GUIDE TO APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS

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DEPARTMENT OF PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH
BRUNEI DARUSSALAM

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1. INTRODUCTION

1.1 The Ministry of Health through the Department of Pharmaceutical Services (DPS) implements the registration system of all medicinal products for human use prior to their use in Brunei Darussalam. Medicinal products in Brunei Darussalam are regulated under the Medicines Order 2007, Medicines (Licensing, Standard Provision and Fees) Regulations 2010, Medicines (Labelling) Regulations 2010 and Poisons Act 1956. Local manufacturers, wholesalers and importers of medicinal products must be licensed before conducting their businesses.

1.2 The objective of registration of medicinal product is to ensure that medicinal product marketed in Brunei Darussalam are safe, efficacious and of good quality.

1.3 The Brunei Darussalam Medicines Control Authority (BDMCA) is established under the Section 5 of Medicines Order, 2007 has the authority to grant, renew, vary, suspend and revoke licences and certificates under this Order.

1.4 The meaning of '**medicinal product'** and related expressions as stated in the Medicines Order, 2007 (Part 1: Section 4):-

(1) Subject to the following provisions of this section, in this Order "**medicinal product**" means any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways:-
   (a) use by being administered to one or more human beings or animals for a medicinal purpose;
   (b) use as an ingredient in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose.

(2) In this Order, "**a medicinal purpose**" means any one or more of the following purposes:-
   (a) treating or preventing disease;
   (b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;
   (c) contraception;
   (d) inducing anaesthesia;
   (e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

(3) Notwithstanding anything in subsection (1), in this Order "medicinal product" **does not include** any substance or article which is manufactured for use wholly or mainly by being administered to one or more human beings or animals, where it is to be administered to them:-
   (a) in the course of the business of the manufacturer or on behalf of the manufacturer in the course of the business of laboratory or research established carried on by another person;
   (b) solely by way of a test for ascertaining what effects it has when so administered; and
   (c) in circumstances where the manufacturer has no knowledge of any evidence that those effects are likely to be beneficial to those human beings, or beneficial to, or otherwise advantageous in relation to, those animals, as the case may be, and which (having been so manufactured) is not sold, supplied or exported for use wholly or mainly in any way not fulfilling all the conditions specified in paragraphs (a), (b) and (c).

(4) In this Order, a "medicinal product" **does not include**:-

- substances used in dental surgery for filling dental cavities;
- bandages and other surgical dressings, except medicated dressings where the medication has a palliative or curative function which is not limited to sterilising the dressings; and
- substances and articles of such other description or classes as may be specified by order made by the Minister.

(5) Where in accordance with subsections (1) to (4) a substance or article is a medicinal product immediately after it has been manufactured, imported or exported as mentioned in subsection (1), or immediately after the first occasion on which it has been sold or supplied as mentioned in that subsection, then it shall not cease to be a medicinal product for the purposes of this Order by reason only that, at any subsequent time, it is sold, supplied, imported or exported for the use wholly or mainly in a way other than those specified in subsection (1).

(6) For the purposes of this Order, medicinal products are of the same description if:-

(a) they are manufactured to the same specification; manufacturing methods and processes; equipment and manufacturing plant; and

(b) they are, are to be, sold, supplied, imported or exported in the same pharmaceutical form.

(7) For the purposes of this Order a document, advertisement or representation shall be taken to be likely to mislead as the uses or effects of medicinal products of a particular description if it is likely to mislead as to any of the following matters:-

(a) any purposes for which medicinal products of that description can with reasonable safety be used;

(b) any purposes for which such products cannot be so used; and

(c) any effects which such products when used, or when used in any particular way referred to in the document, advertisement or representation, produce or are intended to produce.

1.5 The forensic classification of registered medicinal products in Brunei Darussalam can be classified as follows:

- Prescription Only Medicine (POM);
- Pharmacy only medicine (P); or
- General Sale List medicine (GSL)

2. SCOPE

2.1 This document provides a guide to the applicants on the procedures and requirements for applying the registration of medicinal product for human use in Brunei Darussalam, variations and renewals of registered medicinal products.

3. APPLICATION PROCEDURES FOR MEDICINAL PRODUCT REGISTRATION

3.1 A Product Licence will be issued by the BDMCA for a medicinal product that has been approved for registration in Brunei Darussalam. Medicinal products that are registered in any of the benchmark regulatory agencies in countries such as Australia, Canada, EU (centralised), Malaysia, Singapore, United Kingdom and United States of America will facilitate the medicinal product registration process.

3.2 **Application Type**

A new product registration application is divided into 3 types:

i) Innovator product (NCE / Biotech)

Applies to new medicinal product containing:

- a new***** chemical/biological entity;
- a new combination of existing chemical/biological entity(s);
- existing chemical/biological entity(s) in a new dosage form;
- existing chemical or biological entity(s) for use by a different route of administration.

*(*Has not been registered before in Brunei Darussalam)*

ii) Generic product

Applies to any medicinal product that is essentially similar to a currently registered product in Brunei Darussalam. The term generic is not applicable to biological and biotechnological products.

iii) Application for registration of medicinal products via the abridged route

Applies to any medicinal product classified as GSL (for certain categories* only) and registered in at least one benchmark country.

(*antiseptics/skin disinfectants; lozenges/pastilles; health supplements; topical analgesics/counter-irritants; emollients/demulcents; keratolytic; topical nasal decongestants. This list is non-exhaustive.)

3.3 **Registration Dossier**

3.31 All applications for medicinal product registration are to be made by submission of the required documents which are in line with the ASEAN Common Technical Dossier (ACTD) for the registration of pharmaceuticals for human use and ASEAN Common Technical Requirements (ACTR). The application dossier required will consist of 4 parts which are as follows:

Part I	Administrative Data and Product Information
Part II	Quality
Part III	Non-Clinical or Safety
Part IV	Clinical or Efficacy

3.32 The data requirements will be based on the following criteria:

Application Type	Data requirements
1) Innovator product	
• Innovator product registered for less than 5 years in at least one benchmark country	Parts I, II, III and IV
• Innovator product registered for less than 5 years in at least one benchmark country containing existing chemical/biological entity(s) in a new dosage form	Parts I, Part II and pharmacokinetic data
• Innovator product registered more than 5 years in 3 benchmark countries	Parts I and II
2) Generic product*	Parts I and II
3) Abridged application	Part I only

*Notes - *Inclusive of 'Grandfather' Product. 'Grandfather' Product in accordance to BDMCA is referred to medicinal products that are available in the market before 2004.*

3.33 The documents required for Part I, Part II, Part III and Part IV are as follows:

Part I: Administrative Data and Product Information

Section 1 : Application Form - Form No: BDMCA/DPS/01
Section 2 : Letter of Authorisation
Section 3 : Certifications
Section 4 : Labelling
Section 5 : Product Information

Note: For guidance in the preparation of Part I of the application dossier, applicants are advised to read the guidelines in the following annexes:

Annex 1.1 : Guide on how to fill the application form (Form No. BDMCA/DPS/01) for registration of a medicinal product registration (Part I: Section 1)

Annex 1.2 : Guideline on submission of letter of authorisation for application of registration of medicinal products (Part I: Section 2)

Annex 1.3 : Guideline on submission of certifications for application of registration of medicinal products (Part I: Section 3)

Annex 1.4 : Guideline on submission of product labelling for application of registration of medicinal products (Part I: Section 4)

Annex 1.5 : Guideline on submission of product information for application of registration of medicinal products (Part I: Section 5)

Part II: Quality

Section 1 : Application Form for Quality Requirements of the Drug Substance (Form No. BCMCA/DPS/02/A)

Section 2 : Application Form for Quality Requirements of the Drug Product (Form No. BCMCA/DPS/02/B)

Note: For guidance in the preparation of Part II of the application dossier, please refer to ASEAN Technical Requirements Guidance Documents available at http://www.moh.gov.bn/pharmacyservices/guidelines.htm

Part III: Non-Clinical

Section 1 : Table of Contents

Section 2 : Non-clinical Overview

Section 3 : Non-clinical Summary (Written and Tabulated)

Section 4 : Non-clinical Study Reports *(As requested)*

Section 5 : List of Key Literature References

Note: For guide in preparing the documents, applicants are advised to read the Part III of ACTD for the Registration of Pharmaceuticals for Human Use and the guideline in the following annex:

Annex 2 : Guideline on submission of non-clinical documents (Part III)

- Non-clinical Study Reports (Section D) may not be required if the original products are already registered and approved for marketing authorisation in reference countries. Therefore, if required, specific Study Reports may be requested for necessary documents.

- Non-clinical documents (Part III) are not required for Generic Products, Minor Variation Products and some Major Variation Products.

Part IV: Clinical Documents

Section 1 : Table of Contents

Section 2 : Clinical Overview

Section 3 : Clinical Summary

Section 4 : Tabular Listing of All Clinical Studies

Section 5 : Clinical Study Reports *(If applicable)*

Section 6 : List of Key Literature References

Note: For guide in preparing the documents, applicants are advised to read the Part IV of ACTD for the Registration of Pharmaceuticals for Human Use and the guideline in the following annex:

Annex 3 : Guideline on submission of clinical documents (Part IV)

- Clinical Summary (Section C) is not required for *Generic Products*, *Minor Variation Products* and *some Major Variation Products*. For ASEAN member countries, the Clinical Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorisation in Reference Countries. However, if required, the Clinical Study Reports may be requested for additional documents.

- Clinical Study Reports (Section E) may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, if required, specific Study Reports may be requested for necessary documents.

3.4 Application Submission

3.41 The onus of applying for product registration rests with the **firm responsible** for the introduction of the medicinal product into the Brunei Darussalam market, i.e.:

- In the case of an imported product, the manufacturer's local representative or its appointed sole agent.
- In the case of a locally manufactured product, the manufacturer of the product or the local product owner.

3.42 Applications for medicinal product registration are to be made by submission of the letter of intent (refer to **Annex 4** for the recommended model of the letter of intent) and by using the prescribed forms issued by the DPS. Application forms (refer to **Annex 5.1 – 5.3**) can either be obtained from Drug Registration Unit, Drug Administration Section Department of Pharmaceutical Services, Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium, Bandar Seri Begawan, BA1111, Brunei Darussalam or downloaded from the following website:

http://www.moh.gov.bn/pharmacyservices/forms.htm

3.43 For submission, hard copies for Part I and II are required to be submitted. Submission of Part III and IV may be submitted in a CD/DVD.

3.44 Applications must be duly completed and supported by all of the required documents according to the application type (refer to *Registration Dossier* for more details). In order to ensure that the dossier is complete, application checklists are provided for Part I, Part II, Part III and Part IV (refer to **Annex 6.1 - 6.5**). The completed checklists should be attached at the front of each part upon submission to the Drug Registration Unit.

3.45 The application dossier must be arranged in proper order, clearly indicated and filed according to the required ACTD format (refer to **Annex 7** for Organisation of the Dossier for Part I: Administrative Data and Product Information). Failure to arrange the dossier accordingly will lead to non-acceptance of the dossier without screening.

3.46 Applications are to be submitted by the person responsible for the company or its representative to:

Drug Registration Unit
Drug Administration Section
Department of Pharmaceutical Services
Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium
Bandar Seri Begawan, BA1111
Brunei Darussalam
Tel: +673 2230001 / Fax: +673 2230041

3.47 Submission of the applications must be made by appointment with the concerned officer at the above address.

3.5 Application Screening

3.51 The submitted application will be screened and validated for completeness within **10 working days**. DRU may request for further information and additional supporting documents from the applicant through the query letter. Applicant should make available such information or documentation required for each correspondence within **60 calendar days** from the date of the screening query letter. Once the feedback has been received, the requested information and documents will be screened for completeness. The application will not proceed for evaluation if no response is received from applicant after the 60 days given. DRU will issue a non-acceptance letter and the documents will be returned. A new application will have to be submitted if the applicant wishes to pursue registration of the product.

