APPENDIX 13

DESIGNATION AND REGISTRATION OF ORPHAN MEDICINES

Note: This part shall be read in conjunction with other parts of the DRGD that apply to orphan medicines (where applicable), e.g. re-registration procedure, withdrawal of registration, labeling requirements, post-market surveillance, etc.

Please also refer to **Malaysian Orphan Medicines Guideline**, FAQ and documents related to orphan medicines available at **www.pharmacy.gov.my**

As defined in the **Malaysian Orphan Medicines Guideline**, an orphan medicine is a medicinal product that is primarily intended to treat, prevent or diagnose a rare disease. Rare disease refers to a life-threatening and/ or chronically debilitating rare condition as listed in the Malaysian Rare Disease List.

1. DESIGNATION OF ORPHAN MEDICINE

The designation of orphan medicine is under the purview of *Bahagian Regulatori Farmasi Negara* (NPRA) through input from the Drug Evaluation Committee (DEC).

2. ELIGIBILITY CRITERIA FOR DESIGNATION OF ORPHAN MEDICINE

The designation of orphan medicine is subject to the following criteria:

a) "A medicine, vaccine or in vivo diagnostic agent that is primarily intended to treat, prevent or diagnose a rare disease"[1]; and

b) No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized; or, if such a method exists, the medicinal product must be of significant benefit[2] to those affected by the condition.

[1] Rare disease refers to the diseases listed in the latest Malaysian Rare Disease List.
[2] As defined by European Medicines Agency (EMA), significant benefit means that a medicine produces a clinically relevant advantage or makes a major contribution to patients' care, compared with existing methods to treat the condition. Thus, orphan designation is given to a product that will improve patients' current treatment, having considered what else is available.

3. APPLICATION FOR THE DESIGNATION OF ORPHAN MEDICINE

a) The applicant may submit an application for such designation to the NPRA using the *Orphan Medicine Designation Application Form*.

b) The application can be submitted before a product is registered as a New Chemical Entity or a Biologic product.

c) The information required for an application for orphan medicine designation may include but are not limited to the following:

Product Information

i) Product name
ii) Active ingredient
iii) Strength
iv) ATC Code
v) Pharmaceutical form
vi) Route of administration
vii) Manufacturer name and address
viii) Worldwide regulatory status
ix) Worldwide orphan medicine designation status

Proposed Rare Disease and Condition

i) Proposed indication related to the rare disease
ii) Brief description of the rare disease
iii) Current available method in treating/preventing/diagnosing the rare disease
iv) Justification for this product to be designated as orphan medicine
v) Brief description of the product (details on active ingredient(s), drug type/ class, structure, physical-chemical properties)
vi) Mechanism of action explaining how the product works in relevant disease/ condition

Scientific rationale for the orphan medicine use (The scientific rationale should support a medical plausible basis for the orphan medicine to be effective in treating disease/ condition

i) Please briefly describe the scientific evidence to support safety and efficacy of this product to treat/ prevent/ diagnose the proposed indication related to the rare disease
ii) Tabulated pre-clinical data and clinical data
iii) A brief safety update report

