GUIDELINE ON
FACILITATED REGISTRATION PATHWAY: ABBREVIATED AND VERIFICATION REVIEW

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1.0 INTRODUCTION

1.1 OBJECTIVES

The growing awareness of the need for regulators to work together has led to the emergence of new models of cooperation. World Health Organization (WHO) therefore, proposes a scheme for National Regulatory Authorities (NRAs) in which registration and approval of medicines already approved by reference/trusted drug regulatory agencies is facilitated.

This guidance document describes the procedures and requirements for submitting application to register a product via abbreviated or verification review.

1.2 SCOPE

Abbreviated Review applies to a product that has been evaluated and approved by one (1) reference drug regulatory agency

Verification Review applies to a product that has been evaluated and approved by two (2) reference drug regulatory agencies

The scope for product registration according to abbreviated and verification review only applies to new drug products and biologics including biosimilars.

Reference drug regulatory agencies for abbreviated and verification reviews are as follows:
a) European Medicines Agency (EMA)
b) United States Food and Drug Administration (US FDA)

Additionally, WHO Prequalified Medicinal Products (specifically new drug products and biologics including biosimilars) covered by the alternative listing procedure (evaluated by US FDA and EMA) may be accepted under this pathway.

Approval by these reference drug regulatory agencies does not oblige the Drug Control Authority (DCA) to approve the application.

For Verification Review, one of the reference drug regulatory agencies must be declared as the primary reference agency. The chosen primary reference agency is defined as the reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted.

2.0 ELIGIBILITY CRITERIA

a) The application must be submitted to National Pharmaceutical Regulatory Division (NPRA- which acts as the secretariat to the DCA) within two (2) years from the date of approval by the chosen primary reference drug regulatory agency.

b) Manufacturing facilities have been inspected by any Pharmaceutical Inspection Co-operation Scheme (PIC/S) member with valid certification.

c) All aspects of the drug product's quality, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications and primary packaging, are identical to that currently approved by the chosen reference drug regulatory agency at the time of submission. However, a different type of the container closure system (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements. Any difference in manufacturing site of the drug product will be considered if it is clearly justified.

d) If a Drug Master File (DMF) is submitted, then a separate declaration letter issued by the Product Registration Holder (PRH) must also be provided to state that the DMF submitted to NPRA is identical to that submitted to the chosen reference drug regulatory agency.

e) Product requiring a more stringent assessment as a result of differences in local disease patterns and/or medical practices (e.g. some anti-infectives) does not qualify for the facilitated registration pathway.

f) The product and its intended use (indications, dosage information, and patient groups) have not been rejected, withdrawn, suspended, approved via appeal process, or pending deferral by any reference drug regulatory agency for quality, safety and/or efficacy reasons.

g) The proposed Package Insert (PI)/ Patient Information Leaflet (PIL) information should be identical to that approved by the reference drug regulatory agency (with the exception of country-specific information).

h) The proposed indication(s), dosing regimen(s), patient group(s) and/or direction(s) for use should be the most stringent among those approved by the reference drug regulatory agencies. In the event that the chosen drug regulatory agency does not bear the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use among those approved by the reference drug regulatory agencies, a supplemental clinical assessment report from the reference drug regulatory agency that approved the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use is required. Reports from the public domain are acceptable. Specifically for vaccines, differences in dosage regimen are allowed when the regimen is changed to meet the local practices, such as the National Immunisation Programmes.

i) For a product with a proposed indication that has been designated as an orphan drug by one reference drug regulatory agency or a product that has been approved by one reference drug regulatory agency via an accelerated/fast-track approval, approval under exceptional circumstances or equivalent approval process is not eligible, if documentation is deemed insufficient to support for abbreviated and verification review.

3.0 DOCUMENTS REQUIRED (FOR BOTH ABBREVIATED AND VERIFICATION REVIEWS)

The PRH is required to notify NPRA by submitting a formal, written request for facilitated registration pathway and attach the letter of intent under section E14 (Other Supporting Documents) of the QUEST online system. Applicants are encouraged to contact NPRA prior to the submission of an application if questions arise or clarification is required.