3.52 The **stop-clock** starts when DRU issues the screening query letter and ends when DRU receives the required documents/information from the applicant.

3.53 The application will be accepted once the registration dossier is complete. An acknowledgement for the receipt of the application will be issued and a reference number (LOA-P/…/S…) will be generated. The reference number shown in this acknowledgement should be used in all subsequent correspondences relating to the application.

3.54 The flowchart on the procedure of application for registration of medicinal product is as appears on **Annex 8.**

3.6 Application Evaluation

3.61 Review of application for registration of a product will follow the appropriate evaluation queue. Priority review may be granted where the product is intended for treatment of a serious or life-threatening disease.

3.62 During product evaluation, DRU may request for further information and additional supporting documents from the applicant. Applicant should make available such information or documentation required for each correspondence within **60 calendar days** from the date of the request. The application will be rejected / closed if no response is received from applicant after the 60 days given and a new application will have to be submitted if the applicant wishes to pursue registration of the product.

3.63 The **stop-clock** starts when DRU issues the evaluation query letter and ends when DRU receives the required documents/information from the applicant.

3.7 Application Fee

3.71 **Processing fee**

The processing fee of B$200 is payable at the point of submission of the application for a medicinal product registration. Processing fee is **non-refundable** once the application has been submitted, regardless of the final decision by the BDMCA.

3.72 **Product Licence fee**

The Product Licence certificate shall be valid for 5 years. There is no charge in the first year and the fee of B$50 is payable for each subsequent year.

3.73 **Amendment fee**

The amendment fee is payable upon approval of the amendment by the BDMCA. The major and minor amendment fees are B$150 and B$50 respectively.

3.74 The payments can be made in in the form of cash or cheque. Payments by cheque shall be made payable to *'Kerajaan Brunei'* or Government of Brunei.

3.75 Payments can be made on Monday to Thursday from 8.00 a.m. – 12.15 p.m. and 1.30 p.m. – 2.30 p.m. An official receipt will be issued for each payment.

4. BRUNEI DARUSSALAM MEDICINES CONTROL AUTHORITY DECISION

4.1 The applicant will be informed on the decision of the BDMCA in writing as to whether the application has been approved or rejected.

4.2 **Product Registration Number**

A registration number will be given when a product is registered. The registration number is specific for the product registered as specified in the registration documents.

4.3 **Product Licence Certificate**

A Product Licence certificate shall be issued for the registered medicinal product.

4.4 **Rejection, cancellation, suspension of registration**

The BDMCA may reject, cancel or suspend the registration of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with the registration requirements. Such products may not be imported and marketed in Brunei Darussalam. The holder of the Product Licence certificate shall immediately surrender to the BDMCA the Product Licence certificate upon cancellation or suspension of registration of the product.

4.5 **Appeal against the BDMCA's decision**

For products that have been rejected for registration by the BDMCA, applicant may make a written appeal to the Chairperson of the BDMCA by using the prescribed form (Form No: BDMCA/DPS/Appeal/02) issued by the DPS. All notice of appeals must be made within **THIRTY (30) calendar days** from the date of the BDMCA's notification. A soft copy of the application form can be obtained from the Drug Registration Unit or downloaded from *http://www.moh.gov.bn/pharmacyservices/forms.htm.* For submission, a hard copy of the completed form must be submitted. The application form for appeal appears as **Annex 9.**

5. MAINTENANCE OF REGISTRATION

5.1 The conditions for registration of medicinal product are as follows:-

5.11 The product registered with the registration number as stated in the Product Licence certificate shall have the name, composition, characteristics, specifications and origin as specified in the registration documents.

5.12 The Product Licence holder must supply such documents, items, samples, particulars or information as the BDMCA may require in relation to the registered product.

5.13 No change in name, composition, characteristics, origin, specifications, manufacturer, packing, indications, labelling, package insert, product literature or any other particulars of the registered product shall be made without prior approval from the BDMCA.

5.14 The registration number must be:

- printed on the product label or added as a securely fixed adhesive label;
- labelled on the immediate container / packaging and immediate outer container / packaging;
- printed in an indelible manner;
- **NOT** handwritten;
- labelled **before** being imported, sale or supply by the manufacturer (for imported products);
- labelled **before** distribution, sale or supply by the manufacturer (for locally manufactured products);
- labelled **within 3 months** from the date the BDMCA's decision is made known to the applicant (for 'existing' products which are registered); and
- labelled **immediately** (for 'new' products which are registered).

5.15 The labels for the registered product must comply with all of the labelling requirements as specified by the BDMCA.

5.16 The registered product must only be indicated for use as approved by the BDMCA.

5.17 The Product Licence holder must inform the BDMCA of any adverse reactions or complaints on the registered product immediately after he/she receives notice of such adverse reactions or complaints. Please refer to Brunei Darussalam Guideline on Reporting of Adverse Drug Reaction for Product Licence Holders which can be obtained from Drug Registration Unit, Drug Administration Section Department of Pharmaceutical Services, Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium, Bandar Seri Begawan, BA1111, Brunei Darussalam.

5.18 The Product Licence holder must notify the BDMCA of any decision to withdraw the registration of the product and shall state the reasons for the decision. The holder must also notify the BDMCA when he/she is no longer authorised to be the holder of the Product Licence certificate.

5.2 The registration of the product shall be **valid for 5 years** or such period as specified in the Product Licence certificate (unless sooner suspended or cancelled by the BDMCA).

5.3 The **renewal** of product registration should be done **not later than a year** prior to expiry together with an appropriate fee. The application form (Form No.: BDMCA/DPS/RN/01) and Guide to application for renewal of registered medicinal product registration appear as **Annex 10** and **Annex 11** respectively. A soft copy of the application form can also be downloaded from the following website: *http://www.moh.gov.bn/pharmacyservices/forms.htm.* For submission, a hard copy of the completed form and the supporting documents **must** be submitted.

6. CHANGE IN PARTICULARS OF REGISTERED PRODUCTS

6.1 The Product Licence holder must inform the BDMCA on any change(s) to any aspect of the product i.e. variation from what have been specified in the registration documents. The changes may include but are not limited to change in formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling, and product information. Approval by the BDMCA is required before the changes can be made, with the exception of some minor variations that require only notification to the DPS.

6.2 Applications for approval for change must be submitted **well in advance or at least 2 months in advance** prior to the proposed date of change. Relevant supporting data for the change should be submitted. The registration of a product may be cancelled if major changes are made without prior approval from the BDMCA.

6.3 The application form (Form No.: BDMCA/DPS/Vartn/02) and Guideline on Application for Variations to a Registered Medicinal Product appear as **Annex 12** and **Annex 13** respectively. A soft copy of the application form can also be downloaded from the following website: *http://www.moh.gov.bn/pharmacyservices/forms.htm.* For submission, a hard copy of the completed form and the supporting documents **must** be submitted.

ANNEX 1.1

GUIDE ON HOW TO FILL THE APPLICATION FORM FOR REGISTRATION OF A MEDICINAL PRODUCT (PART I: SECTION 1)

Note 1:
All sections of the application form must be completed. Please indicate N.A. (Not applicable) in those sections that are not relevant to the application.

Note 2:
Applications for registration of products shall be made on prescribed form, BDMCA/DPS/02 for all categories of medicinal product.

Note 3:
All entries and documents must be made in English. Where applicable, details in other relevant language, i.e. Malay, may also be included in addition to the English version.

Note 4:
Where continuation sheets are required, separate A4-size paper appropriately cross-referenced to the relevant section should be attached immediately behind the application form.

Note 5:
If more than one application is submitted, there should be no cross-referencing of common information or documents i.e. any common information or documents supplied in one application must be repeated in the next application.

Note 6:
A separate application is required for each product i.e. products containing the same ingredients but made to different specifications (in terms of strength or content of ingredient(s), dosage form, description, etc) or by different manufacturer shall require separate applications for product registration.

Proprietary products manufactured under licence by different manufacturers, or different subsidiaries, or in different countries under the same parent firm shall require separate registration.

One application may be submitted for medicinal product registration of different container closure system or pack sizes (quantity or volume) of a product made by the same manufacturer to the same specifications, strength (content) of ingredients and dosage form. Only the container closure system and pack sizes stated in the registration documents will be registered.

[1.0] COMPANY PARTICULARS

1.1 Name of Company

The company named in this section should be based and registered in Brunei Darussalam.
Each application for a product registration is company-specific. In this document, the company making an application is called an applicant firm.

A company must be authorised by a responsible person in the company or organisation that owns the medicinal product (see Section 3) before it can apply for a product registration for a specific medicinal product in Brunei Darussalam. Letter of authorisation must be enclosed with each application.

For every successful application for registration of a medicinal product, a Product Licence will be issued in the name of the applicant.

[2.0] APPLICANT PARTICULARS

2.1 Name of Company

The person named in this section should be based in Brunei Darussalam and be contactable at all times. During the initial drug evaluation process and after a product is registered in Brunei Darussalam, the Department of Pharmaceutical Services (DPS) will only liaise with this person.

It should be noted that the applicant bears full responsibilities for ensuring that all available and relevant information has been submitted to support an application.

[3.0] PRODUCT DETAILS

3.1 Proprietary Name

This is the name that will be shown on the product labelling i.e. the inner label, outer carton, package insert and Patient Information Leaflet.

Applicants should ensure that the name does not:

- suggest greater safety or efficacy than supported by clinical data;
- imply superiority over another similar product in Brunei Darussalam;
- imply the presence of substance(s) not present in the product.

3.2 Dosage Form

Applicants should state clearly the pharmaceutical dosage form of the product, e.g. tablet, capsule, injection, etc. Any descriptive terms to give an indication of the exact type of dosage form should also be included e.g. sustained-release tablet, oily injection, *etc.* Please refer to **Appendix 1** – List of Recognised Dosage Forms.

3.3 Product Description

Applicants should state visual and physical characteristics of the product which include shape, size, superficial markings, colour, odour, taste, consistency, type of tablet coating, type of capsule, *etc*. where applicable.

3.4 Product Formula

The product formula should provide the composition of all active substances and excipients that appear in the final dosage form. The name(s) of the active substance(s) should be reflected first followed by the names of the excipients. Any alcohol or gelatine component must be included and stated in the formulation if available. The International Non-proprietary Names (INN) and grades of all ingredients including water should be specified in the product formula i.e. BP, USP, Ph. Eur.

International units of measure should be used wherever appropriate. The role of each excipient should be stated i.e. 'C' for colourant, 'F' for flavouring, 'P' for preservative, 'S' for stabilizer, *etc*. Where the active substance is derived from a biological system, the biological source should be specified.

3.5 a) Ingredients Derived From Human Blood

Additional data needs to be provided, Please refer to CPMP Note for Guidance on Plasma-derived Medicinal Products (CPMP/BWP/269/95 Rev.3) and US FDA Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-derived Biological Products, Animal Plasma and Serum-derived Products.

b) Ingredients Derived From Animals

Additional data needs to be provided. Please refer to CPMP-CVMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev.3).

3.6 Pharmacotherapeutic Group

Applicants should indicate the WHO Anatomical Therapeutic Chemical (ATC) code for each distinct therapeutic indication proposed for a product, if such a code is available. Applicants may refer to the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/) for more information.

3.7 Route of Administration

Applicants should state all routes of administration proposed for the product and refer to the list of administration routes in **Appendix 2** – List of Recognised Routes of Administration.

3.8 Indication

Applicants should state the proposed clinical use(s) of a product, indicating clearly also whether curative, palliative, adjustive, etc. State the pharmacological basis for each clinical indication, together with supporting clinical documentation on the safety and efficacy of each use.

