use in Pregnancy and Lactation

Any information on safety of use during pregnancy or breast-feeding that becomes available during clinical development or from other sources should be summarised here.

4.5.4 Overdose

All available clinical information relevant to overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarised and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.

4.5.5 Drug Abuse

Any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in humans should be summarised and cross-referenced to the nonclinical summary. Particularly susceptible patient populations should be identified.

4.5.6 Withdrawal and Rebound

Any information or study results pertinent to rebound effects should be summarised. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound.

Data concerning tolerance should be summarised under Item 3.5 in the Summary of Clinical Efficacy.

4.5.7 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Safety data related to any impairment in the senses, co-ordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarised. This includes relevant adverse effects reported in safety monitoring (e.g., drowsiness) and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.

4.6 Post-marketing Data

If the drug has already been marketed, all relevant post-marketing data available to the applicant (published and unpublished, including periodic safety update reports if available) should be summarised. The periodic safety update reports can be included in Clinical Study Reports. Details of the number of subjects estimated to have been exposed should be provided and categorised, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided.

A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions.

Any post-marketing findings in subgroups should be described.

Appendix 4

Tabular presentations should be provided that summarise the important results from all studies pertinent to the evaluation of safety and particularly to support product labelling. Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

A few illustrative tables are provided, but a clinical summary will routinely need tables and figures that have been developed for the particular drug, drug class, and clinical indication(s). See Items 4.2.1, 4.2.2.3, and 4.3 of this guidance for additional discussion regarding the content of section 4 tables.

Table 4.1	<u>Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure</u>
Table 4.2	<u>Demographic Profile of Patients in Controlled Trials</u>
Table 4.3	<u>Incidence of Adverse Events in Pooled Placebo and Active Controlled Trials</u>
Table 4.4	<u>Incidence of Adverse Events in the Largest Trials</u>
Table 4.5	<u>Patient Withdrawals by Study: Controlled Trials</u>
Table 4.6	<u>Listing of Deaths</u>

5. SYNOPSES OF INDIVIDUAL STUDIES

The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of a study synopsis with each clinical study report, and provides one example of a format for such synopses.

This section should include the table entitled Listing of Clinical Studies, described in guidance for Clinical Study Reports, followed by all individual study synopses organised in the same sequence as the study reports in Clinical Study Reports.

It is expected that one synopsis will be prepared per study for use in all regions, and that the same synopsis will be included in this section and as part of the clinical study report . The length of a synopsis will usually be up to 3 pages, but a synopsis for a more complex and important study may be longer, e.g. 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

Table 1.1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No.(M/F) type Age: mean (range))	Mean Parameters (+/- SD)						Study Report Location
					Cmax (mg/L)	Tmax (hr)	AUC* (mg/Lxhr)	Cmin** (mg/L)	T1/2 (hr)	Other	
192 (Japan)	Pilot relative BA study comparing the absorption from a 200mg tablet batch to a 200mg reference batch.	Open, randomized, cross-over, single 200 mg dose	200mg Tab., p.o. [17762]	20 (10/10) Healthy volunteer 27 y (20-35)	83 ± 21	1	217 ± 20		3.1		
			200mg Tab.. p.o. [19426]		80 ± 32	0.5	223 ± 19		2.9		
195 (Japan)	Comparative BA study of xx under fasted and fed conditions	Open, randomized, cross-over, single dose	200mg Tab, p.o. [19426]	30 (15/15) Healthy volunteer 32 y (26-50)	83 ± 21	1	217 ± 20				
					120 ± 30	2	350 ± 40				

AUC*: AUC_{TAU} or AUC_{inf}

Cmin** : For multiple dose studies

← Formatted: Bullets and Numbering

Table 1.2. Summary of *In vitro* Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection times			Study Report Location
					Mean % Dissolved (range)			
1821	979-03	25mg Cap.	Dissolution: Apparatus 2 (USP) Speed of Rotation: 50 rpm Medium/Temperature: Water 37°	12	10 42 (32-49)	20 71 (58-85)	30 (min) 99 (96-100) (%)	

Table 2.1 Summary of Drug-Drug Interaction PK Studies

Study/ Protocol # (Country)	Product ID/Batch # (NME)	Study Objective	Study Design	# Subjects Entered/ Completed (M/F)	HV/P ¹ (Age: Mean, range)	Treatments		Mean Pharmacokinetic Parameters (%CV) Substrate Drug					Mean ratio ² Confidence interval		Loca tion
						Substrate	Interactin g Drug	Cmax	Tmax	AUC	T1/2	CL/kg	Cmax	AUC	
001 (USA)	19B Batch 0034	Effect of warfarin on Drug X	Randomi zed, Cross over	(8M/4F)/ (7M/4F)	HV (34, 20-41)	Drug X 100 mg bid x 7d	Placebo	45 (18) µg/mL	2.0 (30) hr	456 (24) µg*hr/ mL	4.25 (30) hr	0.05 (20) mL/min/kg	1.16 1.01- 1.30	1.16 1.03- 1.34	
						Drug X 100 mg bid x 7d	Warfarin 10 mg qd x 7d	52 (20) µg/mL	2.1 (35) hr	530 (27) µg*hr/ mL	4.75 (35) hr	0.04 (22) mL/min/kg			
001 (USA)	19B Batch 0034	Effect of drug X on warfarin	Randomi zed, Cross over	(8M/4F)/ (7M/4F)	HV (34, 20-41)	Warfarin 10 mg qd x 7d	Placebo	12 (25) µg/mL	1.5 (30) hr	60 (37) µg*hr/ mL	40 (35) hr	0.04 (30) mL/min/kg	1.08 0.92- 1.24	1.07 0.92- 1.18	
002 (UK)	19B2 Batch 0035	Effect of Cimetidine on Drug X	Cross over, Single sequence	(4M/8F) (4M/8F)	HV (30, 19-45)	Warfarin 10 mg qd x 7d	Drug X 100 mg bid x 7d	13 (20) µg/mL	1.45 (27) hr	64 (39) µg*hr/ mL	42 (37) hr	0.39 (34) mL/min/kg			
						Drug X 50 mg bid x 5d	Placebo	49 (18) µg/mL	2.1 (30) hr	470 (24) µg*hr/ mL	4.4 (30) hr	0.05 (20) mL/min/kg	1.22 1.03- 1.40	1.36 1.11- 1.53	
						Drug X 50 mg bid x 5d	Cimetidine 200 mg bid x 5d	60 (10) µg P /	2.2 (30) hr	640 (24) µg*hr/ mL	5.2 (30) hr	0.03 (20) mL/min/kg			