3.1 General technical requirements (*to be submitted under the relevant field/section of the QUEST online system):*

a) Complete Common Technical Document (CTD) data requirements as submitted in QUEST online system. Protocol of analysis (POA) and analytical method validation (AMV) to be submitted in accordance to Centre of Quality Control (CQC) specific checklist (refer Appendix).

b) Complete assessment report including assessment on the Question & Answer (Q&A) documents between the PRH and reference drug regulatory agency and all annexes (*in English - to be submitted under section E14 of the QUEST online system)*:
- Assessment reports and/or documents pertaining to post-approval variations, if applicable.
- The submitted assessment reports must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, chemistry and clinical review, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable. However, NPRA may consider accepting public assessment reports accompanied by redacted information and Q&A provided that the applicant has shown proof and effort to obtain the unredacted assessment reports.
- For verification review, the complete assessment report and other relevant supporting documents must be submitted from the primary reference agency only.

c) Stability study should comply with the ASEAN stability guideline. A minimum of 6 months real time and accelerated stability data respectively may be accepted at the point of submission. However, upon registration a minimum of 12 months for real time stability data should be provided.

3.2 Additional administrative documents required (*to be submitted under section E14 of the QUEST online system):*

a) Proof of approval from the chosen reference drug regulatory agency is required. Proof of approval must come in the form of:
- an official approval letter, or equivalent document (e.g. Certificate of Pharmaceutical Product; CPP), which certifies the registration status of the drug product
- the Summary of Product Characteristics (SPC), PI and/or PIL approved by the reference drug regulatory agency that issued the approval letter.

b) A declaration letter issued by the product owner/PRH stating that:-
- all aspects of the drug substance's and drug product's quality and intended direction(s) for use, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications, primary packaging and active pharmaceutical ingredient(s) source are identical to that currently approved by the chosen reference drug regulatory agency at the time of submission

(including to the specification reference number, version and effective date). However, a different type of the container closure system (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements; any difference in manufacturing site of drug product will be considered if it is clearly justified.

- the product and its intended use (indications, dosage information, and patient groups) have not been rejected, withdrawn, suspended, approved via appeal process, or pending deferral by any reference drug regulatory agency for quality, safety and/or efficacy reasons.
- the DMF provided is the same as that submitted to the primary reference drug regulatory agency.
- if there is any commitment to reference drug regulatory agency.

NOTE

i. NPRA reserves the right to request additional supporting documents where it is deemed appropriate.
ii. Products assessed under this facilitated pathway will not be eligible for priority review.
iii. During the evaluation process, NPRA may change the evaluation timeline to the standard timeline in the event where there are inconsistencies on the data.

4.0 TIMELINE FOR REGISTRATION PROCESS

Types of Review	Timeline (working days)	
	New Drug Products	Biologics
Abbreviated Review	120	120
Verification Review	90	90

The applicant is allowed to correspond with a maximum of 3 times correspondence within 60 working days in total. NPRA will change the evaluation timeline to the standard timeline if applicant failed to correspond within the stipulated timeline.

5.0 DRUG CONTROL AUTHORITY RIGHTS

Notwithstanding the requirements stipulated in this guideline, DCA reserves the rights to use its own discretion whichever it deems fit.

6.0 GLOSSARY

Abbreviated Review - Applies to a product that has been evaluated and approved by one (1) reference drug regulatory agency. Limited independent assessment of specific parts of the dossier or submission for suitability of use under local conditions and regulatory requirements while relying on prior assessment and inspection outcomes from the reference drug regulatory agencies to inform the local decision. The review is based on the complete assessment report including assessment on the Question & Answer (Q&A) documents, complete common technical document (CTD) including the stability data.