Notes:

- Indications should be specific; phrases such as “associated conditions” or “allied diseases” would not normally be considered appropriate.
- State rationale for combination of active ingredients, where applicable. Supporting data on advantage of combination over single ingredient(s) is required.
- Indications other than those specified and accepted at the time of registration must not be included in any product literature, data sheets, package inserts, labels, *etc*, without prior permission from the BDMCA.
- Should it be desired to include new indications, an application shall be filed with the BDMCA together with supporting clinical documentation on evidence of efficacy and safety for the additional uses (indications).

3.9 Recommended Dosage

Applicants should state the proposed dose (normal dose, dose range), dosage schedule (frequency, duration) appropriate for each therapeutic indication for the product. Dosage for adults, and where appropriate children, should be stated. Dosage adjustments for special conditions, e.g. renal, hepatic, cardiac, nutritional insufficiencies, where relevant, should be stated.

Notes:

- Where appropriate, diluents and instructions for dilution, reconstitution and use or administration of the product should be clearly stated.
- Distinction should be made between therapeutic and prophylactic doses, and between dosages for different clinical uses where applicable.
- Ensure that dosage recommendation is relevant and appropriate for the product.

3.10 Therapeutic Advantage

Applicants should give a summary of the overview of the product i.e. for new drug substances, new combination and new formulation and justify why it should be registered. Applicants should include supporting data to establish therapeutic advantage over other drugs of the same and different pharmacological or therapeutic class(es); in the case of combination products, advantage over single ingredients; and also the need for the product.

3.11 Packaging, Shelf-life and Storage Conditions

Applicants should state all the different container closure systems for the product which is the object of the application, the quantity of product per container, the shelf-life of the product for each container-closure system and the recommended storage conditions. Information on the commercial pack sizes should also be provided. Tabulation should follow the format as shown below.

Container Closure System	Quantity/Container	Shelf-Life	Storage Conditions	Pack Size
e.g. Syringe	5ml/Syringe	24 months	$2^{o}C – 8^{o}C$	4 x 1's

The recommended shelf-life and the storage conditions for the product packed in different container closure systems must be supported by stability data.

Where appropriate, information on shelf-life after first opening e.g. for eyedrops and shelf-life after reconstitution e.g. lyophilized powder for reconstitution, should be provided and supported by stability test data.

3.12 Forensic Classification in Brunei Darussalam

Applicants should state the forensic classification proposed for the product in Brunei Darussalam. However, the BDMCA may approve the product under a different forensic classification depending on the outcome of the evaluation.

The forensic classification should be indicated as:

- Prescription-only medicine (POM);
- Pharmacy medicine (P); or
- General Sale List medicine (GSL)

3.13 Registration Status in Other Countries

Details of the registration status in other countries of the application should be tabulated in the following format. Note that only information pertaining to the same product (i.e. same composition and site of manufacture) that is submitted for local application should be provided.

Country	Application status with details	Date	Approved forensic classification of the product
e.g. EU Centralised	Approved	1/1/2003	POM

The different types of application status and the details to be submitted under each status type are, for:

- an *approved* application, to provide details of the approved indications and dosing regimens;
- a *rejected* or *withdrawn* application, to provide details and reason(s) for rejection or withdrawal;
- an application still *under evaluation* by the BDMCA's benchmark regulatory agencies for drug registration, to provide the proposed Summary of Product Characteristics (SmPC) /

Package Insert (PI) / Patient Information Leaflet (PIL) submitted to the agency for evaluation; and for

- *planned submission* to the BDMCA's benchmark regulatory agencies for drug registration, to provide the expected date of submission.

For detailed information required under this section, please use a separate A4 size

Notes:

- Please enclose one certified copy of the Product Licence issued by the relevant authority (if available);
- Please enclose an original copy of Certificate of Pharmaceutical Product (CPP) endorsed by the relevant authority from the country concerned; and
- Please enclose all certificates under Part 1 Section 3.

Certificate of Pharmaceutical Product (CPP)

The CPP in the country of origin for imported products must be issued by the competent authority recognised by the BDMCA i.e. the authorities listed in the WHO 'Certification Scheme On The Quality of Pharmaceutical Products Moving In International Commerce'.

If the product or diluent is manufactured / packed by a different company which is not stated on the CPP, a copy of the GMP certificate of that company is also required.

- All copies of GMP certificates must be duly endorsed by the Brunei Darussalam Embassy. In the absence of Brunei Darussalam Embassy, the certificate can be endorsed by the Notary Public.

The formula (complete composition) of the dosage form, product information such as Core Data Sheet (CDS) / Summary of Product Characteristics (SmPC) should be appended with the certificate. Details of quantitative composition are preferred but their provision is subject to the agreement of the product licence holder.

3.14 Proposed Price of Product

Applicants should indicate the proposed wholesale price and retail price of products in Brunei Dollars.

3.15 Product Owner Information

Applicants should provide information on the name and address of the company who is the legal/registered owner of the product formulation, and/or the manufacturing process pertaining to the product, submitted for application, and with whom the applicant firm has a contract.

[4.0] MANUFACTURER'S PARTICULARS

4.1 Active Substance Manufacturer

Applicants should provide the names and addresses of the office and manufacturing sites for the active drug substance(s).

4.2 Finished Product Manufacturer

Applicants should provide the names and addresses of the office and manufacturing sites for the finished product and diluent used to reconstitute the product if the latter is packed and sold together with the finished product. Applicants should also indicate the specific operations, e.g. bulk production, repacking, labelling of the finished product and diluent, of each of these manufacturers according to the template given.

4.3 Contract Manufacturer's Particulars (If applicable)

Applicants should provide the names and addresses of the office and manufacturing sites for the finished product and diluent used to reconstitute the product if the latter is packed and sold together with the finished product. Applicants should indicate the specific operations, e.g. bulk production, repacking, labelling of the finished product and diluent, of each of these contract manufacturers according to the template given.

Applicants should also provide documentary evidence to show that the manufacturer(s) of the finished product have been duly authorised by the product owner (see Section 3) and also a letter from the manufacturer(s) themselves that they have been authorised by the product owner to carry out the respective operations, if the product owner is not the manufacturer.

[5.0] REPACKER'S PARTICULARS

Name of Repacker

Applicants should provide the name of the repacker for the finished product and diluent (if applicable).

Site and Office Address

Applicants should provide the addresses of the repacking sites and office for the finished product and diluent (if applicable).

[6.0] BATCH RELEASE DETAILS

5.1 Information on Company / Agency responsible for Batch Release in the Exporting Country

Applicants should provide the name, site and office addresses of the company or regulatory agency responsible for testing and batch release of the finished product in the exporting country and provide the particulars of the contact person in this company or agency.

Applicants should provide documentary evidence to show that this company has been duly authorised by the product owner to carry out the product release.

[7.0] DECLARATION

Application form for registration of product must be duly completed, declared and signed.

APPENDIX 1

LIST OF RECOGNISED DOSAGE FORMS

AEROSOL	GRANULE, EFFERVESCENT, FOR SUSPENSION
AEROSOL, FOAM	GRANULE, FOR SOLUTION
AEROSOL, METERED	GRANULE, FOR SUSPENSION
AEROSOL, POWDER	GRANULE, FOR SUSPENSION, EXTENDED RELEASE
BEAD	GUM
BEAD, IMPLANT, EXTENDED RELEASE	GUM, CHEWING
CAPSULE	IMPLANT
CAPSULE, COATED	INHALANT
CAPSULE, COATED PELLETS	INJECTION
CAPSULE, COATED, EXTENDED	INJECTION, EMULSION
RELEASE	INJECTION, LIPID COMPLEX
CAPSULE, DELAYED RELEASE	INJECTION, POWDER, FOR SOLUTION
CAPSULE, DELAYED RELEASE PELLETS	INJECTION, POWDER FOR SUSPENSION
CAPSULE, EXTENDED RELEASE	INJECTION, POWDER FOR SUSPENSION, EXTENDED RELEASE
CAPSULE, FILM COATED, EXTENDED RELEASE	INJECTION, POWDER, LYOPHILISED, FOR SOLUTION
CAPSULE, GELATIN COATED	INJECTION, POWDER, LYOPHILISED, FOR SUSPENSION
CAPSULE, LIQUID FILLED	INJECTION, POWDER, LYOPHILISED, FOR SUSPENSION, EXTENDED RELEASE
CELL SUSPENSION	INJECTION, POWDER, LYOPHILISED, FOR LIPOSOMAL SUSPENSION
CEMENT	INJECTION, SOLUTION
COLLODION	INJECTION, SOLUTION, CONCENTRATE
CREAM	INJECTION, SUSPENSION
CRYSTAL	INJECTION, SUSPENSION, EXTENDED RELEASE
DIAPHRAGM	INJECTION, SUSPENSION, LIPOSOMAL
DISC	INTRAUTERINE DEVICE
DOUCHE	IRRIGANT
ELIXIR	LINCTUS
EMULSION	LINIMENT
ENEMA	LIQUID
EXTRACT	LOTION
EYE/EAR/NOSE DROP	LOZENGE
FILM	MIXTURE
GAS	MOUTHWASH
GAUZE	OIL
GEL	OINTMENT
GEL, DENTIFRICE	PAD
GENERATOR	PAINT
GRAFT	PASTE
GRANULE	PASTE, DENTIFRICE
GRANULE, DELAYED RELEASE	PASTILLE
GRANULE, EFFERVESCENT FOR SOLUTION	PATCH

LIST OF RECOGNISED DOSAGE FORMS – CONT'D

PATCH, EXTENDED RELEASE
PELLET
PELLETS, COATED, EXTENDED RELEASE
PELLET, IMPLANTABLE
PESSARY
PILL
PLASTER
POULTICE
POWDER
POWDER, DENTIFRICE
POWDER, FOR SOLUTION
POWDER, FOR SUSPENSION
POWDER, METERED
SHAMPOO
SOAP
SOLUTION
SOLUTION, CONCENTRATE
SOLUTION, GEL FORMING, EXTENDED RELEASE
SPONGE
SPRAY
SPRAY, METERED
STICK
STRIP
SUPPOSITORY
SUPPOSITORY, EXTENDED RELEASE
SUSPENSION
SYRUP
TABLET
TABLET, CHEWABLE
TABLET, COATED
TABLET, DELAYED RELEASE
TABLET, DELAYED RELEASE PARTICLES
TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING
TABLET, EFFERVESCENT
TABLET, EFFERVESCENT, FOR SOLUTION
TABLET, EXTENDED RELEASE
TABLET, FILM COATED
TABLET, FILM COATED, EXTENDED RELEASE
TABLET, FOR SOLUTION
TABLET, FOR SUSPENSION
TABLET, MULTILAYER, EXTENDED RELEASE
TABLET, ORALLY DISINTEGRATING
TINCTURE
WAFER
OTHERS

APPENDIX 2

LIST OF RECOGNISED ROUTES OF ADMINISTRATION

BUCCAL
CONJUNCTIVAL
CUTANEOUS
DENTAL
ENDOCERVICAL
EPIDURAL
EXTRA-AMNIOTIC
EXTRACORPOREAL
HEMODIALYSIS
INFILTRATION
INHALATION
INTRA-AMNIOTIC
INTRA-ARTERIAL
INTRA-ARTICULAR
INTRACARDIAC
INTRACARTILAGINOUS
INTRACAVITARY
INTRACEREBRAL
INTRACORPORUS CAVERNOSUM
INTRADERMAL
INTRADISCAL
INTRADUCTAL
INTRALESIONAL
INTRALYMPHATIC
INTRAMUSCULAR
INTRAOCULAR
INTRAPERITONEAL
INTRASPINAL
INTRATENDONOUS
INTRATESTICULAR
INTRATHECAL
INTRATUMOUR
INTRAUTERINE
INTRAVASCULAR
INTRAVENOUS
INTRAVENTRICULAR
INTRAVESICAL
INTRAVITREOUS
IONTOPHORESIS
IRRIGATION
NASAL
OPHTHALMIC
ORAL
OTIC
PERCUTANEOUS
PERIARTICULAR
PERIODONTAL
RECTAL
SUBCUTANEOUS
SUBLINGUAL
SUBMUCOSAL
TOPICAL
TRANSDERMAL
URETERAL
URETHRAL
VAGINAL
OTHERS

ANNEX 1.2

GUIDELINE ON SUBMISSION OF LETTER OF AUTHORISATION FOR APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS

(PART I: SECTION 2)

- Applicant should provide a copy of the Letter of Authorisation from the product owner for the application of registration of medicinal products **(not applicable if the applicant is the product owner)**.