¹HV=Healthy Volunteers, P=Patients

²Value for substrate with interacting drug / value with placebo

Table 3.1 Description of Clinical Efficacy and Safety Studies

Study ID	Number of Study Centers Location(s)	Study start Enrollment status, date Total enrollment / Enrollment goal	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	# subjs by arm Entered/ compl.	Duration	Gender M/F	Diagnosis	Primary Endpoint(s)
								Median Age (Range)	Inclusion Criteria	
PG- 2476	1 U. Antarctica	Aug-94 Completed Apr 98 50 / 50 May-98	Randomised, double blind, parallel Placebo	TP: 30 mg po bid Pbo	Efficacy and Safety	27/24 23/21	4 weeks	27/23 38 (20-64)	Mild hypertension Diastolic 90-100 Systolic 150 -170	Change from baseline systolic and diastolic pressure at 4 weeks.
PG- 2666	4 Affiliated Physicians of Florida, Smith & Jones CRO	Ongoing as of May 2001 126/400	Randomised, open label, parallel Placebo and Dose-response	TP: 100 mg po bid TP: 50 mg po bid TP: 25 mg po bid Placebo	Efficacy and Safety, Long-term efficacy and safety	34/30 30/28 34/32 28/26	4 weeks, followed by 12 weeks open-label	66/60 55 (24-68)	Mild hypertension Systolic 150 -170 Diastolic 90-100	Change from baseline systolic and diastolic pressure at 4 weeks and at 12 weeks.

Table 3.2 Results of Efficacy Studies

Study	Treatment Arm	# Enrolled/Completed	Mean systolic and diastolic BP			Primary Endpoint Placebo-subtracted change in DBP at 40 weeks	Statistical test / P value	Secondary Endpoints % normalised** (ITT analysis)	Other Comments
			Baseline	20 wks	40 wks				
PG- 2678	TP: 100 mg po bid	34/30	162/96	140/85	138/84	6	88		
	TP: 50 mg po bid	30/28	165/97	146/87	146/87	4	78		
	TP: 25 mg po bid	34/32	167/96	148/88	148/88	2	50		
	TP: 10 mg po bid	26/20	162/95	153/93	153/93	-4	20		
	Placebo	28/26	166/97	160/92	159/91		30		

**Provide definition

Table 4.1 Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure Intravenous formulation								
N=		Cutoff Date:						
Duration (Weeks)	Mean Daily Dose (mg)							
	0 < Dose ≤ 5mg	5 < Dose ≤ 10mg	10 < Dose ≤ 20mg	20 < Dose ≤ 30mg	30 < Dose ≤ 50mg	50mg < Dose	Total (Any Dose)	Percent
0 < Dur ≤ 1								
1 < Dur ≤ 2								
2 < Dur ≤ 4								
4 < Dur ≤ 12								
12 < Dur ≤ 24								
24 < Dur ≤ 48								
48 < Dur ≤ 96								
Dur >96								
Total (Any Duration)								
Percent								

Similar tables can be generated for median, for modal, and for maximum dose, or for dose of longest exposure. The same table can be generated for any pool of studies and any subgroup of interest, e.g., on the basis of age groupings, sex, ethnic factors, comorbid conditions, concomitant medications, or any combination of these factors.

Dose can also be expressed as mg/kg, mg/m², or in terms of plasma concentration if such data are available.

Table 4.2 Demographic Profile of Patients in Controlled Trials Cutoff Date:

		Treatment Groups		
		Test Product N =	Placebo N =	Active Control N =
Age (years)				
	Mean ± SD	50 ± 15		
	Range	20-85		
Groups				
	<18	N (%)	N (%)	N (%)
	18 - 40	N (%)	N (%)	N (%)
	40 - 64	N (%)	N (%)	N (%)
	65 - 75	N (%)	N (%)	N (%)
	>75	N (%)	N (%)	N (%)
6H				
	Female	N (%)	N (%)	N (%)
	Male	N (%)	N (%)	N (%)
5 DH				
	Asian	N (%)	N (%)	N (%)
	Black	N (%)	N (%)	N (%)
	Caucasian	N (%)	N (%)	N (%)
	Other	N (%)	N (%)	N (%)
2 WHI DFUV				

