

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

PART II: QUALITY

TABLE OF CONTENTS

Scope of the Guideline	2
Section A: Table of Contents	2
Section B: Quality Overall Summary	2
Section C: Body of Data	9
1. Drug Substance	9
2. Drug Product	14
Section D: Key Literature References	20

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 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	BIOTECH	MaV	MiV	G
S S1	DRUG SUBSTANCE						
	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. – Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass as appropriate.	V	V			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			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
	2.3. Control of Materials	<ul style="list-style-type: none"> - 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. - 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, characterisation and testing. - Viral safety evaluation. 		V			
	2.4. Controls of Critical Steps and Intermediates	<ul style="list-style-type: none"> - 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. - Stability data supporting storage conditions. 	V	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	<ul style="list-style-type: none"> - 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 S 2.2. 	V				
				V			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
S3	Characterisation						
	3.1. Elucidation of Structure and other characteristics	<ul style="list-style-type: none"> - Confirmation of structure based on e.g. synthetic route and spectral analyses. Compendial requirements 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). 	V				V
	3.2. Impurities	<ul style="list-style-type: none"> - Summary of impurities monitored or tested for during and after manufacture of drug substance Compendial requirements or appropriate information from the manufacturer 	V	V			V
S4	Control of Drug Substance						
	4.1. Specification	<ul style="list-style-type: none"> - Detailed specification, tests and acceptance criteria. - Compendial specification or appropriate information from the manufacturer - Specify source, including as appropriate species of animal, type of microorganism etc. 	V	V			V
	4.2. Analytical Procedures	<ul style="list-style-type: none"> - The analytical procedures used for testing of drug substance. Compendial methods or appropriate information from the manufacturer 	V	V			V
	4.3. Validation of Analytical Procedures	<ul style="list-style-type: none"> - Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance Non-compendial methods 	V	V			V
	4.4. Batch Analyses	<ul style="list-style-type: none"> - Description of batches and results of the analysis to establish the specification. 	V	V			
	4.5. Justification of Specification	<ul style="list-style-type: none"> - Justification for drug substance specification. 	V	V			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
S5	Reference Standards or Materials	<ul style="list-style-type: none"> - Information on the reference standards or reference materials used for testing of the drug substance . - Compendial reference standard. 	V	V			V
S6	Container Closure System	<ul style="list-style-type: none"> - Descriptions of the container closure systems. 	V	V			
S7	Stability	<ul style="list-style-type: none"> - Stability report. - Literature data . 	V	V		V*	V
P	DRUG PRODUCT						
P1	Description and Composition	<ul style="list-style-type: none"> - Description - 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. <p>Composition Name, quantity stated in metric weight or measures, function and quality standard reference.</p>	V	V	V*	V*	V
P2	Pharmaceutical Development						
	2.1. Information on Development Studies	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Active ingredient <ul style="list-style-type: none"> • 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. - Literature data. 	V	V			V
					V*		V

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
P3	2.3. Finished Product	– Excipients Justification of the choice of excipients listed in P1, which may influence the drug product performance.	V	V			
		– 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).	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*		V
	2.7. Compatibility	Compatibility of the finished product with reconstitution diluent(s) or dosage devices.	V	V	V*		
		Literature data					V
Manufacture							
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	

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
P4	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
	4.1. Specifications	– Specifications for excipients Compendial requirements or appropriate information from the manufacturer	V	V	V*		V
	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			
P5	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	V	V			
		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				

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
	5.5. Characterisation of Impurities	<ul style="list-style-type: none"> – Information on the characterisation of impurities Compendial requirements or appropriate information from the manufacturer 	V	V	V*		V
	5.6. Justification of Specification(s)	<ul style="list-style-type: none"> – Justification of the proposed finished product specification(s). Compendial requirements or appropriate information from the manufacturer 	V	V	V*		V
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 – In Vivo Bioequivalence study as required 			V*		V
					V*		V

remarks : * if required

NCE : New Chemical Entity

Biotech : Biotechnological Products

MaV : Major Variation

MiV : Minor Variation

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, 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

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 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 30⁰C, 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 Guideline on *Bioequivalence Study*

Section D: Key Literature References

Key literature references should be provided, if applicable.