- The letter of authorisation should be on the product owner's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organisation.

- Below is the recommended model of the Letter of Authorisation from the product owner to applicant for the application of registration of a medicinal product:

Company's Letterhead

LETTER OF AUTHORISATION

We_____
Product Owner's Name and Address

Hereby appoint _____
Applicant's Name and Address

To apply for registration of our medicinal product

Product Name
Dosage Form and Strength

with the Brunei Darussalam Medicines Control Authority (BDMCA) on our behalf. They will be the Product Licence holder of the Product Licence certificate and be responsible for all matters pertaining to the regulation of this product.

Signature: _____

Name: _____

Designation: _____

Date: _____

ANNEX 1.3

GUIDELINE ON SUBMISSION OF CERTIFICATIONS FOR APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS (PART I: SECTION 3)

Applicant should provide a copy of the following types of certifications for the application of registration of medicinal products:

- **For contract manufacturing:**
    a) Licence of pharmaceutical industries and contract manufacturer
    b) Contract manufacturing agreement
    c) GMP certificate of contract manufacturer*
- **For manufacturing "under-licence":**
    a) Licence of pharmaceutical industries
    b) GMP certificate of the manufacturer*
    c) Copy of "under-licence" agreement
- **For locally manufactured products (excluding the above):**
    a) Licence of pharmaceutical industries
    b) GMP certificate of the manufacturer*
- **For imported products:**
    a) Licence of pharmaceutical industries; importer; and wholesaler.
    b) Certificate of Pharmaceutical Product* issued by the competent authority in the country of origin according to the current WHO format
    c) Site master file of manufacturer (Optional)

Notes:

* Original copy must be submitted.

Certificates/licences which are not submitted in the form of original copy, must be duly endorsed by the Brunei Darussalam Embassy. In the absence of Brunei Darussalam Embassy, the certificate can be endorsed by the Notary Public.

MODEL CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Certificate of a Pharmaceutical Product[1]

This certificate conforms to the format recommended by the WHO (general instructions and explanatory notes attached)

Certificate No.: _____

Exporting (Certifying) country: _____

Importing (Requesting) country: _____

1. Name and dosage form of product:

_____

1.1 Active ingredients(s)[2] and amount(s)[3] per unit dose:

_____

_____

_____

For complete qualitative composition including excipients, see attached[4].

1.2 Is this product licensed to be placed on the market for use in the exporting country?[5]

□ Yes □ No

1.3 Is this product actually on the market in the exporting country?

□ Yes □ No □ Unknown

If the answer to 1.2 is yes, continue with section 2A and omit section 2B.

If the answer to 1.2 is no, omit section 2A and continue with section 2B[6].

2A.1 Number of product licence[7] and date of issue:

_____

2A.2 Product licence holder (name and address):

Name : _____

Address : _____

2A.3 Status of product licence holder: [8]

□ a □ b □ c

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are: [9]

Name : _____

Address : _____

2A.4 Summary Basis of Approval appended? [10]

□ Yes □ No

2A.5 Is the attached, officially approved product information complete and consonant with the licence? [11]

□ Yes □ No □ Not provided

2A.6 Applicant for the certificate (name and address):[12]

Name : _____

Address : _____

2B.1 Applicant for certificate (name and address):

Name : _____

Address : _____

2B.2 Status of applicant: [8]

□ a □ b □ c

2B.2.1 For categories b and c, the name and address of the manufacturer producing the dosage form is: [9]

Name : _____
Address : _____

2B.3 Why is marketing authorisation lacking?

□ not required □ under consideration
□ not requested □ refused

2B.4 Remarks: [13]

_____

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? [14]

□ Yes □ No □ N/A

If no or not applicable proceed to question 4.

3.1 Periodicity of routine inspection (years): _____

3.2 Has the manufacture of this type of dosage form been inspected?

□ Yes □ No

3.3 Do the facilities and operations conform to GMP as recommended by the WHO? [15]

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? [16]

If no explain: _____

Address of the certifying authority:

_____

Telephone number: _____

Fax Number: _____

Name of authorised person:

_____

Signature of authorised person:

_____

Stamp and date:

_____

Explanatory notes:

1. This certificate which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2. Use whenever possible, international Non-proprietary Names (INN) or national non-proprietary names.

3. The formula (complete) composition of dosage form should be given on the certificate or be appended.

4. Details of quantitative composition are preferred, but their provision is subject to the agreement of the product licence holder.

5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.

6. Sections 2A and 2B are mutually exclusive.

7. Indicate when applicable, if the licence is provisional, or the product has not yet been approved.

8. Specify whether the person responsible for placing the product on the market:
   (a) manufactures the dosage form;
   (b) packages and/or labels a dosage form manufactured by an independent company; or
   (c) is involved in non of the above

9. This information can be provided only with the consent of the product licence holder or, in the case of non registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.
   It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence must be updated or it will cease to be valid.

10. This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

11. This refers to the product information approved by the competent national regulatory authority, such as a Summary of Product Characteristics (SmPC).

12. In this circumstance, permission for issuing the certificate is required from the product licence holder. This permission must be provided to the authority by the applicant.

13. Please indicate the reason that the applicant has provided for not requesting registration:

    (a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases – not endemic in the country of export;
    (b) the product has been reformulated with a view to improving its stability under tropical conditions;
    (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
    (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
    (e) any reason, please specify.

14. Not applicable means that the manufacturer is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.

15. The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No. 823, 1992 Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992 Annex 1).

16. This section is to be completed when the product licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

ANNEX 1.4

GUIDELINE ON SUBMISSION OF PRODUCT LABELLING FOR APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS (PART I: SECTION 4)

- Applicant should provide samples or proposed drafts of product labelling for the application of registration of medicinal products.
- Language used for labelling shall be **English** and/or **Malay**.
- Samples or proposed drafts of the product labelling are for unit carton, inner label and blister/strips:

A. Labelling Parameters required for **UNIT CARTON**

1) Product Name
2) Dosage Form
3) Name of Active Ingredient(s)
4) Strength of Active Ingredients(s)
5) Batch Number
6) Manufacturing Date
7) Expiration Date
8) Route of Administration
9) Storage Condition
10) Country's Registration Number
11) Name and Address of Marketing Authorisation Holder
12) Name and Address of Manufacturer
13) Special Labelling (if applicable) e.g. Sterile, External Use, Cytotoxic, Alcohol Content, Animal Origin (Bovine, porcine)
14) Recommended Daily Allowance (For Vitamins and Minerals)
15) Warning (if applicable)
16) Pack sizes (Unit/Volume)

B. Labelling Parameters required for **INNER LABEL**

1) Product Name
2) Dosage Form*
3) Name of Active Ingredient(s)
4) Strength of Active Ingredients(s)
5) Batch Number
6) Manufacturing Date*
7) Expiration Date
8) Route of Administration
9) Storage Condition*
10) Country's Registration Number*
11) Name and Address of Marketing Authorisation Holder*
12) Name and Address of Manufacturer*
13) Special Labelling (if applicable) e.g. Sterile, External Use, Cytotoxic, Alcohol Content, Animal Origin (Bovine, porcine)*
14) Recommended Daily Allowance (For Vitamins and Minerals)*
15) Warning (if applicable)*
16) Pack sizes (Unit/Volume)

Note: * (exempted for small ampoule and vial)

C. Labelling Parameters required for **BLISTER/STRIPS**

1) Product Name
2) Name of Active Ingredient(s) #
3) Strength of Active Ingredient(s) #
4) Batch Number
5) Expiration Date
6) Name / Logo of Manufacturer / Product Owner / Marketing Authorisation Holder*
7) Country's Registration Number*

Notes:
 # (exempted for multi-ingredients products with more than 3 ingredients. For example multivitamins and multiminerals it is suggested to label as multivitamins and multiminerals.)

*** (optional)**

ANNEX 1.5

GUIDELINE ON SUBMISSION OF PRODUCT INFORMATION FOR APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS (PART I: SECTION 5)

- Applicant should provide samples or proposed drafts of product information for the application of registration of medicinal products.
- Language used for product information shall be **English** and/or **Malay**.
- Samples or proposed drafts of the product information are for Package Insert, Summary of Product Characteristics (Product Data Sheet) and Patient Information Leaflet (PIL).
- Package Insert is required for generic products; Summary of Product Characteristics (Product Data Sheet) is required for New Chemical Entity and Biotechnology products whereas PIL is required for Over -the Counter Products.

Note 1:
For a generic product, either Summary of Product Characteristics or Package Insert is acceptable.

Note 2:
The Summary of Product Characteristics, Package Insert and/or PIL approved for use in the Country of Origin must be submitted. Where a product has been given marketing authorisation in any of the benchmark regulatory agencies recognised by the Brunei Darussalam Medicines Control Authority (BDMCA) i.e. EU EMEA, UK MHRA, US FDA, Australia TGA, Malaysia DCA, Singapore HSA and Health Canada, the approved Summary of Product Characteristics, Package Inserts and PILs from at least **three** of these agencies should also be provided in the application dossier if applicable.

A. Parameters required for **PACKAGE INSERT:**

1) Product Name
2) Name and Strength of Active Ingredient(s)
3) Product Description
4) Pharmacodynamics/ Pharmacokinetics
5) Indication
6) Recommended Dose
7) Mode of Administration
8) Contraindication
9) Warnings and Precautions
10) Interactions With Other Medicaments
11) Pregnancy and Lactation
12) Undesirable Effects
13) Overdose and treatment
14) Storage Condition
15) Dosage Forms and packaging available
16) Name and Address of Manufacturer/Marketing Authorisation Holder
17) Date of Revision of Package Insert

B. Parameters required for **SUMMARY OF PRODUCT CHARACTERISTICS (PRODUCT DATA SHEET):**

1) Name of the Medical Product

   1.1 Product Name
   1.2 Strength
   1.3 Pharmaceutical Dosage Form

2) Quality and Quantitative Composition

   2.1 *Qualitative Declaration*
   The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.
   2.2 *Quantitative Declaration*
   The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per puff), per unit volume or per unit of weight.

3) Pharmaceutical Form
   Visual description of the appearance of the product (colour, markings, etc) e.g.: "Tablet White, circular flat bevelled edge tablets marked '100' on one side".