Table 4.3 Incidence of Adverse Events in Pooled Placebo and Active Controlled Trial Database

Body System / Adverse Event	Test Drug			Placebo n = 425	Active Control 1 20 mg n = 653	Active Control 2	
	All doses n = 1685	10 mg n = 968	20 mg n = 717			50 mg n = 334	100 mg n = 546
Body as a whole							
Dizziness	19 (1%)	7 (1%)	12 (2%)	6 (1%)	23 (4%)	1 (<1%)	3 (1%)
Etc.							
Cardiovascular							
Postural Hypotension	15 (1%)	10 (1%)	5 (1%)	2 (<1%)	7 (1%)	6 (2%)	12 (2%)
Etc.							
Gastrointestinal							
Constipation							

Table 4.4 Incidence of Adverse Events in Individual Studies

Body System / Adverse Event	Reported incidence by Treatment Groups							
	Study 95-0403			Study 96-0011		Study 97-0007		Study 98-0102s
	Drug x 60 mg bid N =104	Drug x 30 mg bid N =102	Placebo N = 100	Drug x 60 mg bid N = 500	Placebo N=495	Drug x 60 mg bid N=200	Drug y 100 mg qd N=200	Drug x 60 mg bid N=800
Body as a whole								
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular								
Postural Hypotension Etc.								
Gastrointestinal								
Constipation								

Table 4.5 Patient Withdrawals¹ by Study: Controlled Trials
Cutoff Date:

Studies		Total Withdrawal				Reason for Withdrawal			Number without post-withdrawal efficacy data	
		Total	Male/ Female	Age > 65	Race (identify groupings) / / /	Adverse Events N (%)	Lack of Efficacy N (%)	Other N (%)	N	(%)
Study XXX	Drug X	<i>N (%)</i>	<i>N (%) /</i>	<i>N (%)</i>	<i>N (%) / N (%) /</i>					
	Placebo	<i>N (%)</i>	<i>N (%)</i>		<i>N (%)</i>					
Study AAA	Drug X									
Study BBB	Comparator A									
	Drug X									
Study CCC	Comparator B									
	Drug X									
All Trials										

Note: withdrawal data can be subdivided by dose level, if that appears to be useful.

¹ Withdrawals are all subjects who were enrolled but did not complete the planned course of treatment (includes subjects who discontinued treatment or changed to a different treatment prematurely and/or were lost to follow-up)

Table 4.6 Listing of Deaths											
Treatment: Test Product						Cutoff Date:					
Trial / Source¹	Center	Patient ID	Age (yrs)	Sex	Dose (mg)	Duration of exposure (Days)	Diagnosis	Cause of Death	Other medications	Other medical conditions	Location of narrative description

¹PM = deaths from postmarketing experience

This listing should include all deaths meeting the inclusion rule, whether arising from a clinical trial or from any secondary source, e.g., postmarketing experience. In electronic applications, a link to the narrative or other documentation regarding the event should be provided.

A footnote should describe the rule for including deaths in the table, e.g., all deaths that occurred during a period of drug exposure or within a period of up to 30 days following discontinuation from drug and also those occurring later but resulting from adverse events that had an onset during exposure or during the 30 day follow up period. Other rules may be equally appropriate.

Similar lists should be provided for patients exposed to placebo and active control drugs.

D. TABULAR LISTING OF ALL CLINICAL STUDIES

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in E: Clinical Study Reports

Table 1. Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	20	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	Cross-over	Two tablet formulations, 50 mg, oral	32	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	Cross-over	Tablet, 50mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	24 (12 drug, 12 placebo)	Patients with primary hypertension	2 weeks	Ongoing; Interim
Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full

SECTION E: CLINICAL STUDY REPORTS

PREAMBLE

For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biotechnological Products 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 specific Study Reports should ask for the necessary documents. The ICH E3 provides guidance on the organisation of clinical study reports, other clinical data, and references within the ASEAN Common Technical Dossier (ACTD) for registration of a pharmaceutical product for human use. In this case, the applicant will submit Section A, B, C, D and F.

A.	TABLE OF CONTENTS OF CLINICAL STUDY REPORTS	41
B.	TABULAR LISTING OF ALL CLINICAL STUDIES	41
C.	CLINICAL STUDY REPORTS	41
1.	Reports of Biopharmaceutic Studies	41
1.1	Bioavailability (BA) Study Reports	41
1.2	Comparative BA and Bioequivalence (BE) Study Reports	41
1.3	<i>In vitro-In vivo</i> Correlation Study Reports	42
1.4	Reports of Bioanalytical and Analytical Methods for Human Studies	42
2.	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials .	42
2.1	Plasma Protein Binding Study Reports	42
2.2	Reports of Hepatic Metabolism and Drug Interaction Studies	42
2.3	Reports of Studies Using Other Human Biomaterials	42
3.	Reports of Human Pharmacokinetic (PK) Studies.....	42
3.1	Healthy Subject PK and Initial Tolerability Study Reports	43
3.2	Patient PK and Initial Tolerability Study Reports	43
3.3	Population PK Study Reports	43
4.	Reports of Human Pharmacodynamic (PD) Studies.....	43
4.1	Healthy Subject PD and PK/PD Study Reports	44
4.2	Patient PD and PK/PD Study Reports.....	44
5.	Reports of Efficacy and Safety Studies	44
5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	44
5.2	Study Reports of Uncontrolled Clinical Studies	45
5.3	Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses	45
5.4	Other Clinical Study Reports.....	45
6.	Reports of Post-Marketing Experience	45
7.	Case Report Forms and Individual Patient Listings.....	45

Guideline on Organisation of Clinical Study Reports and Related Information

This guideline recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections.