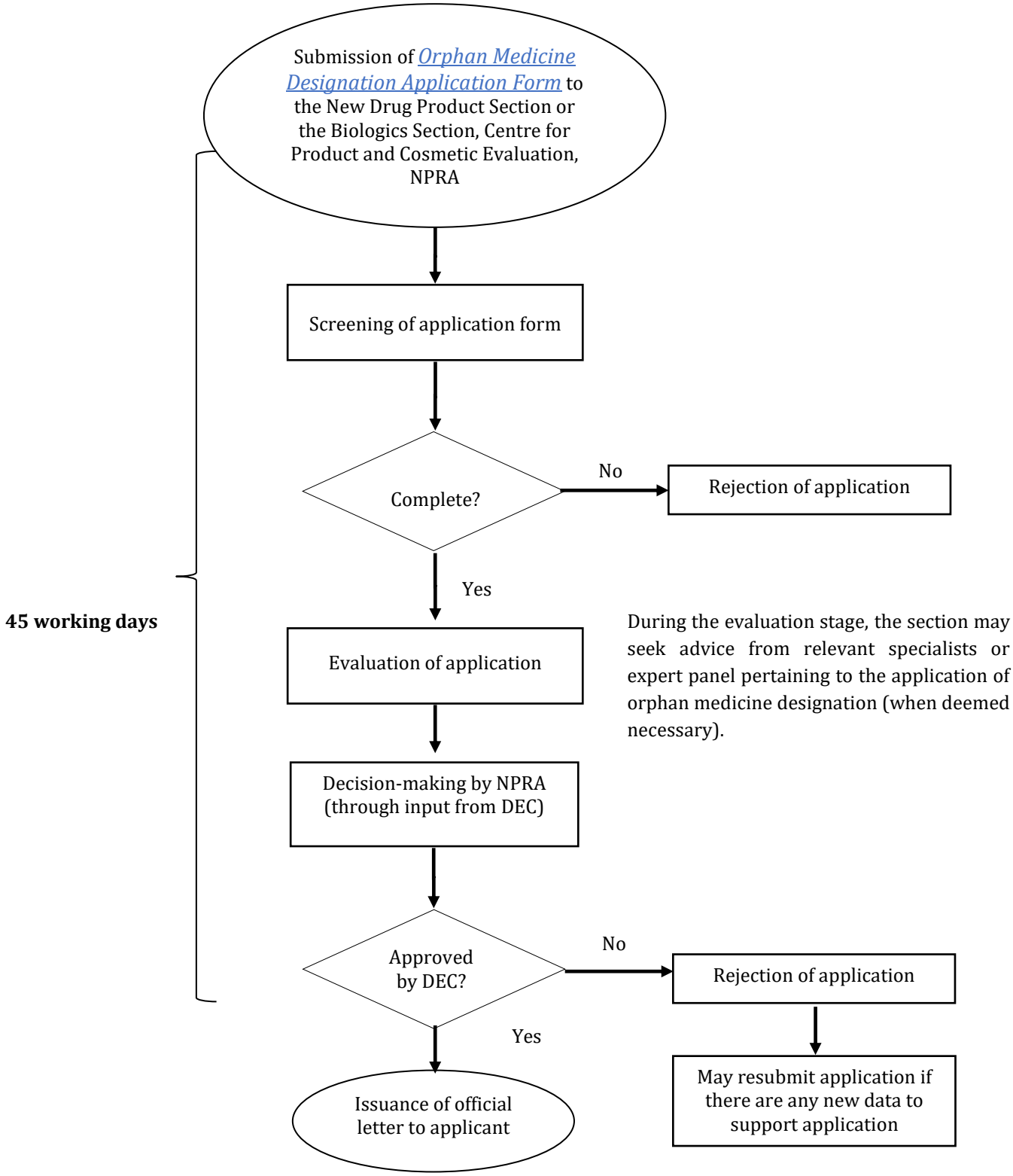
d) A medicinal product that has already been granted an orphan medicine designation in other countries is not automatically designated as an orphan medicine in Malaysia. It is still subject to the decision of NPRA (through input from the DEC).

e) The same medicinal product may also have multiple orphan medicine designations for different rare diseases.

f) NPRA may seek advice/ opinion from relevant experts or representatives from the rare disease society/ patient groups or other key opinion leaders pertaining to the application of orphan medicine designation when deemed necessary.

3.1 APPLICATION WORKFLOW AND PROCEDURE

a) Workflow of ORPHAN MEDICINE DESIGNATION



b) Procedure for ORPHAN MEDICINE DESIGNATION Application

1. **Submission of Orphan Medicine Designation Application Form (refer to 6.) to the New Drug Product Section or the Biologics Section, Centre for Product and Cosmetic Evaluation, NPRA**
   - The applicant can also download the Orphan Medicine Designation Application Form from the **NPRA official website**.
   - The applicant shall submit the completed application form to the relevant section, depending on the product category.
   - The applicant shall submit a separate application form for designation of same orphan medicine to treat a different rare disease (as same medicinal product may be used to treat different rare disease)

2. **Screening of application form**
   - The relevant section shall screen the submitted form (i.e., without the dossier).
   - If the form is found incomplete, the application shall be rejected.
   - A complete application shall be further evaluated.