Verification Review - Applies to a product that has been evaluated and approved by two (2) reference drug regulatory agencies. NPRA only validates the product or submission and ensures the product for local marketing conforms to the registration conditions as approved by

the reference drug regulatory agencies. Verification may be on the basis of the complete assessment report including assessment on the Question & Answer (Q&A) documents, complete common technical document (CTD) including the stability data.

Primary reference drug regulatory agency - For Verification Review, one of the reference drug regulatory agencies must be declared as the primary reference agency. The chosen primary reference agency is defined as the reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted.

7.0 REFERENCES

Adapted from the:

1. WHO Good Regulatory Practices, 2016
2. HSA Therapeutic Products Guidance, 2019

8.0 APPENDIX

Checklist for Protocol of Analysis and Analytical Method Validation: Facilitated Registration Pathway

These checklists are intended to provide guidance on the submission of documents/ information related to protocol of analysis (POA) and analytical method validation (AMV)/ verification for facilitated registration pathway. NPRA reserves the right to request additional data whichever it deems necessary. All submitted documents must be uploaded accordingly in QUEST online system.

Checklist consists of:

Table 1:	Information required for protocol of analysis.
Table 2:	Validation parameters and documents required for validation of identification/ characterisation test, assay/potency/content test, related substances test and dissolution test.
Table 3:	Documents required for validation of microbial contamination test (MCT)
Table 4:	Documents required for validation of sterility test (ST)
Table 5:	Documents required for validation of bacterial endotoxin test (BET)

Justification or explanation must be provided if any information listed in tables below is not available.

Table 1: Information required for protocol of analysis

TEST	INFORMATION REQUIRED	
General Requirement	**i. Complete test method shall be provided** **ii. Statement 'as per pharmacopoeia' shall not be acceptable** **iii. Justification shall be provided if test listed in BP/USP is not conducted.**	
Physical Tests • Appearance • Colour, Clarity and Opalescence • Visible particles • Subvisible particles • pH • Osmolarity • Moisture content • Extractable volume • Dissolution time • Homogeneity test • Others	**Details of test methods shall include the following items:**	
	1	List of equipment and apparatus (if applicable)
	2	List of chemical, reagents and media (if applicable)
	3	Preparation of solutions such as sample, reference standard (if applicable), medium, buffer, etc
	4	Volume and temperature of sample solution (if applicable)
	5	Setting up of analytical instrumentation (if applicable)
	6	Testing condition/ parameter (if applicable)
	7	Testing procedure
	8	System suitability tests (if applicable)
Identification / Characterisation Tests • Peptide Mapping • Identification of preservative and active substance • Precipitate reaction • Microscopic examination • Colony morphology • Virus identification • Others	**Details of test methods shall include the following items:**	
	1	List of equipment and apparatus
	2	List of chemical, reagents and media
	3	Preparation of solutions such as sample, standard, system suitability solution, mobile phase, medium, buffer, etc (the amount of chemical/sample/ standard and volume of diluents used in the preparation must be stated)
	4	Instrumentation and testing conditions / parameters
	5	Testing procedure
	6	System suitability tests and acceptance criteria of system suitability test.
	7	Complete formula for calculation (if applicable) and interpretation of results
	8	Image of SDS PAGE/ IEF/ electropherogram/ TLC/ UV spectrum/ IR spectrum/HPLC chromatogram etc for blank, sample, standard and system suitability solution
Assay/ Potency/ Content/ Dissolution test	**Details of test methods shall include the following items:**	
• Protein concentration • Content of active ingredient and preservative • Bioassay/ Potency (animal- based, cell culture- based and biochemical- based) • Dissolution test	1	List of equipment and apparatus
	2	List of chemical, reagents and media
	3	Preparation of solutions such as sample, standard, system suitability solution, mobile phase, medium, buffer, etc (the amount of chemical/sample/ standard and volume of diluents used in the preparation must be stated). Stability and storage condition of sample and standard solutions
	4	Instrumentation and testing conditions / parameters
	5	Testing procedure
	6	System suitability tests and acceptance criteria of system suitability test.
	7	Data analysis, complete formula for calculation (the formula must provide