An explanation such as “not applicable” or “no study conducted” should be provided when no report or information is available for a section or subsection.

A. TABLE OF CONTENTS FOR STUDY REPORTS

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

B. TABULAR LISTING OF ALL CLINICAL STUDIES

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

C. CLINICAL STUDY REPORTS

1. Reports of Biopharmaceutical Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Item 3.1, and referenced in Items 1.1 and/or 1.2.

1.1 Bioavailability (BA) Study Reports

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

1.2 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between 1) the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, 2) the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and 3) similar drug products from different manufacturers.

1.3 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in Item 1.3.

Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the ACTD.

1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

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

2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used *in vitro* or *ex vivo* to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways.

Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Part III).

2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here.

Protein binding data from PK blood and/or plasma studies should be provided in Item 3.

2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

2.3 Studies Using Other Human Biomaterials

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

3. Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity. The PK studies whose reports should be included in Item 3.1 and 3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or feces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells.

On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Item 3.1 to 3.2, as appropriate. These studies should characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Item 3.1 and/or 3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability.

3.1 Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

3.3 Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials, should be placed in this section.

4. Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Item 5.

This section should include reports of 1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers), 2) short-term studies of the main clinical effect, and 3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration - response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

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

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

4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in this section

4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

5. Reports of Efficacy and Safety Studies

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

Within Item 5, studies should be organised by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

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

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

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

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

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

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

5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included. This includes studies in conditions that are not the subject of the marketing application.

5.3 Reports of Analyses of Data from More than One Study

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

5.4 Other Clinical Study Reports

This section can include:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports of clinical experiences with the medicinal product that are not included in Item 5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Item 5.1
- Reports of ongoing studies

6. Reports of Post-Marketing Experience

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

7. Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	20	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	Cross-over	Two tablet formulations, 50 mg, oral	32	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	Cross-over	Tablet, 50mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	24 (12 drug, 12 placebo)	Patients with primary hypertension	2 weeks	Ongoing; Interim
Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full

SECTION F. LIST OF KEY LITERATURE REFERENCES

List of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes all references cited in the Clinical Overview, and important references cited in the Clinical Summary or in the individual technical reports that were provided in Clinical Study Reports. Finally, copies of referenced documents should be available upon request.

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

PART III: NONCLINICAL DOCUMENT*¹

SECTION A. TABLE OF CONTENTS

1. Guide on the Nonclinical Overview and Summaries.....2

SECTION B. NONCLINICAL OVERVIEW2

1. General Aspects2

2. Content and Structural Format3

SECTION C. NONCLINICAL WRITTEN AND TABULATED SUMMARIES..4

1. Nonclinical Written Summaries4

1.1 Introduction4

1.2 General Presentation Issues5

2. Content of Nonclinical Written and Tabulated Summaries6

2.1 Pharmacology7

2.2 Pharmacokinetic8

2.3 Toxicology10

3. Guidance on Nonclinical Tabulated Summaries.....13

SECTION D. NONCLINICAL STUDY REPORTS14

SECTION E. LIST OF KEY LITERATURE REFERENCES15

Appendix A: Nonclinical Tabulated Summaries: Templates16

¹ *Adapted from ICH-CTD on Nonclinical Overview

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 biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included, along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical 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-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, C_{max}, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

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

- Pharmacodynamics
- Toxic signs
- Causes of death
- Pathologic findings
- Genotoxic activity ---- the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data

- 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
- Pharmacology 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
- Secondary pharmacodynamics
- Safety pharmacology
- Pharmacodynamic 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

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.

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 pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effects in humans. In such cases, these secondary pharmacodynamic studies should be considered, along with safety pharmacology studies.

2.1.1.4 Pharmacodynamic Drug Interactions

If they have been performed, pharmacodynamic 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 TABULATED 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
- 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 be 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 and 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)

3. 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, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries². This guidance presents an agreed upon format for the organization of the nonclinical reports in the Common Technical Dossier 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
- 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
- 3.1.5 Excretion

² **Reference Countries** : to be defined ASEAN member states. (*Marketing +Registered country & Listed*)

*It should be noted that protection of animals in the conduct of nonclinical studies should be taken into consideration to avoid unnecessary use of animals.

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*
- 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
- 2.3.2.2 Toxicokinetics: Overview of Toxicokinetics Studies
- 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)

III.	V.	<u>Method of</u>	Testing	Study Number	Location
IV. Type of Study	VI. Test System	<u>Administration</u>	Facility	(4)	<u>Vol.</u> <u>Page</u>
Primary Pharmacodynamics (2)					(3)
Secondary Pharmacodynamics					
Safety Pharmacology					
Pharmacodynamic Drug Interactions					

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

The Common Technical Document – Safety

2.1.2.4 Safety Pharmacology (1)

Test Article: (2)

<u>Organ Systems Evaluated</u>	<u>Species / Strain</u>	<u>Method of Admin.</u>	<u>Doses^a (mg/kg)</u>	<u>Gender and No. per Group</u>	VII. Noteworthy Findings	<u>GLP Compliance</u>	<u>Study Number (3)</u>
--------------------------------	-------------------------	-------------------------	----------------------------------	---------------------------------	---------------------------------	-----------------------	-------------------------

Notes: (1) All safety pharmacology studies should be summarized.
 (2) International Nonproprietary Name (INN).
 (3) Or Report Number (on all tables)
 a - Single dose unless specified otherwise.