3. **Evaluation of application**
   - The section may seek advice from relevant specialists or expert panel when deemed necessary. A timeframe of two weeks is allocated for the reply.
   - The section shall prepare an evaluation report to be tabled in the DEC meeting.

4. **DEC Meeting**
   - The DEC shall make the decision to grant the designation of orphan medicine or otherwise.

5. **Issuance of official letter to applicant**
   - The decision of the DEC shall be informed to the applicant via official letter.

3.2 Timeline

The decision of the DEC to grant the designation of orphan medicine or otherwise will be made within **45 working days** upon receipt of application.

3.3 Cancellation of Orphan Medicine Designation

- The NPRA (through input from the DEC) may, at any time and by notice, cancel any orphan medicine designation of an unregistered/registered medicinal product that no longer meets the criteria for such designation.
- However, the registration status of that medicinal product shall remain valid.

4. REGISTRATION OF ORPHAN MEDICINE

The registration requirements, conditions and fees outlined shall be applicable only to **new medicinal products** that have not been registered before.

4.1 Procedure, Fees and Timeline

a) The PRH may proceed to submit an application for the registration of a medicinal product designated as an orphan medicine via the NPRA QUEST online system.

b) The orphan medicine designation letter issued by NPRA shall be submitted as part of the registration dossier via Quest3+ under Part I- Section E (E14. Other Supporting Documents)

c) The medicinal product that has been granted designation as an orphan medicine will be automatically granted **priority review**. Please refer to **Appendix 12: Priority Review**.

The timeline for evaluation for that medicinal product is as below:

No.	Product Category	Duration
1.	New Chemical Entities	120 working days
2.	Biologics	

The timeline shall commence after payment has been confirmed by the PRH (i.e., post-screening approval).

d) Fee for the registration of orphan medicine shall follow the fees stated in the DRGD, according to product category.

4.2 Registration Requirements and Conditions

This part shall be read in conjunction with the other parts in the DRGD that apply to the registration of orphan medicine, e.g., labelling requirement, etc.

For medicinal products (i.e. new chemical entities and biologics), **certain flexibilities** are permitted for their registration as orphan medicine as follows:

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
1.	**Substantial efficacy and safety evidence of the product for the proposed indication**	Phase III clinical data is required	Phase II clinical data may be acceptable, depending on justification (e.g. why Phase III trial is not conducted, approved in a DCA reference country and supported by real-world evidence data) and may be subjected to certain approval obligations. These obligations may include but not limited to the following: • the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of an assessment of the benefit/risk profile. • the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person.

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
			• the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.
2.	**Stability study data and storage condition of the product according to Zone IVb requirements**	Mandatory (except cold chain products)	Not Mandatory
3.	**Protocol of analysis, analytical method validation and Certificate of Analysis**	Protocol of analysis, analytical method validation and Certificate of Analysis for 3 batches	Protocol of analysis, analytical method validation and Certificate of Analysis for at least 1 batch
4.	**GMP requirements**	a) <u>Foreign Manufacturer:</u> An acceptable GMP evidences (GMP certificate/ GMP inspection report) from any PIC/S Participating Authority (as listed in PIC/S website) or others as stipulated under Directive No.4, 2018 issued by the Senior Director of Pharmaceutical Services.	The product can be manufactured in countries where the health authorities are not the participating authority in the Pharmaceutical Inspection Cooperation/ Scheme (PIC/S). Conditional product registration for the period of 2 years may be granted subjected to an acceptable GMP evidences (GMP certificate/ GMP inspection report) from any PIC/S Participating Authority (as listed in PIC/S website) or others as stipulated under directive

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
		Acceptable GMP evidences must be provided prior to product registration. b) <u>Local Manufacturer:</u> GMP inspection by NPRA is mandatory.	No.4, 2018 issued by the Senior Director of Pharmaceutical Services can be provided within the specified time-frame.
5.	**Fees for GMP inspection**	a) <u>Foreign Manufacturer:</u> • Processing fee : RM5,000 • Inspection fee : RM20,000 • Inspection Expenses* **Includes flight ticket, accommodation and other associated expenses*	Fee waiver as follows: a) <u>Foreign Manufacturer:</u> • Processing fee, RM5,000 is waived. • Inspection fee, RM20,000 is waived. ***Note:*** • *Only applicable to foreign manufacturers that produce a registered orphan medicine with no other registered medicinal product produced by the same manufacturer.* • *The fee waiver is granted for a period of 5 years only, and it shall be revised after the specified period.* • *Inspection expenses includes flight ticket, accommodation and other associated expenses still applicable.*