• Uniformity of Content • Others		in the unit stated in COA) and interpretation of results
	8	HPLC chromatogram/ UV spectrum (if applicable) for blank, sample, standard and system suitability solution
Purity/ Impurities Tests	**Details of test methods shall include the following items:**	
• Known impurities • Unknown Impurities • High Molecular Weight Protein • Monomer • Dimer • Aggregates • Residual solvent	1	List of equipment and apparatus
	2	List of chemical, reagents and media
	3	Preparation of solutions such as sample, standard, system suitability solution, mobile phase, medium, buffer, etc (the amount of chemical/sample/ standard and volume of diluents used in the preparation must be stated) Stability and storage condition of sample and standard solutions
	4	Instrumentation and testing conditions / parameters
	5	Testing procedure
	6	System suitability tests and acceptance criteria of system suitability test.
	7	Data analysis, complete formula for calculation (the formula must provide in the unit stated in COA) and interpretation of results
	8	Image of SDS PAGE/ IEF/ electropherogram/ TLC/ HPLC chromatogram etc for blank, sample, standard and system suitability solution.
Other Safety Test	**Details of test methods shall include the following items:**	
• Pyrogen Test • Bacterial Endotoxins Test • Sterility Test • Microbial Contamination Test	1	Refer to DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) under GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA) Note: Procedure on preparation of media, growth promoting test, inhibitory and indicative properties of media is not required.
Others	**Details of test methods shall include the following items:**	
• Test for absence of virulent mycobacteria • Test for excessive dermal reactivity • Specific toxicity test • Abnormal toxicity test (innocuity) • Others	1	List of equipment and apparatus
	2	List of chemical, reagents and media
	3	Preparation of solutions such as sample, standard, medium, buffer, etc
	4	Testing condition /animal criteria
	5	Testing procedure
	6	Calculation of the result (if applicable) or calculation method used
	7	animal test: - specific requirement for the animal used such as weight, age, sex (if applicable) etc - dose used and injection technique

Table 2: Validation parameters and documents required for validation of identification/ characterisation test, assay/potency/content/dissolution test and related substances test.

PARAMETER	NO.	DOCUMENTS REQUIRED	TESTS		
			IDENTIFICATION / CHARACTERISA-TION	ASSAY / POTENCY / CONTENT / DISSOLUTION	RELATED SUBSTANCES
General	1	Validation method / protocol	√	√	√
	2	Acceptance criteria	√	√	√
Specificity*#	1	Data to prove the method is specific Eg. Chromatograms/ Images/ Electropherograms/ spectrums / data on retention time, peak area, absorbance, etc.	√	√	√
Linearity	1	Minimum five (5) levels of standard solutions		√	√
	2	Data such as: a) linear regression equation b) r^2/ r c) linearity graph		√	√
Range	1	80% - 120% (Assay and Potency Test), 70% - 130% (Uniformity of Content Test), LOQ – 120% of specification (Related Substance), ±20% over the specified range (Dissolution Test)		√	√
Accuracy	1	Minimum three (3) levels of concentration in triplicates covering the specified range		√	√
	2	Tabulated data on theoretical and observed value, % recovery/ difference between mean and accepted true value and confidence interval		√	√
Precision (Repeatability)	1	Minimum three (3) levels of concentration in triplicates covering the specified range, OR minimum six (6) replicates at 100% of working concentration		√	√
	2	Tabulated result in unit as per stated in COA eg: mg/ml or IU/ml or percentage or others, standard deviation, relative standard deviation (coefficient of variant) and confidence interval		√	√
Precision# (intermediate precision/ ruggedness)	1	Minimum three (3) levels of concentration in triplicates covering the specified range, OR minimum six (6) replicates at 100% of the working concentration		√	√

	2	Cover at least 2 parameters among variation of analyst, date and equipment		√	√
	3	Tabulated result in unit as per stated in COA eg: mg/ml or IU/ml or percentage or others, standard deviation, relative standard deviation (coefficient of variant) and confidence interval		√	√
Quantitation Limit / Detection Limit*[#]	1	Testing Method : visual observation / signal-to-noise / standard deviation of the response and the slope			√
	2	Data to demonstrate the determination of LOQ/LOD.			√
System Suitability Testing	1	Data to prove the system suitability tests are fulfilled Eg. Chromatograms / data on RSD of retention time, RSD of peak area, tailing factor, theoretical plate etc.	√[@]	√[@]	√[@]

* For qualitative related substances/ limit test, only parameters specificity, detection limit is required.

[#] Parameters required for verification of **COMPENDIAL METHOD (if applicable)** and **SECOND SOURCE***.

[@] System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated.

Table 3: Document required for validation of microbial contamination test (MCT)

VALIDATION TEST	No.	DOCUMENTS REQUIRED
Total Viable Aerobic Count (Total Aerobic Microbial Count (TAMC) & Total Yeasts and Moulds Count (TYMC)) (aka Suitability of Counting Method)	1	Procedure for validation of TAMC and TYMC
	2	Preparation of test sample (including neutralizing of preservatives for samples that contain preservatives)
	3	Acceptance criteria: Mean count of any test organisms must not differ by a factor greater than 2 (50% – 200%)
	4	Tabulated data of test results
Test for Specified Microorganism (aka Suitability of the test)	1	Procedure for validation of Test for Specified Microorganism
	2	Tabulated data of results on spiked microorganisms

The requirements are based on the ICH guidelines (ICH Q2 (R1))

Table 4: Document required for validation of sterility test (ST)

VALIDATION TEST	No.	DOCUMENTS REQUIRED
Bacteriostasis & Fungistasis Test	1	Complete procedure for validation of sterility test consist information below shall be provided: a) Quantity and volume of sample b) Method used (Membrane filtration/Direct Inoculation) c) Open System or Closed System (if membrane filtration method is used) d) Type and volume of rinsing fluid used for each membrane (membrane filtration) e) List of media and reagents f) List of neutralizing agent (if any) g) Microorganisms used and size of inoculum
	2	Tabulated data of validation test results

The requirements are based on pharmacopoeia (BP and USP)

Table 5: Documents required for validation of bacterial endotoxin test (BET)

VALIDATION TEST	No.	DOCUMENTS REQUIRED
Confirmation of Labeled Lysate Sensitivity (Gel Clot) / Standard Curve (Photometric Method)	1	Complete procedure consist of information below shall be provided: **Gel Clot Method**: i. At least 4 concentration of standard endotoxin (2 λ, λ, 0.5 λ, 0.25 λ) ii. 4 replicates iii. Geometric Mean of End Point= 0.5 λ - 2 λ **Photometric Method**: For the generation of standard curve applicant must provide the following information: i. 3 endotoxin concentration to generate standard curve ii. 3 replicates for each concentration iii. correlation coefficient (r) must be ≥ 0.98 (linear graph must be demonstrated)
	2	Data below shall be provided ✓ **Gel Clot:** Geometric Mean of End Point= 0.5 λ - 2 λ (tabulated data is acceptable) ✓ **Photometric:** Standard Curve which fulfil the criteria in the method.
Test for Interfering Factor (Gel Clot/ Photometric Method)	1	**Gel Clot Method** must consist of the following information: - i. Complete procedure for Test for Interfering Factor ii. A: sample only - 4 replicates iii. B: sample + endotoxin (2λ or 4 different λ concentration) - 4 replicates iv. C: LAL water + endotoxin (4 different λ concentration) - 2 replicates v. D: LAL water only - 2 replicates **Photometric Method:** PPC Recovery must be between 50% - 200%
	2	Tabulated data of validation test results
MVD Calculation & ELC Calculation (if applicable) (Gel Clot/Photometric Method)	1	Formula calculation of MVD or ELC (if applicable)
	2	Product specific calculation of MVD or ELC (if applicable)

The requirements are based on pharmacopoeia (BP and USP)