4) Clinical Particulars

   4.1 Therapeutic indications
   4.2 Posology and method of administration
   4.3 Contraindications
   4.4 Special warning and precautions for use
   4.5 Interaction with other medicinal products and other forms of interactions
   4.6 Pregnancy and lactation
   4.7 Effects on ability to drive and use machine
   4.8 Undesirable effects
   4.9 Overdose

5) Pharmacological Properties
   5.1 Pharmacodynamic Properties
   5.2 Pharmacokinetic Properties
   5.3 Preclinical safety Data

6) Pharmaceutical Particulars

   6.1 List of excipients
   6.2 Incompatibilities
   6.3 Shelf-life
      - Shelf-life of the medicinal product as packages for sale. Shelf-life after dilution or reconstitution according to directions. Shelf-life after first opening the container.
   6.4 Special precautions for storage
   6.5 Nature and contents of container

7) Marketing Authorisation Holder

8) Marketing Authorisation Number

9) Date of first authorisation/renewal of the authorisation

10) Date of revision of the text

C. Parameters required for **PATIENT INFORMATION LEAFLET (PIL):**

1) Name of Product
2) Description of Product
3) What is in the medicine?
4) Strength of the medicine
5) What is this medicine used for?
6) How much and how often should you use this medicine?
7) When should you not take this medicine?
8) Undesirable effects
9) What other medicine or food should be avoided whilst taking this medicine?
10) What should you do if you miss a dose?
11) How should you keep this medicine?
12) Signs & Symptoms of over dosage
13) What to do when you have taken more than the recommended dosage?
14) Name/Logo of Manufacturer/Importer/Marketing Authorisation Holder
15) Care that should be taken when taking this medicine?
16) When should you consult your doctor?
17) Date of Revision of PIL

ANNEX 2

GUIDE ON SUBMISSION OF NON-CLINICAL DOCUMENTS (PART III)

Non-clinical document is required for a submission of New Chemical Entity, Biotechnological Products and some Major Variation Products. It consists of 5 sections:

Section A: Table of Contents

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

Section B: Nonclinical Overview

1. General Aspect

2. Content and Structural Format

Section C: Nonclinical Summary (Written and Tabulated)

1. **Nonclinical Written Summaries**

   1.1 Introduction
   1.2 General Presentation Issues

2. **Nonclinical Written and Tabulated Summaries**

   2.1 Pharmacology

   2.1.1 Written Summary
   2.1.1.1 Primary Pharmacodynamics
   2.1.1.2 Secondary Pharmacodynamics
   2.1.1.3 Safety Pharmacology
   2.1.1.4 Pharmacodynamic Drug Interactions

   2.1.2 Tabulated Summary

   2.2 Pharmacokinetics

   2.2.1 Written Summary
   1.2.1.1 Absorption
   1.2.1.2 Distribution
   1.2.1.3 Metabolism
   1.2.1.4 Excretion
   1.2.1.5 Pharmacokinetic Drug Interaction (Non-clinical)
   1.2.1.6 Other Pharmacokinetic Studies

   2.2.2 Tabulated Summary

   2.3 Toxicology

   2.3.1 Written Summary
   2.3.1.1 Single-Dose Toxicity
   2.3.1.2 Repeat-Dose Toxicity
   2.3.1.3 Genotoxicity
   2.3.1.4 Carcinogenicity
   2.3.1.5 Reproduction and Developmental Toxicity
   2.3.1.5.1 Fertility and Early Embryonic Development
   2.3.1.5.2 Embryo-Fetal Development

2.3.1.5.3 Prenatal and Postnatal Development
2.3.1.6 Local Tolerance
2.3.1.7 Other Toxicity Studies (if available)

2.3.2 Tabulated Summary

Section D: Nonclinical Study Reports (As requested)

1. **Table of Contents**

2. **Study Report**

2.1 Pharmacology

2.1.1 Primary Pharmacodynamics
2.1.2 Secondary Pharmacodynamics
2.1.3 Safety Pharmacology
2.1.4 Pharmacodynamic Drug Interactions

2.2 Pharmacokinetics

2.2.1 Analytical Methods and Validation Reports
2.2.2 Absorption
2.2.3 Distribution
2.2.4 Metabolism
2.2.5 Excretion
2.2.6 Pharmacokinetic Drug Interaction (Non-clinical)
2.2.7 Other Pharmacokinetic Studies

2.3 Toxicology

2.3.1 Single-Dose Toxicity
2.3.2 Repeat-Dose Toxicity
2.3.3 Genotoxicity
2.3.3.1 *In-vitro* Reports
2.3.3.2 *In-vivo* Reports
2.3.4 Carcinogenicity
2.3.4.1 Long Term Studies
2.3.4.2 Short or Medium Term Studies
2.3.4.3 Other Studies
2.3.5 Reproductive and Developmental Toxicity
2.3.5.1 Fertility and Early Embryonic Development
2.3.5.2 Embryo-Fetal Development
2.3.5.3 Prenatal and Postnatal Development
2.3.5.4 Studies in which the Offspring Are Dosed and/or Further Evaluated
2.3.6 Local Tolerance
2.3.7 Other Toxicity Studies (if available)
2.3.7.1 Antigenicity
2.3.7.2 Immunotoxicity
2.3.7.3 Dependence
2.3.7.4 Metabolites
2.3.7.5 Impurities
2.3.7.6 Other

Section E: List of Key Literature References

A list of references used, stated in accordance with 1979 "Vancouver Declaration" on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", or the system used in "Chemical Abstracts", should be provided. Copies of important references cited in the Non-clinical Overview should be provided in this section. All references that have not been provided should be available upon request.

ANNEX 3

GUIDE ON SUBMISSION OF CLINICAL DOCUMENTS (PART IV)

Applications for registration of Medicinal Products that are classified as *New Chemical Entities (NCE), Biotechnological Products* and *other Major Variation Products* must be submitted using the following requirements:-

SECTION A: TABLE OF CONTENTS

A table of contents must be provided for each filed application.

SECTION B: CLINICAL OVERVIEW

The Clinical Overview is intended to provide a critical analysis of the clinical data and should provide as a useful reference to the overall clinical findings. It should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

This Clinical Overview should include:

1. Product Development Rationale
2. Overview of Biopharmaceutics
3. Overview of Clinical Pharmacology
4. Overview of Efficacy
5. Overview of Safety
6. Benefits and Risks Conclusions

SECTION C: CLINICAL SUMMARY

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the product dossier. This includes information provided in Clinical Study Reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Clinical Study Reports and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations.
This is in contrast to the Clinical Overview document which should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

The Clinical Summary should contain the following topics:

C1. Summary of Biopharmaceutic Studies and Associated Analytical Methods

1.1 Background and Overview
1.2 Summary of Results of Individual Studies
1.3 Comparison and Analyses of Results Across Studies

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

C2. Summary of Clinical Pharmacology Studies

2.1 Background and Overview
2.2 Summary of Results of Individual Studies
2.3 Comparison and Analyses of Results Across Studies
2.4 Special Studies
Example 1: Immunogenicity
Example 2: Clinical microbiology

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

C3. Summary of Clinical Efficacy

3.1 Background and Overview of Clinical Efficacy
3.2 Summary of Results of Individual Studies
3.3 Comparison and Analyses of Results Across Studies
3.4 Analysis of Clinical Information Relevant to Dosing Recommendations
3.5 Persistence of Efficacy and/or Tolerance Effects

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

C4. Summary of Clinical Safety

4.1 Exposure to the Drug
4.2 Adverse Events
4.3 Clinical Laboratory Evaluations
4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety
4.5 Safety in Special Groups and Situations
4.6 Post-marketing Data

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

C5. Synopses of Individual Studies

The length of a synopsis will usually be up to 3 pages, but a synopsis for a more complex and important study may be longer, e.g. 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

SECTION D: TABULAR LISTING OF ALL CLINICAL STUDIES

A tabular listing of all clinical studies and related information provided for each study should generally include the type of information identified in table 1 as appears in Appendix 5. Other information may be included in this table if it is considered useful. The sequence in which the studies are listed should follow the sequence described in E: Clinical Study Reports.

SECTION E: CLINICAL STUDY REPORTS (IF APPLICABLE)

The ICH E3 provides guidance on the organisation of clinical study reports, other clinical data, and references within the ASEAN Common Technical Dossier (ACTD) for registration of a pharmaceutical product for human use. In this case, the applicant will submit Section A, B, C. D and F.

The Clinical Study Report should consist of the following documents:

A. Table of Contents of Clinical Study Reports

B. Tabular Listing of All Clinical Studies

C. Clinical Study Reports:

1. Reports of Biopharmaceutic Studies -
   1.1 Bioavailability (BA) Study Reports
   1.2 Comparative BA and Bioequivalence (BE) Study Reports
   1.3 *In vitro-In vivo* Correlation Study Reports
   1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

2. Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials -
    2.1 Plasma Protein Binding Study Reports
    2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
    2.3 Reports of Studies Using Other Human Biomaterials

3. Reports of Human Pharmacokinetic (PK) Studies
    3.1 Healthy Subject PK and Initial Tolerability Study Reports
    3.2 Patient PK and Initial Tolerability Study Reports
    3.3 Population PK Study Reports

4. Reports of Human Pharmacodynamic (PD) Studies
    4.1 Healthy Subject PD and PK/PD Study Reports
    4.2 Patient PD and PK/PD Study Reports

5. Reports of Efficacy and Safety Studies
    5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    5.2 Study Reports of Uncontrolled Clinical Studies
    5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses
    5.4 Other Clinical Study Reports

6. Reports of Post-Marketing Experience

7. Case Report Forms and Individual Patient Listings

SECTION F: LIST OF KEY LITERATURE REFERENCES

This section should consist of a list of referenced documents comprising important published articles, official meeting minutes, or other regulatory guidance or advice. This includes all references cited in the Clinical Overview, and important references cited in the Clinical Summary or in the individual technical reports that were provided in Clinical Study Reports. Copies of referenced documents should be made available upon request.

APPENDIX 3

TABLE 1: LISTING OF CLINICAL STUDIES

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	20	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	Cross-over	Two tablet formulations, 50 mg, oral	32	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	Cross-over	Tablet, 50mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	24 (12 drug, 12 placebo)	Patients with primary hypertension	2 weeks	Ongoing; Interim
Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full

ANNEX 4

RECOMMENDED MODEL OF LETTER OF INTENT

COMPANY LETTERHEAD

APPLICANT'S COMPANY NAME
AND ADDRESS

DATE

Drug Registration Unit
Drug Administration Section
Department of Pharmaceutical Services
Block 2G:8:03, 8th Floor
Ong Sum Ping Condominium
Bandar Seri Begawan BA1111
Brunei Darussalam

Dear Sir / Madam

Re: Application for Medicinal Product Registration

We would like to apply for a registration of the following product::

PRODUCT NAME
DOSAGE FORM AND STRENGTH

with the Brunei Darussalam Medicines Control Authority (BDMCA). We enclose herewith the following documents as required, for your perusal:

Part I
Section I : Application Form (Form No: BDMCA/DPS/01)
Section II : Letter of Authorisation
Section III : *(Please list the certificates enclosed as appropriate)*
Section IV : Proposed artworks of Product Labelling for unit carton, inner label & blister strips.
Section V : Proposed Product Information for use in the Package Insert / Summary of Product Characteristics / Patient Information Leaflet.

Part II
Section I : Application Form for Quality requirements of the Drug Substance (Form No: BDMCA/DPS/02/A)
Section II : Application Form for Quality requirements of the Drug Product (Form No: BDMCA/DPS/02/B)

Part III & Part IV (If applicable)

With regards,

Applicant's signature

- -

Applicant's Name
& Designation

ANNEX 5.1

FORM NO.: BDMCA/DPS/01

DEPARTMENT OF PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH
BRUNEI DARUSSALAM

APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS

PART I - ADMINISTRATIVE DATA AND PRODUCT INFORMATION

SECTION 1: APPLICATION FORM

APPLICATION NO. (for DRU use only):	L	O	A	-	P	/			/	S							

Instruction:

1. Applicants are advised to refer to the 'DPS Guide to Application for Registration of Medicinal Products' and 'DPS Guide on How to Fill Up the Application Form for Registration of a Medicinal Product (Part I: Section 1) for guidance before filling up application form.
2. Only **one original copy** of the application form is required to be submitted per product. Form must be typed.
3. Completed form is to be sent to the Drug Registration Unit, Drug Administration Section, Department of Pharmaceutical Services, Block 2G:8:04, 8th Floor, Ong Sum Ping Condominium, Bandar Seri Begawan, BA1111, Brunei Darussalam.

1. 0	**COMPANY PARTICULARS**		
1.1	Name of Company (in block letters) (Please enclose a copy of the Letter of Authorisation from the Manufacturer under Part I – Section 2)		
	Address		
	Company Registration no. *(Please enclose a copy of certificate)*	Telephone no.	Fax no.

2.0	**APPLICANT PARTICULARS**			
2.1	Person authorised to submit and handle application on behalf of the company:			
	Name (Mr/Ms/Mrs/Mdm/Dr)			
	Designation			
	Address			
	Telephone no.	Fax no.	Official e-mail	Passport/IC no.

3. 0	**PRODUCT DETAILS**
3.1	Proprietary Name
3.2	Dosage Form
3.3	Product Description

3.4 Product Formula (If space is not sufficient please write on a separate sheet of A4 paper)

Name of substance	Grade	Strength
Active ingredient 1		
Active ingredient 2		
Excipient 1		
Excipient 2		
Excipient 3		
Excipient 4		

Note : Please state roles of excipient in the respective column indicated as as follows:
F – Flavouring, **C –** Colourant, **P** – Preservatives, **S** – Stabilisers

3.5 Please indicate whether any part of the product is derived from:

a) Human blood:
□ No □ Yes (State source: _____)

b) Animal source:
□ No □ Yes (State source: _____)

Additional data that needs to be submitted, please refer to Guide on How to Fill Up the Application Form (Form No: DPS/DRS/01) for Registration of Medicinal Products (Part 1:Section 1) Item 3.5a & 3.5b

3.6 Pharmacotherapeutic group by ATC Code, if available
[WHO ATC Code for the proposed indication(s)]

3.7 Route of Administration

3.8 Indication

3.9 Recommended Dosage

3.10 Therapeutic Advantage *(Please enclose Bioequivalence Studies under Part II – Section 2:P9)*

(If space is not sufficient please write on a separate sheet of A4 paper)

3.11 a) Packaging, Shelf-life & Storage Conditions

Container Closure System	Quantity/Container	Shelf-life	Storage Conditions	Pack size

b) Other shelf-life information:

(i) Shelf-life after first opening: _____(hours/days/months)
(ii) Shelf-life after reconstitution: _____ (hours/days/months)

3.12 Forensic Classification in Brunei Darussalam:

☐ Prescription Only Medicine(POM) ☐ Pharmacy Medicines(P) ☐ General Sale List Medicines(GSL)

3.13 Registration status in other countries (Please fill in where appropriate)

Country	Registration status with details and corresponding dates	Date	Approved classification of the product

Reminder:
1. Please enclose one certified copy of the Product Licence issued by the relevant authority (if available).
2. Please enclose an *original copy* of Certificate of Pharmaceutical Product (CPP) endorsed by the relevant authority from the country concerned.

Note: *Enclose all Certificates under Part I Section 3*

3.14 Proposed price of product:

a) Wholesale price: _____ b) Retail Price: _____

3.15 Product Owner Information

Name		
Address		
Telephone no.	Fax no.	Official e-mail

4.0 MANUFACTURER'S PARTICULARS

4.1 ACTIVE SUBSTANCE MANUFACTURER

No.	Name of Active Substance	Name of Manufacturer	Site Address	Office Address
1.				
2.				

Telephone no.	Fax no.	Official e-mail

4.2 FINISHED PRODUCT MANUFACTURER

No.	Name of Manufacturer	Manufacturing Operation	Site Address	Office Address
1.				
2.				

Telephone no.	Fax no.	Official e-mail

4.3 CONTRACT MANUFACTURER'S PARTICULARS (If applicable)

No.	Name of Contract Manufacturer	Manufacturing Operation	Site Address	Office Address
1.				
2.				

Telephone no.	Fax no.	Official e-mail

(For contract manufactured products, please enclose authentication from the contract provider and contract manufacturer)

5.0	**REPACKER'S PARTICULARS (If applicable)**		
5.1	Name of Repacker		
5.2	Site Address	Office Address	
	Telephone no.	Fax no.	Official e-mail

6.0	**BATCH RELEASE DETAILS**		
6.1	Information on Company / Agency Responsible For Batch Release In The Exporting Country		
	Name		
	Site Address	Office Address	
	Contact Person		
	Telephone no.	Fax no.	Official e-mail

7.0 DECLARATION

I, on behalf of the company named in Section 1.1, hereby

7.1 Declare that all particulars given in this application form are true

7.2 Declare that all annexes attached to this application form are true and that all existing data, reports and information, which are relevant to the benefit/risk assessment of the medicinal product, have been supplied.

7.3 Undertake to abide to the laws and legislations stated in the Medicines Order 2007.

7.4 Undertake to notify the Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam of any change in the particulars submitted in this application and of any new safety information during the course of evaluation and as long as the product remains on the market.

7.5 Confirm that the product will be recommended for use, sold and supplied in accordance with the approved package insert and in compliance with all licence conditions, applicable legislation and guidelines.

7.6 Undertake to notify the Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam if a product is rejected for registration in any drug regulatory authority.

I understand that a wilfully false statement is an offence under the Medicines Order 2007 and that all documents submitted for evaluation are not returnable.

Name (in block letters)
Passport/ IC No.
Designation
Signature Company Stamp

Date

FOR OFFICIAL USE	
PROCESSING FEE DETAILS Receipt No: …….. Amount Paid: ……. Name of Payee: ……	
Name & Signature of officer receiving the processing Fees: ……	**Received date:** ……
Notes:	

ANNEX 5.2

BDMCA/DPS/02/A

APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS

QUALITY REQUIREMENTS FOR DRUG SUBSTANCE (PART II – SECTION 1)

PRODUCT: REF.NO.

N.B. This is the recommended format for Part II – Section 1. Spacing should be adjusted by Applicant as and when necessary.

SECTION A

Table of contents for the filed application.

SECTION B

Checklist of tabulated information required for registration of medicinal product.

SECTION C

S1. IDENTITY OF DRUG SUBSTANCE

S1.1 Nomenclature
(State name against appropriate headings. Indicate clearly if heading is not applicable)

S1.1.1 International Non-Proprietary Name (INN)

S1.1.2 Compendial Name
i) British Approved Name (BAN)

ii) U.S Adopted Name (USAN)

S1.1.3 Chemical Abstract Service Registry Number (CAS)

S1.1.4 Laboratory Code, if applicable

S1.1.5 Chemical Name (IUPAC)

S1.2 Structural Formula

S1.2.1 Structural Formula (where applicable)

S1.2.2 Molecular Formula

S1.2.3 Relative Molecular Mass

S1.2.4 Schematic Amino Acid Sequence
(For biotechnological products only)

S1.3 General Properties

S1.3.1 Physicochemical Properties

S1.3.2 Biological Properties
(Biotechnological Products Only)

S2. MANUFACTURE OF DRUG SUBSTANCE

S2.1 Name and Address of Manufacturer

S2.2 Manufacturing Process and Process Control

Brief description of each stage of manufacturing / synthesis process, isolation and final purification of drug substance, including methods, materials used, reaction parameters and conditions, and precautions. Clearly state alternative steps, process and chemicals used.

Bibliography of Manufacturing Process and Process Control

Route of synthesis / chemical reactions / biological reactions, and flow chart for synthesis / manufacture. [ ]

S2.3 Quality Control of Starting Materials

S2.3.1 Specifications and Analytical Control of Materials used in Manufacture of Drug Substance

Materials	Control Specification(s)	Acceptance Limits	Source (For biotechnological products only)

S2.3.2 Criteria for Acceptance or Rejection

S2.4 Control of Critical Steps and Intermediates

S2.4.1 Critical Steps

Critical Steps	Control Specification(s)	Acceptance Limits

S2.4.2 Intermediates

Intermediates	Control Specification(s)	Acceptance Limits

S2.5 Process Validation and/or Evaluation

S2.6 Manufacturing Process Development
(Description of changes made to Manufacturing Process or Site)

S3. CHARACTERISATION

S3.1 Elucidation of Sructure and Characteristics

S3.1.1 Structure of Drug Substance
(Evidence of chemical structure, configuration, conformation, potential isomerism, polymorphism, etc. should be supported by infra-red spectra, UV characteristics, diagnostic chemical reaction, elemental analysis, etc.)

S3.1.2 Characteristics of Drug Substance

S3.1.3 Bibliography [ ]
(Structure and characteristics of drug substance)

S3.2 Impurities

S3.2.1 Research and Development Studies
(Give list and brief discussion of impurities considered and studied during research and development of ingredient. Negative results should also be included.)

S3.2.2 Routine Impurities Control – Summary of impurities monitored or tested for during and after manufacture of ingredient.

Impurities Monitored	Analytical Method Used (E.g. TLC, HPLC,	Acceptance Limits

chemical test, IR

spectroscopy, atomic

absorption, etc)

S3.2.3 Bibliography [ ]
(Research and Development Studies on Impurities; Routine Impurities Control)

S4. QUALITY CONTROL OF DRUG SUBSTANCE

S4.1 Specifications for Drug Substance
(N.B. – If information is substantially the same as that already supplied in Part II – Section 2, Item 5.2, appropriate references may be made)

S4.1.1 Test and Specifications
(Release Specification)

List quality control specifications and tests for the drug substance. Indicate clearly, if test is not performed / specification not checked for every batch of material, the frequency of test or circumstance under which test is done.

Specification (Tests)	Acceptance Limits (B.P/U.S.P./ Manufacture's/etc)	Reference for Specification	Frequency of Test/ Circumstance for test, if not done on every batch

S4.1.2 Source of Drug Substance

S4.1.3 Responsible Laboratory

S4.2 Analytical Procedures

Certificate of Analysis of Drug Substance [ ]

S4.3 Validation of Analytical Procedures

S4.4 Batch Analyses

Experimental data that demonstrates the nine validation characteristics [ ]

Analytical reports of recent batches of active ingredient (about 3 batches) which are representative of material used for manufacture of product seeking registration

enclosed. [ ]

Analytical reports for batches used for toxicity tests and clinical work submitted in support of the drug registration application, if different from the above. [ ]

S4.5 Justification of Specification

Specification	Analytical Procedure	Acceptance Criteria	Justification

S5. REFERENCE STANDARDS OR MATERIALS

S6. CONTAINER CLOSURE SYSTEM

S6.1 Immediate Container Closure System / Packaging

Type:

Material :

Capacity (where applicable):

Closure and liner (type and material) :
(where applicable)

Name and Address of Manufacturer:

Specifications:

S6.2 Outer Container(s) / Packaging(s)

Type:

Material :

Capacity (where applicable):

Closure and liner (type and material) :

(where applicable)

Name and Address of Manufacturer:

Specifications:

S6.3 Suitability of Packagings

S7. STABILITY

S7.1 Stability Studies Summary and Conclusion

Outline of stability studies (batches examined, study parameters, length of study characteristics, or degradation products monitored, storage conditions, analytical methods, etc.)	Summary of results and conclusions of study

General Observations and Conclusions on Stability of Active Ingredient

Details of completed stability studies, place of study, protocols, analytical methods, results and conclusions, etc. enclosed. [ ]

S7.2 Post-Approval Stability Protocol and Stability Commitment

On-going / Proposed Stability Studies
(Outline of on-going or proposed stability studies)

Details of on-going/proposed stability studies, protocols, analytical methods, etc. enclosed. [ ]
N.B. Results and conclusions of studies shall be submitted to The Authority on completion of such studies.

S7.3 Stability Data

Report on stability study that includes batches examined, conditions of storage, containers, duration of study, monitoring changes, analytical methods, results from data generated and conclusion.