<table>
<tr><th rowspan="2">No.</th><th rowspan="2">Registration Requirements and Conditions</th><th colspan="2">Comparison of Registration Requirements and Conditions</th></tr>
<tr><th>Normal Registration Pathway</th><th>Orphan Medicine</th></tr>
<tr><td></td><td></td><td>b) <u>Local Manufacturer:</u>
<table><tr><th>Inspection type</th><th>Charges</th></tr><tr><td>Inspection period not more than one (1) working day</td><td>RM1000.00</td></tr><tr><td>Inspection period more than one (1) working day</td><td>RM1000.00/ personnel/ working days</td></tr><tr><td>Inspection involving more than three (3) inspectors and/or period of more than three (3) working days</td><td>RM10000.00 (Maximum rate)</td></tr></table></td><td>b) <u>Local Manufacturer:</u>
Upon registration of the orphan medicine by the Authority, a one-off fee waiver will be given for the subsequent GMP inspection.</td></tr>
</table>

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
6.	**Submission of Periodic Safety Updates Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER)**	As part of the post-registration requirement for newly-approved NDP (New Drug Products) and Biologics products in Malaysia, the Product Registration Holder (PRH) is required to routinely submit Periodic Benefit Risk Evaluation Reports (PBRERs) every 6 months for the first 2 years after approval and once a year for the subsequent 3 years. The first PBRER submitted should have a Data Lock Point (DLP) no later than 6 months after approval in Malaysia.	To submit PSUR/PBRER every 6 months for the first 2 years and once a year for the following 3 years. If the requirements cannot be fulfilled, the PRH shall provide an annual safety report, which includes: • A summary (line listing and summary tabulation) report of all the ADR cases received during a period of twelve months. It is preferably submitted in the PRH ADR Summary report format defined in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021. • A review of ongoing clinical study. • Any risk minimisation activities/ programmes requested by other regulatory authorities relevant to the orphan medicine registered. • A description of the investigation plan for the coming year. The first Annual Safety Report should be submitted no later than one month after the anniversary of the registration date in Malaysia.

4.3 Listing of DCA Registered Orphan Medicine

A list of orphan medicine registered with the DCA shall be published on the NPRA website. The list will be updated regularly as and when updates have been made to it.

4.4 Re-registration

The re-registration procedure in DRGD shall apply to the re-registration of an orphan medicine.

4.5 Cancellation of Orphan Medicine Registration

a) The DCA may, cancel any registered orphan medicine that no longer meets the criteria for registration. Cancellation shall only be done during the re-registration of orphan medicine.

b) The cancellation procedure/ details throughout DRGD shall apply to the cancellation of a registered orphan medicine.

5. POST-MARKETING ACTIVITIES

All registered orphan medicine used in Malaysia shall be subjected to post-marketing activities. As such, the Product Registration Holder (PRH) shall be the responsible entity to implement the requirements.

The PRH shall appoint a responsible person in handling post-marketing issues in Malaysia. The details of the current responsible person, such as name, postal address, e-mail address, telephone, and fax numbers shall be provided to the NPRA and are required to be promptly informed if there is any change.

5.1 Surveillance and Product Complaint

The requirement for registered product quality monitoring is described in 21.2 Product Quality Monitoring (PQM).

5.2 Pharmacovigilance

The PRH is responsible to ensure that an appropriate system of pharmacovigilance is in place. The PRH shall continuously monitor and determine whether benefits continue to outweigh risks, and to consider the necessity of steps to improve the benefit-risk balance through risk minimization activities. The PRH is responsible and liable for their products on the market and must take appropriate action, when necessary.

