APPENDIX 3

GUIDELINE ON REGISTRATION OF NEW DRUG PRODUCTS

IMPORTANT NOTES:

This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD)**, which is in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984**.

1. DEFINITION

New Drug Products (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the CDCR 1984.

An NDP may be classified according to the following categories:

1.1 New Chemical Entity (NCE) (single/ combination products with an active substance never registered by DCA)

Defined as an **active moiety**/ radiopharmaceutical substance that has not been registered in any pharmaceutical product.

An **active moiety** is defined as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

A radiopharmaceutical substance is defined as a radionucleotide, ligand or the coupling mechanism to link the molecule and the radionucleotide that has not been registered in any pharmaceutical product.

1.2 Hybrid (single/ combination products with registered active moieties)

All other products registrable at New Drug Section which do not fall under **(1.1)**.

Examples of Hybrid (single/ combination) products:

i. Registered chemical entity(s) in a new chemical form(s)
ii. Registered chemical entity(s) in a new dosage form(s)
iii. Registered chemical entity(s) in a new dosage strength(s) with a change in dosing/ posology
iv. Registered chemical entity(s) for use by a new route of administration
v. Registered chemical entity(s) for new indication(s), dosage recommendation(s) and/ or patient population(s)
vi. Combination of registered chemical entity(s) in new chemical form(s) and registered chemical entity(s)
vii. A product for which its innovator has never been registered by DCA
viii. Second source product
ix. Replacement product

For medicinal gases classified as new drug products, please refer to Directive No. 8, 2021 and Guideline on Registration of Medicinal Gases.

Reference:

- Directive No. 8, 2021, NPRA.600-1/9/13 (18): *Direktif Berkenaan Pengukuhan Pelaksanaan Kawalan Regulatori Ke Atas Produk-Produk Gas Perubatan dan Penggunaan Guideline on Registration of Medicinal Gases* (11 February 2021)

2. REGISTRATION REQUIREMENT AND EVALUATION TIMELINE

2.1 Requirements for Registration of NDP

Table 1: Registration Requirement and Evaluation Timeline for NDP

ITEMS	REGISTRATION REQUIREMENTS	
	HYBRID	**NCE**
ACTD Module: **1) Part I** **2) Part II (S)[1]** **3) Part II (P)** **4) Part III** **5) Part IV**	 Yes Yes Yes No[2] BA/BE/pivotal study report(s), clinical overview and RMP	 Yes Yes Yes Yes[3] Full, including RMP
	HYBRID	**NCE**
Consultation with local clinical specialists[4]	No[5]	Yes
Evaluation timeline	210 working days	245 working days

[1] Please refer to "GUIDANCE NOTES: ACTIVE PHARMACEUTICAL INGREDIENT (API) INFORMATION (PART II S) FOR QUEST3+ PRODUCT REGISTRATION APPLICATION", which outlines the requirements when preparing submission of a new product application using the same source of an approved API of a registered product; API evaluation is manufacturer and PRH specific.

[2] Non-clinical overview only, if applicable.

[3] Good Laboratory Practice (GLP) Compliance Form is to be submitted at E14 during initial evaluation (screening process).

[4] Selected clinical publications/ study synopsis are sent to local clinical specialists to gather comments on product efficacy and safety.

[5] Consultation with local clinical specialists is required for a product for which its innovator has never been registered by DCA and other hybrid application, when deemed necessary.

NOTE:

For a product in which the reference innovator product has never been registered in Malaysia, **specific requirements for Parts III and IV**:

i. Nonclinical Overview, Nonclinical Summary & List of Key Literature References, by referring to studies by the innovator product
ii. Clinical Overview, Clinical Summary & List of Key Literature References, by referring to studies by the innovator product
iii. Bioequivalence study report(s)
iv. Other pivotal study reports, if applicable
v. Risk Management Plan (RMP)
vi. Consultation with local clinical specialists

2.2 Stability Data Requirements

2.2.1 Stability Data of Drug Substance

The submitted stability data should be from batches manufactured at the drug substance manufacturing site proposed for registration in Malaysia. At the time of submission of the new product application, the stability data requirements are as follows:

Study condition	Minimum time period covered by data during submission	Number of batches required
Long term	12 months	A minimum of 3 primary batches of the drug substance. The batches should be at least pilot scale, manufactured by the same manufacturing process and packaged in the same container closure system as that proposed for registration.
Accelerated	6 months	

Primary batch *refers to a batch used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life, respectively. A primary batch of a drug substance should be at least a pilot scale batch - ICH Q1A(R2)*

Where multiple drug substance manufacturers are proposed for registration, drug substance stability data of at least 6 months for 3 batches from each of the other sites are required, unless otherwise justified. Full real time data covering the proposed drug substance retest period from one of the drug substance manufacturing site intended to be registered in Malaysia should be available. Where full real time data is not available from each drug substance manufacturing site to support the proposed drug substance retest period, it may be acceptable to extrapolate the stability data from other sites if comparability can be demonstrated.

Drug substance is considered representative when the following criteria are fulfilled:

- The quality to the drug substance used in the stability batches are comparable (e.g., physical characteristics/attributes, established process validation)
- Manufactured using the same synthetic route and process. Scientific justification should be provided to demonstrate equivalence between the sites if differences exist
- Controlled by the same set of specifications
- Packaged in the same type of container closure system

If any of the above criteria are not met, complete site-specific stability data are required to support the application.

2.2.2. Stability Data of Drug Product

The submitted stability data should be from batches manufactured at the drug product manufacturing site proposed for registration in Malaysia. At the time of submission of the new product application, the stability data requirements are as follows:

Study storage	Minimum time period covered by data at submission	Number of batches
Long term	12 months	A minimum of 3 primary batches of the drug product. The batches should be at least pilot scale, manufactured by the same manufacturing process and packaged in the same container closure system as that proposed for registration.
Accelerated	6 months	

Primary batch *refers to a batch used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a shelf-life. A primary batch of a for a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch. - ICH Q1A(R2)*

Drug product stability in the case of multiple drug substance manufacturers.

Where possible, batches of the drug product should be manufactured using different batches of drug substance including different drug substance manufacturers intended to be registered. If multiple drug substance manufacturers are proposed for the drug product, a commitment to conduct drug product stability studies for 1 production batch using the drug substance from each drug substance manufacturer that is not represented in the drug product stability batches is required.

Multiple primary packaging sites

If more than one primary packaging (PP) site is proposed for registration, stability data from three drug product (DP) batches using PP from at least one of these sites must be provided.

For additional PP sites (using the same manufacturing process and container closure system), a commitment is required to conduct stability studies on two (conventional dosage form) or three (critical dosage form) DP batches.

NON-SITE SPECIFIC STABILITY DATA FOR DRUG PRODUCT

In the case of technology transfer where site-specific stability data for drug product is not available from the manufacturing site proposed for registration, it may be acceptable to extrapolate the stability data from another site to the site proposed for registration if it can be demonstrated that the submitted data is representative of the proposed drug product manufacturing site (the data must be from primary batches manufactured using drug substance intended to be registered in Malaysia).

Drug product is considered representative when the following criteria are fulfilled:

- The quality of the drug product used in the stability batches is comparable (e.g., dissolution profile and established process validation)
- Manufactured using the same formulation
- Manufactured using the same manufacturing process, including equipment type, process parameters and in-process tests. Scientific justification should be provided to demonstrate equivalence between the sites if differences exist.
- Controlled by the same set of specifications
- Packaged in the same type of container closure system

In addition, a commitment to conduct stability studies for drug product for at least one production batch of drug substance is required for each site that is not represented in the submitted stability studies.

If any of the above criteria are not met, site-specific stability data are required to support the application.