SECTION D

Summary of Other Data

Bibliography of Relevant Data

N.B. Details of data particulars, full reports of studies including methodology, protocols, analytical methods, results, interpretation, conclusion, copies of papers, articles, etc. referenced and relevant supporting documents shall be kept by the applicant and submitted to the Authority immediately on request.

Manufacturer

SIGNATURE : .....

NAME : .....

OFFICIAL DESIGNATION : .....

Applicant

SIGNATURE : .....

NAME : .....

DATE : .....

ANNEX 5.3

BDMCA/DPS/02/B

APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS

QUALITY REQUIREMENTS FOR DRUG PRODUCT (PART II – SECTION 2)

PRODUCT: REF.NO.

N.B. This is the recommended format for Part II – Section 2. Spacing should be adjusted by Applicant as and when necessary. Extension sheets for details and supporting documents should be appropriately numbered and referenced.

SECTION A

Table of contents for the filed application.

SECTION B

Checklist of tabulated information required for registration of medicinal product.

SECTION C

P1. DRUG PRODUCT

P1.1 Description (Physical Characteristics)

P1.2 Composition (Complete Formula)

P1.2.1 Active Ingredient(s)

Name of Active Ingredient(s)	Content

P1.2.2 Other Ingredients
(adjunct, excipients, colour, preservative, flavour, etc)

Name of Ingredient(s)	Content	Function

P1.2.3 Overages (where applicable)

Name of Ingredient(s)	Overage (To include reasons for including overage)

P1.3 Description of Reconstitution Diluents, if applicable

P1.4 Type of Container Closure System / Pack Size (Briefly)

P2. PHARMACEUTICAL DEVELOPMENT

P2.1 Information on Development Studies
(Applicable to NCE and Biotechnological Products Only)

P2.1.1 Product Development and its Manufacturing Process

P2.1.2 Bibliography of Development Studies

P2.2 Component of Drug Product

P2.2.1Drug Substance

State briefly the characteristics-performance relationship of the drug substance, mentioning also, where applicable, and its compatibility with excipients listed in Item P2.1.1 and other drugs in the same formulation.

P2.2.2 Excipients

State briefly the concentration and characteristics of excipients that can influence product performance, also mentioning, compatibility of the excipients with each other.

P2.3 Drug Product

P2.3.1 Formulation Development

i) State briefly structure-active relationship of drug substance putting into consideration the proposed route of administration and usage.

ii) Highlight evolution of formulation design from initial concept to final

design of drug substance.

iii) Summarise all formulations used, including changes made, between proposed commercial formulation and those used in pivotal clinical batches and primary stability batches. Also provide the rationale for changes made, if any.

iv) Manufacturer's comparative in-vitro studies and standards, as well as in-vivo studies and standards for the release of active ingredients. (For example, dissolution, diffusion, etc.)

v) Identification of special design features and rationale for their use.

vi) Rationale for special formulations.

Detail of tests, analytical methods and test protocols enclosed. [ ]

Summary of in-vitro and in-vivo studies on release rates of product by other investigators. [ ]

Details of test/studies, analytical methods, test protocols reports of studies, and supporting documents enclosed. [ ]

Bibliography of comparative in-vitro and in-vivo studies for release rates. [ ]

P2.3.2 Overages

P2.3.3 Physicochemical and Biological Properties

P2.4 Manufacturing Process Development

P2.4.1 Development of Manufacturing Process for Commercial Production Batches

P2.4.2 Differences between Manufacturing Process(es) Used for Pivotal Clinical Batches and Commercial Production Batches that can Influence Performance and Manufacturability of Drug Product

P2.5 Container Closure System

P2.5.1 Suitability of Container Closure System

P2.5.2 Performance of Dosing Device

P2.6 Microbiological Attributes

P2.6.1 Non-Sterile Products

P2.6.2 Selection of Preservative Systems

P2.6.3 Container Closure System of Sterile Preparation

P2.7 Compatibility

Summary of compatibility studies of drug product with primary container closure system, product accessories and reconstitution diluents.

P3. MANUFACTURE OF PRODUCT

P3.1 Batch Manufacturing Master Formula

Name of Ingredients (Active and otherwise)	Quantities Used per Batch	Batch Size

Stages of Manufacturing

P3.2 Manufacturing Process & Process Control

P3.2.1 Brief Description and Principles

Detailed manufacturing process enclosed [ ]

P3.2.2 In-process Quality Control (IPQC)

Tests performed during manufacturing process and sampling protocols.

Tests	Stage at which test is done	Frequency of sampling	Quality of sample taken each time

Details of test, test protocols, analytical methods specification limits and sampling plans enclosed [ ]

P3.3 Controls of Critical Steps and Intermediates

P3.3.1 Critical Steps

Critical Steps	Control Specifications	Acceptance Limits

P3.3.2 Intermediates

Intermediates	Control Specifications	Acceptance Limits

P3.4 Process Validation and/or Evaluation

P4. QUALITY CONTROL OF EXCIPIENTS

P4.1 Specification for Excipients

Name of Excipients	Specifications (State whether B.P/ U.S.P/ manufacturer's, etc)	Acceptance Limits (Manufacturer and country of origin)	Source

Details of specifications tests, test protocols, analytical methods, sampling protocols, etc. enclosed. [ ]

P4.2 Analytical Procedures
(Refer to Annex A)

P4.2.1 Description of Analytical Procedures

P4.2.2 Source of Compliance

State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.

If quality control tests are done by an external laboratory, state the following:

i) Name and address of the laboratory;
ii) Tests done by the external laboratory;
iii) Reasons why the tests are not done by the manufacturer;
iv) Whether the manufacturer or the external laboratory is responsible for deciding if a batch of product is suitable for release for marketing.

Certificate of Analysis for Compliance of Purchase Specifications [ ]

P4.3 Excipients of Human and Animal Origin

P4.3.1 Description

P4.3.2 Specification

P4.3.3 Sources

P4.3.4 Viral Safety Data

P4.4 Novel Excipients

P4.4.1 Manufacture of Excipients

P4.4.2 Safety Characteristics

P5. QUALITY CONTROL OF FINISHED PRODUCT

P5.1 Specifications for Ingredients
(active and otherwise)

Name of Ingredients	Specifications (State whether B.P/U.S.P/ manufacturer's, etc)	Acceptance Limits	Source (Manufacturer and country of origin)

Details of specifications tests, test protocols, analytical methods, sampling protocols, etc. enclosed. [ ]

Certificate of Analysis of two recent batches of finished product enclosed. [ ]

P5.2 Analytical Procedures
(Refer to Annex A)

State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.

If quality control tests are done by an external laboratory, state the following:

i) Name and address of the laboratory;
ii) Tests done by the external laboratory;
iii) Reasons why the tests are not done by the manufacturer;
iv) Whether the manufacturer or the external laboratory is responsible for deciding if a batch of product is suitable for release for marketing.

Certificate of Analysis for Compliance to Purchase Specification [ ]

P5.3 Validation of Analytical Procedures Used
(Refer to Annex C)

P5.4 Batch Analyses Report

P5.4.1 Description of Batches Analysed

P5.4.2 Results of Tests Conducted on All Relevant Batches

Analytical reports of recent batches of finished product which are representative of product seeking registration. [ ]

P5.5 Characterisation of Impurities

Summary of impurities monitored or tested for during and after manufacture of drug product.

Impurities Monitored	Analytical Method Used (E.g. TLC, HPLC, chemical test, IR spectroscopy, atomic absorption, etc)	Acceptance Limits

Analytical reports for batches used for toxicity tests and clinical work submitted in support of the drug registration application, if different from the above [ ]

P5.6 Justification of Specification

Specification	Analytical Procedure	Acceptance	Justification Limits

P6. REFERENCE STANDARDS OR MATERIALS

P6.1 Reference Standards or Materials Used for Testing

P6.2 Purity
(Measurement by Quantitative Procedures)

P7. CONTAINER CLOSURE SYSTEM / PACKAGING

P7.1 Immediate Container Closure System / Primary Packaging

Type:

Material :

Capacity (where applicable):

Closure and liner (type and material) :
(where applicable)

Name and Address of Manufacturer:

Specifications:

P7.2 Outer Container(s) / Secondary Packaging(s)

Type:

Material :

Capacity (where applicable):

Closure and liner (type and material) :
(where applicable)

Name and Address of Manufacturer:

Specifications:

Product Accessories

Description/Type:

Material :

P7.3 Packaging Inclusions
(Dose-measuring device/applicators/administration set/desiccant/ fillers/ etc., if any)

Description:

Material and Composition:

Reasons for Inclusion:

Capacity (where applicable):

Name and address of Manufacturer:

Specification:

Duration of Satisfactory Performance:
(where applicable)

Instruction to users:

P7.4 Other Supporting Data

The application must have ready details of containers and packaging materials - composition of material and added substances, technical properties and specifications, methods for testing relevant properties/specifications, safety or toxicity of material and added substances, efficacy of closures in manufacturing sterile products, compatibility of inclusions with finished product, etc.

However, DO NOT enclose such details and supporting documents. The applicant shall be notified when such details are needed; they shall be made available to the Authority immediately on request.

Suitability information should be referred under Item P2.5.

P8. PRODUCT STABILITY

P8.1 Storage Conditions Included on Label

P8.2 Proposed Shelf-life of Product

P8.3 Stability Studies Summary and Conclusion

Completed Stability Studies
(Summary of stability studies, characteristics and degradation products monitored, results and conclusions of completed stability studies). Results of studies on at least 2 batches are required.

Details of completed stability studies, place of study, protocols, analytical methods, results and conclusions, etc. enclosed. [ ]

P8.4 Post-approval Stability Protocol and Stability Commitment

On-going / Proposed Stability Studies
(Outline of on-going or proposed stability studies)

Details of on-going/proposed stability studies, protocols, analytical methods, etc. enclosed. [ ]

N.B. Results and conclusions of studies shall be submitted to The Authority on completion of such studies.

P8.5 Stability Data Reports

Report on stability study that include batches examined, conditions of storage, container closure systems, duration of study, monitoring of changes, analytical methods, results of study, and conclusion.

P9. PRODUCT INTERCHANGEABILITY
(Applies to Major Variation and Generic Products Only)

P9.1 Type of Studies Conducted

P9.2 Protocols Used & Result of Studies Conducted

SECTION D

Summary of Other Data

Bibliography of Relevant Data

N.B. Details of data particulars, full reports of studies including methodology, protocols, analytical methods, results, interpretation, conclusion, copies of papers, articles, etc. referenced and relevant supporting documents shall be kept by the applicant and submitted to the Authority immediately on request.

Manufacturer

SIGNATURE : .....

NAME : .....

OFFICIAL DESIGNATION: .....

Applicant

SIGNATURE : .....

NAME : .....

DATE : .....