For full details on the requirements related to pharmacovigilance, please refer to the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

i. Management of adverse drug reaction

The PRH shall have in place written procedures describing the handling of all adverse drug reactions (ADRs) related to their products. The system and procedures in place must be adequate for receipt, handling, evaluation and reporting of ADRs to the NPRA within the stipulated timelines stated in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

ii. Annual submission of safety reports

Submission of Periodic Safety Updates Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER) every 6 months for the first 2 years and once a year for the following 3 years is required for new drug products and biologic products.

If the requirements cannot be fulfilled, the PRH shall provide an annual safety report, which includes:

- A summary (line listing and summary tabulation) report of all the ADR cases received during a period of twelve months. It is preferably submitted in the PRH ADR Summary report format defined in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.
- A review of ongoing clinical study.
- Any risk minimization activities or programmes requested by other regulatory authorities relevant to the registered orphan medicine.
- A description of the investigation plan for the coming year.

iii. Emerging Safety Issues

Events/ observations related to a registered orphan medicine may occur, which may have major impact on the risk-benefit balance of the product and/or on patients or public health. They may require urgent attention of the DCA and could warrant prompt regulatory action and communication to

patients and healthcare professionals. These important new evidences should be considered as emerging safety issues.

The PRH shall:

- alert the NPRA of any emerging global safety issue(s).
- submit all relevant safety information such as post-registration study reports and risk management plan as instructed by the NPRA.
- respond promptly to the NPRA on request for additional risk-benefit information of the products concerned.

Any emerging safety issue shall be notified to the NPRA within the stipulated timeline stated in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

iv. Safety Communication

Please refer to the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021 for further details.

6. ORPHAN MEDICINE DESIGNATION APPLICATION FORM

<table>
<tr><td colspan="3">BAHAGIAN REGULATORI FARMASI NEGARA (NPRA)
ORPHAN MEDICINE DESIGNATION APPLICATION FORM</td></tr>
<tr><td colspan="3">1. Date of Application:</td></tr>
<tr><td colspan="3">2. Information of Applicant (Product Registration Holder, PRH)</td></tr>
<tr><td>Name of company:</td><td colspan="2">Name of Contact Person:</td></tr>
<tr><td rowspan="2">Address:</td><td>Tel No:</td><td>Fax No:</td></tr>
<tr><td colspan="2">E-mail address:</td></tr>
<tr><td colspan="3">3. Product Information</td></tr>
<tr><td>Product Name:</td><td>Strength:</td><td>ATC Code:</td></tr>
<tr><td>Pharmaceutical Form:</td><td colspan="2">Route of administration:</td></tr>
<tr><td>Active Ingredient:</td><td colspan="2">Strength:</td></tr>
<tr><td colspan="3">Manufacturer name and address:</td></tr>
<tr><td colspan="3">Worldwide regulatory status:</td></tr>
<tr><td colspan="3">Worldwide orphan medicine designation status:</td></tr>
<tr><td colspan="3">4. Proposed Rare Disease and Condition</td></tr>
<tr><td colspan="3">Proposed Indication related to the Rare Disease:

☐ Treatment ☐ Prevention ☐ Diagnosis</td></tr>
<tr><td colspan="3">Brief Description of Rare Disease:</td></tr>
<tr><td colspan="3">Current available method in treating/ preventing/ diagnosing the rare disease:</td></tr>
<tr><td colspan="3">4. Proposed Rare Disease and Condition (continued)</td></tr>
<tr><td colspan="3">Justification for this product to be designated as orphan medicine:</td></tr>
</table>

Brief description of the product (details on active ingredient(s), medicines type/class, structure, physical-chemical properties):
Mechanism of action explaining how the product works in relevant disease/condition:
5. Scientific rationale for the orphan medicine use (the scientific rationale should support a medical plausible basis for the orphan medicine to be effective in treating disease/condition)
Please briefly describe the scientific evidence to support safety and efficacy of this product to treat/prevent/diagnose the proposed indication related to the rare disease:
Tabulated pre-clinical trial and clinical studies(Please enclose together with this form):
A brief safety update report:
6. Declaration of Applicant
i) I hereby declare that all the information and attachment(s) provided are true. ii) I am fully aware of the consequences of rejection of this application if this form is incomplete. …… Name: Company Stamp: