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

Part II: QUALITY

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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), Biologics (Biotechnological Products and Vaccines), MaV (Major Variations), MiV (Minor Variations) and G (Generics). The ACTR Quality only provides the requirements for new product registration (NCE, Biologics, and Generics). For the requirements for variation of pharmaceuticals, reference should be made to the ASEAN Variation Guideline. For the requirements for variation of biotechnological products and vaccines, reference should be made to the WHO Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products (2017) and WHO Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines (WHO TRS 993, Annex 4) respectively.

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 Biologics requirements please refer to the relevant ICH Guidelines.

Section A : Table of Contents

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

Section B: Quality Overall Summary (QOS)

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
S	**DRUG SUBSTANCE**				
S1	**General Information**				
	1.1. Nomenclature	– Information from the S1	**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		**V**	

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
		appropriate. (Note: This section is applicable for biotech products and recombinant polysaccharide/protein vaccines)			
	1.3. General Properties	– Physicochemical characteristics and other relevant properties including biological activity for biologics.	**V**	**V**	**V**
		– For each biological starting material used to obtain or extract the active ingredient, include a summary of viral safety of the material)if applicable(		**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**	
		– Flowchart of manufacturing process, Description of batch identification system, Description of inactivation or detoxification process, Description of purification process Stabilization of active ingredient, reprocessing, Filling procedure, in process control		**V**	
	2.3. Control of Materials	– Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs subtance 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**	

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
		– Cell banking system, characterisation and testing.		V	
		– Viral safety evaluation.		V	
	2.4. Controls of Critical Steps and Intermediates	– Critical steps : Tests and acceptance criteria, with justification including quality specifications and 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	V	
		– The development history of the manufacturing process as described in S 2.2.		V	
S3	**Characterisation**				
	3.1. Elucidation of Structure and other characteristics	– Confirmation of structure based on e.g. synthetic route and spectral analyses.	V	V	
		– Compendial requirements or appropriate information from the manufacturer		V	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	

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
		– Compendial requirements or appropriate information from the manufacturer		V	V
S4	**Control of Drug substance**				
	4.1. Specification	– Detailed specification, tests and acceptance criteria.	V	V	
		– Compendial specification or appropriate information from the manufacturer		V	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	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	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	V
S6	**Container Closure System**	– Descriptions of the container closure systems.	V	V	
S7	**Stability**	– Literature data.			V
		– Stability Summary and conclusion	V	V	

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
		– Post approval stability protocol and stability commitment	V	V	
		– Stability Data	V	V	
P	DRUG PRODUCT				
P1	Description and Composition	**Description**	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			
		Name, quantity stated in metric weight or measures, function and quality standard reference.	V	V	V
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 • In case of combination products, justification of the compatibility of active ingredients with each other.	V	V	
		– Literature data.			V
		– Excipients Justification of the choice of excipients listed in P1, which may influence the drug product performance.	V	V	

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
	2.3. Finished Product	– 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 Biologics).	**V**	**V**	**V**
		– 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**
	2.4. Manufacturing Process Development	– 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**
	2.7. Compatibility	- Compatibility of the finished product with reconstitution diluent(s) or dosage devices.	**V**	**V**	
		- Literature data			**V**
P3	**Manufacture**				
	3.1. Manufacturer	Name, address, and responsibilities of each manufacturer involved	**V**	**V**	**V**
	3.2. Batch Formula	Name and quantities of all ingredients	**V**	**V**	**V**

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
	3.3. Manufacturing Process and Process Control	Description of manufacturing process and process control	**V**	**V**	**V**
	3.4. Control of Critical Steps and Intermediates	Tests and acceptance criteria	**V**	**V**	**V**
	3.5. 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**
		Viral safety information		**V**	
P4	**Control of Excipients**				
	4.1. Specifications	– Specifications for excipients	**V**	**V**	
		– Compendial requirements or appropriate information from the manufacturer		**V**	**V**
	4.2. Analytical Procedures	– Analytical procedures used for testing excipients where appropriate.	**V**	**V**	
		– Compendial requirements or appropriate information from the manufacturer		**V**	**V**
	4.3. Excipient of Human or Animal Origin	– Information regarding sources and or adventitious agents.	**V**	**V**	
		– Compendial requirements or appropriate information from the manufacturer			**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**	
P5	**Control of Finished Product**				
	5.1. Specification	– The specification(s) for the finished product.	**V**	**V**	**V**

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
	5.2. Analytical Procedures	– Analytical procedures used for testing the finished product	**V**	**V**	**V**
	5.3. Validation of Analytical Procedures	– Information including experimental data, for the validation of the analytical procedure used for testing the finished product	**V**	**V**	
		– Non-compendial method	**V**	**V**	**V**
		– Verification of compendial method applicability - precision & accuracy		**V**	**V**
	5.4. Batch Analyses	– Description and test results of all relevant batches.	**V**	**V**	
		– Summary protocol of the production and control		**V**	
	5.5. Characterisation of Impurities	– Information on the characterisation of impurities	**V**	**V**	
		– Compendial requirements or appropriate information from the manufacturer		**V**	**V**
	5.6. Justification of Specification(s)	– Justification of the proposed finished product specification(s).	**V**	**V**	
		– Compendial requirements or appropriate information from the manufacturer		**V**	**V**
P6	**Reference Standards or Materials**	– Information on the reference standards or reference materials used for testing of the finished product.	**V**	**V**	
		– Compendial requirements or appropriate information from the manufacturer		**V**	**V**
P7	**Container Closure System**	– 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**
P8	**Stability**	– Stability Summary and conclusion	**V**	**V**	**V**
		– Commitment on post approval stability monitoring	**V**	**V**	**V**
		– Stability report : data demonstrating that product is stable through its proposed shelf life.			

No	PARAMETERS	COMPONENTS	REQUIREMENTS		
			NCE	BIOLOGICS	G
		– Description of procedures to guarantee cold chain (where applicable)	**V**	**V**	**V**
			V	**V**	**V**
P9	**Product Interchangeability/ Equivalence evidence**	– In Vitro Comparative dissolution study as required			**V**
		– In Vivo Bioequivalence study as required			**V**
A	**ANNEX**				
A1	**Adventitious Agents Safety Evaluation**	– A discussion on measures implemented to control endogenous and adventitious agents in production should be included.		**V**	
		– A tabulated summary of the reduction factors for viral clearance, should be provided.		**V**	

Remarks : * if required

NCE : New Chemical Entity

Biologics : Biotechnological Products and Vaccines

G : Generics

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

Biologics :

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

For example, in synthetic vaccines containing polysaccharides or proteins include the schematic amino acid sequence, indicating the glycosylation sites or other modifications and relative molecular mass.

Generics :

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 Biologics.

Biologics

For each biological starting material used to obtain or extract the active ingredient, include a summary of viral safety of the material)if applicable) in Annex A.1.

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.

Biologics:

- 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. Where applicable, include the number of passages.
- Flow chart of manufacturing process: Showing all the manufacturing steps, including intermediate processes.
- Description of batch identification system: Identification of the lot in each stage of the process, including when mixtures are made. Also submit information on the manufacturing scale and lot size.
  Methods and agents used, parameters controlled, and production stage in which it is performed, when applicable.
- Description of inactivation or detoxification process: Method, reagents, and materials used, operating parameters controlled, and specifications.
- Description of purification process: Conditions for the use and re-use of membranes and chromatography columns and the respective validation studies.
- Stabilization of active ingredient
  Description of the steps performed to stabilize the active ingredient, for example, the addition of stabilizers or other procedures, when applicable.
- Reprocessing
  Description of the procedures established for reprocessing the active ingredient or any intermediate product; criteria and justification.
- Filling procedure, in-process controls
  Description of the procedure for packaging the active ingredient, process controls, acceptance criteria, type of container closure system, type of seal on the container used to store the active ingredient, storage and transfer conditions, when applicable.

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

Biologics (as applicable):

- Control of source and starting materials of biological Origin.
- 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.
- Viral safety evaluation. Summaries of viral safety information for biologically-sourced materials should be provided in Annex A.1.

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 quality specifications and 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.

Stability data supporting storage conditions.

Virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be provided. Detailed information on viral safety should be provided in Annex A.1.

Reference ICH Guidelines : Q6A, Q6B
Additionally for Biologics: 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.

Biologics
Sufficient information on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate 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 in Annex A.1.

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

Biologics
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 should be provided.

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 batches should be provided. 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.

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 polymorphs should also be included.

Reference ICH Guidelines : Q6A

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

Reference ICH Guidelines : Q6B

Generics:
Compendial requirement or equivalent information from the manufacturer.

S 3.2 Impurities
Summary of Impurities monitored or tested for during and after manufacture of drug substance.

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

Generics and Biologics:
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: Q6B

Biologics :

Compendial specification or appropriate information from the manufacturer.

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

Reference ICH Guidelines : Q6B

Generics:

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.

Compendial requirement or equivalent information from the manufacturer.

Reference ICH Guidelines : Q2; Biotech : Q6B

Generics:
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 : Q2, Biotech : Q6B, ASEAN Guideline for Method Validation for Vaccine

Generics:

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 : Q3A, Q3C , Q6A and 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.

Compendial reference standard should be used if applicable.

Reference ICH Guidelines : NCE : Q6A ; Biotech : Q6B

Generics:

Compendial requirement or equivalent information from the manufacturer

S 6 Container Closure System
NCE and Biologics :

A description 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

S.7.1 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

S.7.2 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

S.7.3 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, Q2, and Q5C

Generics:

Manufacturer stability data or equivalent information

P DRUG PRODUCT

P 1 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 Biologics:

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 Biologics:

The compatibility of the drug substances with excipients listed in P.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.

In case of combination products, compatibility between the active ingredients should be discussed.

Generics:

Literature data is sufficient.

P 2.2.2 Excipients

The choice of excipients listed in 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 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 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 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 P 3.2 that can influence the performance of the product should be discussed.

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 contraction, 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 from 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 with reconstitution diluents(s) or dosage devices, e.g. solubility of drug product, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

Generics:
Literature data are acceptable

P 3 Manufacture

P.3.1. Manufacturer

Name, address, and responsibilities of each manufacturer involved, including contract manufacturers for production and quality control.

P 3.2 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 should be stated.
- A description of all stages involved in the manufacture of the dosage form is required.

Reference ICH Guidelines : Biotech : Q6B

P 3.3 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 including 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).
- Description of batch identification system, define the lot in the stages of filling, lyophilization)if it applies(and packaging.

P 3.4 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 in P3.2 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.

Virological tests that are conducted during manufacturing should be provided. Detailed information on viral safety should be provided in Annex A.1.

Reference ICH Guidelines: Q2, Q6A and Q6B

P 3.5 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).

It is also necessary to provide information on the viral safety of the product, when applicable, in Annex A.1.

Reference : NCE : Q6A, Biotech : Q6B

Generics:
ASEAN Guideline on process validation

P 4 Control of Excipients

P 4.1 Specification
The specification for the excipients should be provided.

Compendial requirements or equivalent information from the manufacturer.

Reference ICH Guidelines: NCE: Q6A ; Biotech : Q6B

Generics:
Compendial requirements or equivalent information from the manufacturer

P 4.2 Analytical Procedures
The analytical procedure used for the testing of the excipient should be provided, where appropriate.

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate (e.g. for in-house test methods).

Justification for the proposed excipient specifications should be provided, where appropriate (e.g. for non-compendial specifications).

Compendial requirements or equivalent information from the manufacturer.

Reference ICH Guidelines: NCE : Q2 ; Biotech : Q6B

Generics:
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). Detail information of viral safety should be provided in Annex A.1.

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

Reference ICH Guidelines : Biologics Q5A, Q5D and Q6B

Generics:
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 according to the drug substance format.

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.
Detailed description on the analytical procedures used for testing the finished product should be provided.

Reference ICH Guidelines : NCE : Q2 ; Biotech : Q6B

P 5.3 Validation of Analytical Procedures
Analytical validation information, including experimental data for the validation of the analytical procedures use for the testing the finished product should be provided.

For compendial methods, verification should be provided.

Reference ICH Guidelines : NCE : Q2; Biotech : Q6B

Generics:

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 : Q3A, Q3C, aQ6A Q6B

Biologics

Summary protocol of batch production and control of three consecutive lots of finished product. This protocol should follow the available format recommended by the WHO in the specific requirements for the production and control of the specific biologics submitted for market authorization.

Generics:

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 S.3.2 Impurities.

Compendial requirements or appropriate information from the manufacturer.

Reference ICH Guidelines :Q3B, Q6A; and Q6B

Generics:

Compendial requirements or appropriate information from the manufacturer.

P 5.6 Justification of Specification
Justification for the proposed finished product should be provided.

Compendial requirements or equivalent information from the manufacturer.

Reference ICH Guidelines : Q3B Q6Aand Q6B

Generics:
Compendial requirements or equivalent information from the manufacturer.

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.

Compendial requirement or equivalent information from the manufacturer.

Compendial reference standard should be used if applicable.

Reference : NCE : Q6A, Biotech : Q6B

Generics:
Compendial requirements or equivalent information from the manufacturer.

P 7 Container closure system

A description of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component, and each specification. 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.

P.8.1. Stability Summary and Conclusion

NCE and Biologics:

Stability summary demonstrating that product is stable through its proposed shelf life.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2 and Q5C

Generics:
ASEAN Guideline on Stability Study of Drug Product

P.8.2. Post-approval stability protocol and stability commitment

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

Commitment on post approval stability monitoring include the stability program or stability commitment to be carried out once the product is in the market, including the number of lots to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the product evaluated, if required.

References ICH Guidelines : Q1A (R2) Q5C

Generics:

ASEAN Guideline on Stability Study of Drug Product

P.8.3 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, WHO Guideline on stability evaluation of Vaccines

P.8.4 Description of procedures to guarantee cold chain (where applicable)

Describe in detail the measures used to guarantee adequate temperature and humidity conditions for shipping the finished product from the place of production to the place of final sale, including all the storage and distribution stages and indicating the controls performed in each of the stages. This description should be signed by the professional responsible for it.

P 9 Product Interchangeability
This requirement applies to Generics.

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 Guideline on Bioequivalence Study.

Section D: Key Literature References
Key literature references should be provided, if applicable.

A. ANNEX

A.1 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

Reference ICH Guidelines: Q5A, Q5D, and Q6B

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in S.2.3, and P.4.3). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in S.2.3).

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in S.2.4 and P.3.4).

Viral Testing of Unprocessed Bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in S.2.5 and P.3.5).

Reference ICH Guidelines: Q5A, Q5D, and Q6B