The Common Technical Document – Safety

2.2.2 Pharmacokinetics

Overview

Test Article: (1)

Location

VIII.

IX. Type of Study

Test
System

Method of
Administration

Testing
Facility

Study
Number

Vol.

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.

The Common Technical Document – Safety

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 ¹⁴C-labeled compound.
 - (3) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
 - (4) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be indicated.
-

The Common Technical Document – Safety

2.2.2.4 Pharmacokinetics: Absorption after Repeated Doses

Test Article:

(Data can be tabulated as in the format of 2.3, if applicable)

The Common Technical Document – Safety

Format A
2.2.2.5 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)					
T(1)	T(2)	T(3)	T(4)	T(5)	T _{1/2}

Tissues/organs

Additional Information:

¹⁾ [Tissue]/[Plasma]

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

PART II: QUALITY

TABLE OF CONTENTS

Section A: Quality Overall Summary	2
1. Drug Substance	2
2. Drug Product	5
Scope of the Guideline	9
Section B: Table of Contents	9
Section C: Body of Data	9
1. Drug Substance	9
2. Drug Product	15
Section D: Key Literature References	21

Section A : Quality Overall Summary (QOS)

No.	PARAMETERS	COMPONENTS	REQUIREMENTS					
			NCE	BIOTECH	MaV	MiV	G	
S	DRUG SUBSTANCE							
S1	General Information							
	1.1. Nomenclature	– Information from the S1	V	V	V*			V
	1.2. Structure	– Structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.	V					V
		– Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass as appropriate.		V				
	1.3. General Properties	– Physico chemical characteristics and other relevant properties including biological activity for biotech.	V	V	V*			V
S2	Manufacture							
	2.1. Manufacturer(s)	Name and address of the manufacturer (s).	V	V				V
	2.2. Description of Manufacturing Process and Process Controls	– The description of the drug substance manufacturing process and process control that represents the applicant's commitment for the manufacture of the drug substances.	V	V				
		– Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions.		V				
	2.3. Control of Materials	– Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs substance indicating where each material is used in the process. Tests and acceptance criteria of these materials.	V	V				
		– Control of source and starting materials of biological origin.		V				
		– Source, history and generation of the cell substrate .		V				
		– Cell banking system, characterisation and testing.		V				
		– Viral safety evaluation.		V				

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
S3	2.4. Controls of Critical Steps and Intermediates	– Critical steps : Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.	V	V			
		– Intermediates : Specifications and analytical procedure, if any, for intermediates isolated during the process.	V	V			
		– Stability data supporting storage conditions.		V			
	2.5. Process Validation and/or Evaluation	Process validation and/or evaluation studies for aseptic processing and sterilization.	V	V			
	2.6. Manufacturing Process Development	– Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing non-clinical, clinical, scale-up, pilot and if available, production scale batches.	V				
		– The development history of the manufacturing process as described in S 2.2.		V			
3.1. Elucidation of Structure and other characteristics	– Confirmation of structure based on e.g. synthetic route and spectral analyses.	V					
	Compendial requirements or appropriate information from the manufacturer					V	
	– Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).		V				
3.2. Impurities	– Summary of impurities monitored or tested for during and after manufacture of drug substance	V	V				
	Compendial requirements or appropriate information from the manufacturer					V	
S4	Control of Drug Substance						

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
4.1.	Specification	- Detailed specification, tests and acceptance criteria.	V	V			
		- Compendial specification or appropriate information from the manufacturer					V
		- Specify source, including as appropriate species of animal, type of microorganism etc.		V			
4.2.	Analytical Procedures	- The analytical procedures used for testing of drug substance.	V	V			
		- Compendial methods or appropriate information from the manufacturer					V
4.3.	Validation of Analytical Procedures	- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance	V	V			
		- Non-compendial methods					V
4.4.	Batch Analyses	- Description of batches and results of the analysis to establish the specification.	V	V			
4.5.	Justification of Specification	- Justification for drug substance specification.	V	V			
S5	Reference Standards or Materials	- Information on the reference standards or reference materials used for testing of the drug substance .	V	V			
		- Compendial reference standard.					V*
S6	Container Closure System	- Descriptions of the container closure systems.	V	V			
S7	Stability	- Stability report.	V	V			
		- Literature data .					V*

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
P P1	DRUG PRODUCT Description and Composition	– Description	V	V	V*	V*	V
		– Dosage form and characteristics.					
		– Accompanying reconstitution diluent (s) if any.					
		– Type of container and closure used for the dosage form and reconstitution diluent (s), if applicable.					
		Composition	V	V	V*	V*	V
		Name, quantity stated in metric weight or measures, function and quality standard reference.					
P2	Pharmaceutical Development						
	2.1. Information on Development Studies	– Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application.	V	V			
	2.2. Components of the Drug Product	– Active ingredient					
		– Justification of the compatibility of the active ingredient with excipients listed in P1	V	V			
		– In case of combination products, justification of the compatibility of active ingredients with each other.					
		– Literature data.			V*		V
		– Excipients	V	V			
		Justification of the choice of excipients listed in P1, which may influence the drug product performance.					
	2.3. Finished Product	– Formulation Development	V	V			V
		A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and usage for NCE and Biotech).					

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
P3	2.4. Manufacturing Process Development	– Overages Justification of any overage in the formulation(s) described in P1 .	V	V			V
		– Physicochemical and Biological Properties Parameters relevant to the performance of the finished product e.g pH, dissolution.	V	V			V
		– Selection and optimisation of the manufacturing process	V	V			
		– Differences between the manufacturing process (es) used to produce pivotal clinical batches and the process described in P.3.2, if applicable	V	V			
	2.5. Container Closure System	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.	V	V			V
	2.6. Microbiological Attributes	Microbiological attributes of the dosage form, where appropriate	V	V	V*		V
	2.7. Compatibility	Compatibility of the finished product with reconstitution diluent(s) or dosage devices. Literature data	V	V	V*		V
	3.1. Batch Formula	Name and quantities of all ingredients	V	V	V*		V
	3.2. Manufacturing Process and Process Control	Description of manufacturing process and process control	V	V	V*	V*	V
	3.3. Control of Critical Steps and Intermediates	Tests and acceptance criteria	V	V			V
3.4. Process Validation and/or Evaluation	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process.	V	V			V	
P4	Control of excipients						
	4.1. Specifications	– Specifications for excipients Compendial requirements or appropriate information from the manufacturer	V	V	V*		V

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
P5	4.2. Analytical Procedures	– Analytical procedures used for testing excipients where appropriate. Compendial requirements or appropriate information from the manufacturer	V	V	V*	V*	V
	4.3. Excipient of Human or Animal Origin	– Information regarding sources and or adventitious agents. Compendial requirements or appropriate information from the manufacturer	V	V	V*	V*	V
	4.4. Novel Excipients	– For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterization and controls, with cross reference to supporting safety data (non-clinical or clinical)	V	V			
	Control of Finished Product						
	5.1. Specification	– The specification(s) for the finished product.	V	V	V*	V*	V
	5.2. Analytical Procedures	– Analytical procedures used for testing the finished product	V	V	V*	V*	V
	5.3. Validation of Analytical Procedures	– Information including experimental data, for the analytical procedure used for testing the finished product Non-compendial method Verification of compendial method applicability - precision & accuracy	V	V	V*	V*	V
	5.4. Batch Analyses	– Description and test results of all relevant batches.	V	V			
	5.5. Characterisation of Impurities	– Information on the characterisation of impurities Compendial requirements or appropriate information from the manufacturer	V	V	V*		V
	5.6. Justification of Specification(s)	– Justification of the proposed finished product specification(s). Compendial requirements or appropriate information from the manufacturer	V	V	V*		V

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
P6	Reference Standards or Materials	<ul style="list-style-type: none"> - Information on the reference standards or reference materials used for testing of the finished product. Compendial requirements or appropriate information from the manufacturer 	V	V	V*		V
P7	Container Closure System	<ul style="list-style-type: none"> - Specification and control of primary and secondary packaging material, type of packaging and the package size, details of packaging inclusion (e.g. desiccant, etc) 	V	V	V*	V*	V
P8	Stability	<p>Stability report : data demonstrating that product is stable through its proposed shelf life.</p> <p>Commitment on post approval stability monitoring</p>	V	V	V*		V
P9	Product Interchangeability Equivalence evidence	<ul style="list-style-type: none"> - In Vitro Comparative dissolution study as required 			V*		V
		<ul style="list-style-type: none"> - In Vivo Bioequivalence study as required 			V*		V

remarks : * if required
NCE : New Chemical Entity
Biotech : Biotechnological Products
MaV : Major Variation
MiV : Minor Variation
G : Generics

SCOPE OF THE GUIDELINE

This document is intended to provide guidance on the format of a registration application for drug products regarding ASEAN CTR. This format is appropriate for NCE (New Chemical Entity), Biotech (Biotechnological Products), MaV (Major Variations), MiV (Minor Variations) and G (Generics). To determine the applicability of this format for a particular type of product, applicant should consult with the appropriate National Regulatory Authorities. The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guideline and both may depend upon national guidance and or accepted leading international references (pharmacopoeias).

For NCE and Biotech requirements please refer to the relevant ICH Guidelines.

Section B: Table of Contents

A table of contents for the filed application should be provided.

Section C: Body of Data

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

- International non-proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)

S 1.2 Structural formula

NCE :

The structural, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

Biotech :

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

Generic :

Compendial requirement or equivalent information from the manufacturer.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

Reference ICH Guidelines: NCE : Q6A, Biotech : Q6B

S 2 Manufacture

S 2.1 Manufacturer(s)

Name and full addresses including the city and country of the manufacturer of active ingredient.

S 2.2 Description of Manufacturing Process and Process Controls

The description of the drug substances manufacturing process represents the applicant's commitment for the manufacture of drug substances. The following information should be provided to adequately describe the manufacturing process and process controls:

NCE:

- A schematic flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights and yields, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.
- A sequential procedural narrative of the manufacturing process that provides quantities of raw materials, solvent, catalysts and reagent reflecting the representative batch scale, and includes process controls, equipment and operating conditions, such as temperature, pressure, pH, time etc.
- Alternative process should be explained and described with the same level of details as the primary process. Reprocessing steps should be identified and justified.

Biotech:

- Information on the manufacturing process, which typically starts with a vial(s) of the cell bank and includes cell culture, harvest(s), purification and modification reaction, filling storage and shipping conditions.

Reference ICH Guidelines : Q5A, Q5B and Q6B.

S 2.3 Control of Materials

Material used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

Reference ICH Guidelines : NCE : Q6A; Biotech : Q6B

Biotech:

- Control of source and starting materials of biological Origin.
Summaries of viral safety information for biologically -sourced materials should be provided.
- Source, history and generation of the cell substrate.
Information of the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.
- Cell banking system, characterization and testing.

Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in Q5B and Q5D.

Reference ICH Guidelines : Q5A, Q5B, Q5C, and Q5D

S 2.4 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

Reference ICH Guidelines : Q6A, Q6B,
Additionally for Biotech: Stability data supporting storage conditions.
Reference ICH Guidelines : Q5C

S 2.5 Process Validation and/or Evaluation

Process validation or evaluation studies for aseptic processing and sterilization.

Biotech

Sufficient information on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiated selection of critical process controls (operational parameters and in-process test) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification).

Information should include a description of the plan for conducting the study and the results, analysis and conclusions from the executed study(ies). The validation of corresponding assay and analytical methods should be cross-referenced or provided as part of justifying the selection of critical process controls and limits.

For manufacturing steps, intended to remove or inactive viral contaminants, the information from evaluation studies should be provided

Reference ICH Guidelines Q5A, Q5D, and Q6B

S 2.6 Manufacturing Process Development

NCE

Description and discussion of significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing non-clinical, clinical scale-up, pilot and if available, production scale batches.

Reference ICH Guidelines : Q3A

Biotech

The developmental history of the manufacturing process, as described in S. 2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. non-clinical or clinical

studies) including for example, changes to the process or critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale and use (e.g. stability, non clinical reference material) in relation to the change.

The significance of change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance. A discussion of the data including a justification for selection of the test and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) may also include non-clinical and clinical studies in other modules of the submission should be included.

Reference ICH Guidelines : Q6B

S 3 Characterization

S 3.1 Elucidation of Structure and Characteristic

NCE :

Confirmation of structure based on e.g. synthetic route and spectral analysis. Information on the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorph should also be included.

Reference ICH Guidelines : Q6A

Biotech:

Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).

Reference ICH Guidelines : Q6B

MaV, MiV, G:

Compendial requirement or equivalent information from the manufacturer.

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH guidelines : Q3A, Q3C, Q5C, Q6A and Q6B

Generic :

Compendial requirement or equivalent information from the manufacturer.

S 4 Control of Drug Substance

Specification and justification of specification (s).
Summary of analytical procedure and validation.

S 4.1 Specification

Detailed specification, tests and acceptance criteria for the drug substance should be provided.

Reference ICH Guidelines NCE : Q6A

Biotech :

Specify source, including as appropriate species of animal, type of microorganism, etc.

Reference ICH Guidelines : Q6B

MaV, MiV, G :

Compendia specification are adequate. Indicate clearly whether the drug substance is purchased based on specification with a certificate of analysis, or tested by applicant.

S 4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Reference ICH Guidelines : NCE : Q2A ; Biotech : Q6B

MaV, MiV, G :

Compendial requirement or equivalent information from the manufacturer

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Reference ICH Guidelines : NCE : Q2A and Q2B ; Biotech : Q6B

MaV, MiV, G :

Required for non-compendial method only

Reference ASEAN Guideline for Validation of Analytical Procedure

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided

Reference ICH Guidelines : NCE : Q3A, Q3C and Q6A ; Biotech : Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

Reference ICH Guidelines : NCE : Q6A ; Biotech : Q6B

S 5 Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided.

Reference ICH Guidelines : NCE : Q6A ; Biotech : Q6B

MaV, MiV, G :

Compendial requirement or equivalent information from the manufacturer

S 6 Container Closure System

NCE and Biotech :

A descriptions of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component, and each specifications. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

S 7 Stability

Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines : Q1A (R2), Q1B, and Q5C

Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines : Q1A (R2) and Q5C

Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines : Q1A (R2), Q1B, Q2A, Q2B, and Q5C

MaV, MiV, G:

Manufacturer stability data or equivalent information

P DRUG PRODUCT

P1 Description and Composition

A description of the drug product and its composition should be provided. The information provided should include, for example :

- Description of the dosage form;
- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)
- Description of accompanying reconstitution diluent(s); and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Reference ICH Guidelines : NCE : Q6A ; Biotech : Q6B

P 2 Pharmaceutical Development

P 2.1 Information on Development Studies

NCE and Biotech:

The section of Pharmaceutical Development presents information and data on the development studies conducted to establish that the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usages instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and

drug product quality. Supportive data and result from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the relevant non-clinical sections of the application.

Reference ICH Guidelines : NCE : Q6A; Biotech : Q6B

P 2.2 Component of Drug Product

P 2.2.1 Active Ingredients

NCE and Biotech:

The compatibility of the drug substances with excipients listed in Item 2.1 should be discussed. Additionally, key physicochemical characteristics (e.g. Water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance, which may influence the performance of the drug product should be discussed.

MaV, MiV, G:

Literature data is sufficient.

P 2.2.2 Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

P 2.3 Finished Product**P 2.3.1 Formulation Development**

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

P 2.3.2 Overages

Any overages in the formulation(s) described in Item P 1 should be justified.

P 2.3.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

P 2.4 Manufacturing Process Development

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

Generics : refer to P.3.2.

