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

PART I : ADMINISTRATIVE DATA AND PRODUCT INFORMATION

1. Application Form
2. Letter Of Authorisation
3. Certification

3.1 For contract manufacturing
- (a) License of pharmaceutical industries and contract manufacturer
- (b) Contract manufacturing agreement
- (c) GMP certificate of contract manufacturer

3.2 For manufacturing "under-lincese' (country specific)
- (a) License of pharmaceutical industries
- (b) GMP certificate of manufacturer
- (c) Copy of "under-license" agreement

3.3 For imported products
- (a) License 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.
- (c) Site master file of manufacturer (unless previously submitted within the last 2 years) (country specific)

4. Labelling

4.1 Unit Carton

4.2 Inner Label

4.3 Blister/Strips

5. Product Information

5.1 Package insert (package insert is required for generic products)

5.2 Summary of Product Characteristic (Product Data Sheet)(required for NCE & Biotechnology products)

5.2.1 Name of the Medicinal Product
- (a) Product Name
- (b) Strength
- (c) Pharmaceutical Dossage Form

5.2.2 Quality and Quantitative Compoistion
- (a) Qualitative Declaration, The active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant
- (b) Quantitative Declaration The quantity of the active substance must be expressed per dossage unit

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

5.2.4 Clinical Particulars
- (a) Therapeutic indications
- (b) Posology and method of administration
- (c) Contraindications
- (d) Special warnings and precautions for use
- (e) Interation with other medicinal products and other froms of interactions
- (f) Pregnancy and lactation
- (g) Effects on ability to drive and use machine

(h) Undesirable effects
(i) Overdose

5.2.5 Pharmacological Properties.
(a) Pharmacodynamic Properties
(b) Pharmacokinetic Properties
(c) Preclinical safety Data

5.2.6 Pharmaceutical Particulars
(a) List of excipients
(b) Incompatibilities
(c) Shelf life
Shelf life of the medicinal product as packages for sale. Shelf life after dilution or reconsti tution according to directions. Shelf - life first opening the container.
(d) Special precautions for storage
(e) Nature and contents of container

5.2.7 Marketing Authorization Holder

5.2.8 Marketing Authorization Numbers

5.2.9 Date of first authorization/ renewal of the authorization

5.2.10 Date of revision of the text

5.3 Patient Information Leaflet (PIL)
(PIL is required for Over-the-Counter Products)

Part II Quality

S. Drug Substance

SI General Information

SI.1 Nomenclature
- Information from the SI

SI.2 Structure
- Sturctural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.

SI.3 General Properties
- Physico chemical characteristics and other relevant properties including biological acitvity for biotech.
- Schematic amino acid sequence indicating glycosylation sites or the post-translational modifica tions and relative molecular mass as appropriate.

S2 Manufacture

S2.1 Manufacturer (s)
- Name and address of the manufacturer (s).

S2.2 Description of Manufacturing Process and Process Control.*

S2.3 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.
- Control of source and starting materials of biological origin.
- Source, history and generation of the cell substrate
- Cell banking system, characterization and testing.
- Viral safety evaluation.

S2.4 Controls of Critical Steps and Intermediates
- Critical steps : Test 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. *

S2.5 Process Validation and/or Evaluation. *

- process validation and/or evaluation studies for aseptic processing and sterilization.

S2.6 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.
- The development history of the manufacturing process as described in S2.2

S3 Characterisation. *

*** required for NCE (New Chemical Entity)/New products for Myanmar.**

S3.1 Elucidation of Structure and other characteristics

- Confirmation of structure based on e.g synthetic route and spectral analyses.
- Compendial requirement or appropriate information from the manufacturer
- Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).

S3.2 Impurities *

- Summary of impurities monitored or tested for during and after manufacture of drug substance.
- Compendial requirements or appropriate information from the manufacturer

S4. Control of Drug Substance

S4.1 Specification *

- Detailed specification, test and acceptance criteria.
- Compendial specification or appropriate information from the manufacturer
- Specify source, including as appropriate species of animal, type of microorganism etc...

S4.2 Analytical Procedures *

- The analytical procedures used for testing of drug substance.
- Compendial methods appropriate information from the manufacturer.

S4.3 Validation of Analytical Procedures *

- The analytical information, including experimental data for the analytical procedures used for testing of drug substance.
- Non-compendial methods

S4.4 Batch Analyses *

- Description of batches and results of the analysis to establish the specification.

S4.5 Justification of Specification *

- Justification for drug substance specification. *

S5. Reference Standard or Materials. *

- Information on the reference standards of reference materials used for testing of the drug sub stance. *
- Compendial reference standards

S6 Container Closure System *

- Descriptions of the container closure systems.

S7 Stability

- Stability report. *
- Literature data

P DRUG PRODUCT

P1 Description and Composition

Description

- Dosage form and characteristics
- Accompanying reconstitution diluent (s) if any.
- Type of container and closure used for the dosage form and reconstitution diluent, if applicable.

Composition

- Name quantity stated in metric weight or measures, function and quality

P2.1 Information on Development Studies. *

- Data on the development studies conducted to establish that the dosage form, Formulation, Manufacturing process, container closer system.

P2.2 Components of the Drug Product

P2.2.1 Active ingredient

- Justification of the compatibility of the active ingredient with excipients Lised in P1 In case of combination products, justification of the compatibility of active-ingredients with each other.*
- Literature data.

P2.2.2 Excipients *

- Justification of the choice of excipients used in P1. which may influence the drug product performance.

P2.3 Finished Product

P2.3.1 Formulation Development

- A brief summary describing the development of the finished product (taking into consideration the proposed route of administration and usage for NCE and Biotech)

P2.3.2 Overages

- Justification of any overage in the formulation(s) described in P1.
- Physicochemical and Biological Properties Parameters revelant to the performance of the finished product. e.g pH, dissolution.

P2.4 - Manufacturing Process Development

- Selection and optimisation of the manufacturing process.
- Differences between the manufacturing process(es)used to produce pivotal clinical batches and the process described in P.3.2, if applicable.*

P2.5 - Container Closure System

- Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.

P2.6 - Microbiological Attributes

- Microbiological attributes of the dosage form, where appropriate.

P2.7 - Compatibility

- Compatibility of the finished product with reconstitution diluent(s) or dosage devices. Literature data. *

P3 Manufacture

P3.1 Batch Formula

- Name and quantities of all ingredients.

P3.2 Manufacturing Process and Process Control.

- Description of manufacturing process and process control.

P3.3 Control of Critical Steps and Intermediates

- Tests and acceptance criteria

P3.4 Process Validation and/or Evaluation

- Description documentation and results of the validation and evaluation studies for critical steps or critical assays used in the manufacturing process.

P4 Control of excipients

P4.1 - Specifications for excipients. *

- Compendial requirement or appropriate information from the manufacturer

P4.2 Analytical Procedures used for testing excipients where appropriate.

- Compendial requirements or appropriate information from the manufacturer.

P4.3 Excipient of Human or Animal Origin Information regarding sources and or adventious agents.*

- Compendial requirements or appropriate information from the manufacturer.

P4.4 Novel Excipients *
- For excipients(s) used for the first time in a finished Product or by a new route of administration, full details of manufacture, characterization.

P5. Control of Finished Product

P5.1 Specification
- The specification(s) for the finished product.

P5.2 Analytical Procedures
- Analytical procedures used for testing the finished product.

P5.3 Validation of Analytical Procedures
- Information including experimental data for the analytical procedure used for testing the finished product. *
- Non Compendial Method.
- Verfication of compendial method applicability - precision & accuracy.

P5.4 Batch Analyses
- Description and test results of all relevant batches.

P5.5 Characterisation of Impurities
- Information on the characterisation of impurities. *
- Compendial requirements or appropriate information from the manufacturer

P5.6 Justification of Specification(s)
- Justification of the Proposed finished product specification.

P6 Container Closure System
- Specification and control of primary and secondary packaging material, type of packaging & the package size, details of packaging inclusion(e.g desiccant, etc.)

P8 Stability
- Stability report : data demonstrating that product is stablet through its proposed shelf life.
- Commitment on post approval stability monitoring.

P9 Product Interchangeability (Generic only)
Equivalence evidence
- In Vitro
Comparative dissolution study as required.
- In Vivo
Bioequivalence study as required.

Part III : NONCLINICAL (For NCE/ New products for Myanmar).

1. General Aspect
2. Content and structural format
1. Nonclinical Written Summaries

1.1 Pharmacology
1.1.1 Primary Pharmacodynamics
1.1.2 Secondary Pharmacodynamics
1.1.3 Safety Pharmacology
1.1.4 Pharmacodynamics Drug Interactions.

1.2 Pharmacokinetics
1.2.1 Absorption
1.2.2 Distribution
1.2.3 Metabolism
1.2.4 Excretion
1.2.5 Pharmacokinetics Drug Interaction (non-clinical)
1.2.6 Other Pharmacokinetics Studies

1.3 Toxicology
1.3.1 Single dose toxicity

1.3.2 Repeat dose toxicity
1.3.3 Genotoxicity
1.3.4 Carcinogenicity
1.3.5 Reproductive and development toxicity
1.3.5.1 Feritlity & early embryonic development
1.3.5.2 Embryo-fetal development
1.3.5.3 Prenatal and postanatal development
1.3.6 Local tolerance
1.3.7 Other toxicity studies, if available
- Antigenicity
- Immunotoxicity
- Dependence
- Metabolites
- Impurities

Part IV Clinical (for NCE/ New Product for Myanmar)

" Clinical Overview "

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

- " Clinical Summary "

1. Summary of Biopharmaceutic Studies and Associated Analytical Method
1.1 Background and Overview
1.2 Summary of Results of Individual Studies
1.3 Comparison and Analyses of Result Across Studies

2. **Summary of Clinical Pharmacology Studies**
2.1 Background and Overview
2.2 Summary of Results of Individual Studies
2.3 Comparison and Analyses of Results Across Studies
2.4 Special Studies

3. **Summary of Clinical Efficacy**
3.1 Background and Overview of Clinical Efficacy
3.2 Summary of Results of Individual Studies
3.3 Comparison and Analyses of Results Across Studies
3.4 Analysis of Clinical Information Relevant to Dosing Recommendations
3.5 Persistence of Efficacy and/ or Tolerance Effets.

4. **Summary of Clinical Safety**
4.1 Exposure to the Drug
4.2 Adverse Events
4.3 Clinical Laboratory Evaluations
4.4 Vital Sign, Physical Findings, and Other Observations Related to Safety
4.5 Safety in Special Groups and Situations
4.6 Post- marketing Data

5. **Synopses of Individual Studies**

‘ Clinical Study Reports’’ (if applicable)

1. Reports of Biopharmaceutic Studies

1.1 B.A study Reports

1.2 Comparative BA or BE Study Reports

1.3 In vitro- In vivo Correlation Study Reports

1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

2. Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

2.1 Plasma Protein Binding Study Reports

2.2 Reports of Hepatic Metabolism and Drug Interaction Study

2.3 Reports of Studies Using Other Human Biomaterials

3. **Report of Human Pharmacokinetic(PK) Studies**

3.1 Healthy Subject PK and Initial Tolerability Study Reports.

3.2 Patient PK and Initial Tolerability Study Reports

3.3 Population PK Study Reports

4. Reports of Human Pharmacodynamic (PD) Studies

4.1 Healthy Subject & PD and PK/PD Study Reports.

4.2 Patient PD and PK/PD Study Reports.

5. Reports of Efficacy and Safety studies

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

5.2 Study Reports of Uncontrolled Clinical Studies

5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal integrated Analyses, Meta - analyses & Bridging Analyses

5.4 Other Clinical Study Reports

6. Reports of Post-Marketing Experience

7. Case Report Forms and Individual Patient Listing

8. List of Key Literature References *

Well-established Drug Products. (WHO)

- Pharmaceutical Product that contain well established drugs & which:
  - have been marketed for at least five years that undertake active post marketing monitoring;
- have been widely used in sufficiently large number of patients to permit the assumption that safety & efficacy are well known, have the same route of administration & strength & the sameor similar indication as in those countries.