P 2.5 Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed *as necessary*. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of construction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing anti microbial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility

The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

MaV, MiV, G :

Literature data are acceptable

P 3 Manufacture

P 3.1 Batch Formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

- The actual quantities (g, kg, liters) etc. of ingredient should be stated.
- Overage: Supporting data and the reason for including the overage shall be enclosed.
- The total number of dosage unit per batch must stated.
- A description of all stages involved in the manufacture of the dosage form is required.

Reference ICH Guidelines : Biotech : Q6B

P 3.2 Manufacturing Process and Process Control

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

- The full description of manufacturing process must sufficient details to cover the essential point of each stage of manufacture.
- For sterile product the description includes preparation and sterilization of components (i.e. Containers, closures, etc).

P 3.3 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines : Q2A, Q2B, Q6A and Q6B

P 3.4 Process Validation and/or Evaluation

Description, documentation, and result of the validation studies should be provided from critical steps or critical assays used in the manufacturing process.

(e.g. Validation of the sterilization process or aseptic processing or filling).

Reference : NCE : Q6B, Biotech : Q6B

MaV, MiV, G :

ASEAN Guideline *on process validation*

P 4 Control of Excipients

P 4.1 Specification

The specification for the excipients should be provided.

Reference ICH Guidelines : NCE : Q6A ; Biotech : Q6B

MaV, MiV, G :

Compendial requirements or equivalent information from the manufacturer

P 4.2 Analytical Procedures

The analytical procedures used for the testing the excipient should be provided, where appropriate.

Reference ICH Guidelines : NCE : Q2A ; Biotech : Q6B

MaV, MiV, G :

Compendial requirements or equivalent information from the manufacturer.

P 4.3. Excipients of Human and Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents(e.g. sources, specifications, description of the testing performed, viral safety data).

(Reference ICH Guidelines : NCE : Q5A, Q5D ; Biotech : Q6B)

MaV, G :

Use compendial requirements if available, otherwise the same requirements apply.

P 4.4 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) should be provided

P 5 Control of Finished Product

Specification and justification of the specification, summary of the analytical procedure and validation, and characterization of impurities.

P 5.1 Specification

The specification for the finished product should be provided.

Reference ICH Guidelines : NCE : Q6A; Biotech : Q6B

P 5.2 Analytical Procedures.

The analytical procedures use for the testing the finished product should be provided.

Reference ICH Guidelines : NCE : Q2A ; Biotech : Q6B

P 5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures use for the testing the finished product should be provided.

Reference ICH Guidelines : NCE : Q2A and Q2B; Biotech : Q6B

MaV, MiV, G :

Required for non-compendial method only however, verification for the applicability of compendial method used is required.

Reference : ASEAN Guideline for validation of analytical procedure.

P 5.4 Batch analyses

Description (including size, origin and use) and test result of all relevant batches e.g pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided.

Reference ICH Guidelines : NCE : Q3A, Q3C, and Q6A; Biotech : Q6B.

Generics : refer to P.3.4.

MaV, MiV, G :

A tabulated summary of the batch analyses, with graphical representation where appropriate, should be provided.

P 5.5 Characterization of Impurities

Information on the characterization of impurities should be provided, if not previously provided in Item 1.3.2 Impurities.

Reference ICH Guidelines : NCE : Q3B and Q6A; Biotech : Q6B

MaV, MiV, G :

Compendial requirements or appropriate information from the manufacture.

P 5.6 Justification of Specification

Justification for the proposed finished product should be provided

Reference ICH Guidelines : NCE : Q3B and Q6A; Biotech : Q6B

MaV, MiV, G :

Compendial requirements or equivalent information from the manufacture.

P 6 Reference Standards or Materials

Requirement : Quality information and tabulated presentation of Reference standard or materials used for testing of drug product should be included.

Reference : NCE : Q6A, Biotech : Q6B

MaV, MiV, G :

Compendial requirements or equivalent information from the manufacture.

P 7 Container closure system

A descriptions of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component, and each specifications. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2

P 8 Product Stability

Evidence is required to demonstrate that product is stable, meets the finished product specifications throughout its proposed shelf-life, that toxic decomposition products are not produced in significant amount during this period, and that potency, efficacy of preservative etc. are maintained.

Stability Summary and Conclusion

NCE and Biotech:

All criteria under ICH Guidelines are acceptable with the exception of *real time* storage conditions which should be 30°C, 75% RH. Provision of moisture protection of the packaging should be taken into consideration.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B and Q5C

MaV, G:

ASEAN Guideline on *Stability Study* of Drug Product

Post-approval stability protocol and stability commitment

The post-approval stability protocol and stability commitment should be provided.

References ICH Guidelines : NCE, Biotech : Q1A (R2) and Q5C

Generic :

ASEAN Guideline on *Stability Study* of Drug Product

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference : ASEAN Guideline on *Stability Study* of Drug Product, ASEAN Guideline on *Validation of Analytical Procedure*

P 9 Product Interchangeability

This requirement applies to MaV, G.

The type of studies conducted, protocol used and the result of the studies should be presented in the study report.

Type of studies conducted should refer to ASEAN (proposed) Bioavailability and Bioequivalence requirement, Guideline for Bioavailability and Bioequivalence Studies or WHO Manual for Drug Regulatory Authority.

Reference: - WHO, Regulatory Support Series No 5 , "Bioequivalence Studies in Humans."

- ASEAN Guide line on *Bioequivalence Study*

Section D: Key Literature References

Key literature references should be provided, if applicable.