ANNEX 6.1

CHECKLIST FOR SUBMISSION OF APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS
PART 1 REQUIREMENT (ADMINISTRATIVE DATA & PRODUCT INFORMATION)

Application No:	**L O A - P / / S**
Product Name:	
Name of Applicant:	

No.	Items	Applicant	DRU
1.	Letter of Intent		
2.	**Section 1** - **Application form (Form No: BDMCA/DPS/01)**		
	2.1 Form signed by applicant		
3.	Processing fee of B$200.00		
4.	Company Registration Certificate		
5.	**Section 2** - **Letter of authorisation from the product owner / manufacturer**		
6.	**Section 3** – **Certifications**		
	6.1 For contract manufacturing**:**		
	6.1.1 Copy of licence of pharmaceutical industries and contract manufacturer endorsed by the Brunei Darussalam Embassy / Notary Public		
	6.1.2 Copy of contract manufacturing agreement endorsed by the Brunei Darussalam Embassy / Notary Public		
	6.1.3 Original copy of GMP certificate of contract manufacturer		
	6.2 For manufacturing "under licence":		
	6.2.1 Copy of licence of pharmaceutical industries endorsed by the Brunei Darussalam Embassy / Notary Public.		
	6.2.2 Original copy of GMP certificate of the manufacturer		
	6.2.3 Copy of "under-licence" agreement endorsed by the Brunei Darussalam Embassy / Notary Public		
	6.3 For locally manufactured products (excluding the above):		
	6.3.1 Copy of licence of pharmaceutical industries		
	6.3.2 Original copy of GMP certificate of the manufacturer		
	6.4 For imported products		
	6.4.1 Copy of Licence of pharmaceutical industries; importers and wholesalers		
	6.4.2 Original copy of certificate of pharmaceutical product issued by the competent authority in the country of origin. Certificate is not more than 2 years from the date of issue		
	6.4.3 Copy of GMP certificate of the manufacturer endorsed by the Brunei Darussalam Embassy/Notary Public or site master file of the manufacturer (unless previously submitted within the last 2 years and if GMP certificate cannot be produced) [Optional]		
7.	**Section 4** – **Product Labelling**		
	7.1 Unit carton		
	7.2 Inner label		
	7.3 Blister / strips		
8.	**Section 5** – **Product Information**		
	8.1 Proposed Package Insert for generic products.		
	8.2 Proposed Summary of Product Characteristics (SPC) for generic products (*optional*), new chemical entity and biotechnology products		
	8.3 Patient Information Leaflet (PIL) for over-the counter products		
	8.4 Approved Summary of Product Characteristic / package insert / PIL from at least three benchmark regulatory agencies (*if applicable*) recognised by DPS including the regulatory agency of the Country of Origin.		
9.	Application documents arranged in proper order, clearly indicated and filed		
10.	Additional documents required by DRU from the applicant:		

ANNEX 6.2

CHECKLIST ON DOCUMENTS SUBMITTED
PART II - SECTION 1: QUALITY REQUIREMENTS FOR DRUG SUBSTANCE

PRODUCT:	REFERENCE NO:

No.	Documents Required		APPLICANT					DRU	DRU REMARKS
			APPLICATION TYPE						
			NCE	Biotech	MaV	MiV	G		
SECTION A – Drug Substance									
	Table of Contents		☐	☐	☐	☐	☐	☐	
SECTION B – Quality Overall Summary									
S1.	**General Information**								
	1.1	Nomenclature	☐	☐	*☐		☐	☐	
	1.2	Structure	☐	☐			☐	☐	
	1.3	General Properties	☐	☐	*☐		☐	☐	
S2.	**Manufacture**								
	2.1	Manufacturer(s) Name and Address	☐	☐			☐	☐	
	2.2	Description of Manufacturing Process and Process Controls	☐	☐				☐	
	2.3	Quality Control of Starting Materials	☐	☐				☐	
	2.4	Controls of Critical Steps and Intermediates	☐	☐				☐	
	2.5	Process Validation and/or Evaluation	☐	☐				☐	
	2.6	Manufacturing Process Development	☐	☐				☐	

No.	Documents Required		APPLICANT					DRU	DRU REMARKS
			APPLICATION TYPE						
			NCE	Biotech	MaV	MiV	G		
S3.	**Characterisation**								
	3.1	Elucidation of Structure and Other Characteristics	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			☐	☐	☐	☐	
	3.2	Impurities	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.					☐	☐	
S4.	**Control of Drug Substance**								
	4.1	Specification	☐	☐				☐	
		• Compendial specifications or equivalent information from the manufacturer.			☐	☐	☐	☐	
	4.2	Analytical Procedures	☐	☐				☐	
		• Compendial methods or equivalent information from the manufacturer.			☐	☐	☐	☐	
	4.3	Validation of Analytical Procedures	☐	☐				☐	
		• Required for non-compendial method only.			☐	☐	☐	☐	
	4.4	Batch Analyses	☐	☐				☐	
		• Analytical Reports of <u>three recent batches</u> is required.	☐	☐				☐	
	4.5	Justification of Specification	☐	☐				☐	
S5.	**Reference Standards or Materials**		☐	☐				☐	
		• Compendial requirements or equivalent information from manufacturer.			*☐	*☐	☐	☐	

No.	Documents Required	APPLICANT					DRU	DRU REMARKS
		APPLICATION TYPE						
		NCE	Biotech	MaV	MiV	G		
S6.	**Container Closure System**	☐	☐				☐	
S7.	**Stability**							
	Stability Report	☐	☐				☐	
	• Manufacturer stability data or equivalent information.			*☐	*☐	☐	☐	
S8.	**Other Data, if any**	☐	☐	☐	☐	☐	☐	

Note: Please refer to the **Guide to Application for Registration of Medicinal Products** for the specific requirements of each Application Type

Key:

*****	**:**	If required	**MaV**	**:**	Major Variation
NCE	**:**	New Chemical Entity	**MiV**	**:**	Minor Variation
Biotech	**:**	Biotechnological Products	**G**	**:**	Generics

ANNEX 6.3

CHECKLIST ON DOCUMENTS SUBMITTED
PART II - SECTION 2: QUALITY REQUIREMENTS FOR DRUG PRODUCT

PRODUCT:	REFERENCE NO:

No.	Documents Required		APPLICANT					DRU	DRU REMARKS
			APPLICATION TYPE						
			NCE	Biotech	MaV	MiV	G		
SECTION A – Drug Product									
	Table of Contents		☐	☐	☐	☐	☐	☐	
SECTION B – Quality Overall Summary									
P1.	**General Information**								
	1.1	Description (Physical Characteristics)	☐	☐	*☐	*☐	☐	☐	
	1.2	Composition (Complete Formula)	☐	☐	*☐	*☐	☐	☐	
P2.	**Pharmaceutical Development**								
	2.1	Information on Development Studies	☐	☐				☐	
	2.2	Components of Drug Product	☐	☐				☐	
		• Literature data.			*☐	*☐	☐	☐	
	2.3	Finished Product							
		• Formulation Development	☐	☐			☐	☐	
		• Overages	☐	☐			☐	☐	
		• Physicochemical & Biological Properties	☐	☐			☐	☐	
	2.4	Manufacturing Process Development	☐	☐				☐	
	2.5	Container Closure System	☐	☐			☐	☐	
	2.6	Microbiological Attributes	☐	☐	*☐		☐	☐	

No.	Documents Required		APPLICANT					DRU	DRU REMARKS
			APPLICATION TYPE						
			NCE	Biotech	MaV	MiV	G		
	2.7	Compatibility	☐	☐				☐	
		• Literature data.			*☐	*☐	☐	☐	
P3.	**Manufacture**								
	3.1	Batch Formula	☐	☐	*☐		☐	☐	
	3.2	Manufacturing Process and Process Control	☐	☐	*☐	*☐	☐	☐	
	3.3	Controls of Critical Steps and Intermediates	☐	☐			☐	☐	
	3.4	Process Validation and/or Evaluation	☐	☐			☐	☐	
P4.	**Control of Excipients**								
	4.1	Specifications	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			*☐	*☐	☐	☐	
	4.2	Analytical Procedures	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			*☐	*☐	☐	☐	
	4.3	Excipients of Human and Animal Origin	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			*☐	*☐	☐	☐	
	4.4	Novel Excipients	☐	☐				☐	
P5.	**Control of Finished Products**								
	5.1	Specifications	☐	☐	*☐	*☐	☐	☐	
		• Certificate of Analysis of two recent batches of finished product.	☐	☐	*☐	*☐	☐	☐	
	5.2	Analytical Procedures	☐	☐	*☐	*☐	☐	☐	

No.	Documents Required		APPLICANT					DRU	DRU REMARKS
			APPLICATION TYPE						
			NCE	Biotech	MaV	MiV	G		
	5.3	Validation of Analytical Procedures	☐	☐	*☐	*☐	☐	☐	
	5.4	Batch Analyses	☐	☐				☐	
		• A tabulated summary of batch analyses should be provided.			☐	☐	☐	☐	
	5.5	Characterisation of Impurities	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			*☐	*☐	☐	☐	
	5.6	Justification of Specification	☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			*☐	*☐	☐	☐	
P6.	**Reference Standards or Materials**		☐	☐				☐	
		• Compendial requirements or equivalent information from the manufacturer.			*☐	*☐	☐	☐	
P7.	**Container Closure System**		☐	☐	*☐	*☐	☐	☐	
P8.	**Stability**								
		Stability Report	☐	☐	*☐		☐	☐	
P9.	**Product Interchangeability**				*☐		☐	☐	

Note: Please refer to the **Guide to Application for Registration of Medicinal Products** for the specific requirements of each Application Type

Key:

*****	**:**	If required	**MaV**	**:**	Major Variation
NCE	**:**	New Chemical Entity	**MiV**	**:**	Minor Variation
Biotech	**:**	Biotechnological Products	**G**	**:**	Generics

ANNEX 6.4

CHECKLIST FOR SUBMISSION OF APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS
PART III REQUIREMENTS (NONCLINICAL DOCUMENT)

The table below provides as a checklist of information required for the application of registration of medicinal products for the various product classifications.

Product Name:		**Reference No.:**

Part III: Document	**APPLICANT Application Type**							**DRU**	**DRU Remarks**
			MaV			**MiV**	**GP**		
	NCE	**BIOTECH**	**RT**	**S/P**	**IND**				
Section A. Table of Content	☐	☐	☐	☐	☐				
Section B. Nonclinical Overview	☐	☐							
1. General Aspect	☐	☐							
2. Content and structural format	☐	☐							
Section C. Nonclinical Summary (Written and Tabulated)	☐	☐							
3. **Nonclinical Written Summaries**	☐	☐							
3.1 Introduction	☐	☐							
3.2 General Presentation Issues	☐	☐							
4. **Nonclinical Written and Tabulated Summaries**	☐	☐							
4.1 Pharmacology									
2.1.1 Written summary	☐	☐							
2.1.1.1 Primary Pharmacodynamics	☐	☐							
2.1.1.2 Secondary Pharmacodynamics	☐	☐							
2.1.1.3 Safety Pharmacology	☐	☐							
2.1.1.4 Pharmacodynamics Drug Interactions	☐	☐							
2.1.1.5 Tabulated Summary	☐	☐							

Part III: Document	APPLICANT Application Type							DRU	DRU Remarks
			MaV			MiV	GP		
	NCE	BIOTECH	RT	S/P	IND				
4.2 Pharmacokinetics									
Written summary	☐	☐							
1.2.1.1 Absorption	☐	*☐	*☐	*☐					
2.2.1.1 Distribution	☐	*☐	*☐	*☐					
3.2.1.1 Metabolism	☐	*☐	*☐	*☐					
4.2.1.1 Excretion	☐	*☐	*☐	*☐					
5.2.1.1 Pharmacokinetics Drug Interactions (non-clinical)	☐								
6.2.1.1 Other Pharmacokinetic Studies	☐		*☐						
Tabulated Summary	☐	☐							
4.3 Toxicology									
Written Summary	☐	☐							
1.2.1.1 Single dose toxicity	☐	☐							
2.2.1.1 Repeat dose toxicity	☐	☐							
3.2.1.1 Genotoxicity	☐								
4.2.1.1 Carcinogenicity	☐	**☐							
5.2.1.1 Reproductive and developmental toxicity	☐	☐							
4.3..5.1 Fertility and early embryonic development	☐	☐							
4.3..5.2 Embryo-fetal development	☐	☐							
4.3..5.3 Pre-natal and post-natal development	☐	☐							
6.2.1.1 Local tolerance	**☐	**☐	**☐	**☐	**☐				
7.2.1.1 Other toxicity studies, if available	**☐	**☐	**☐	**☐	**☐				
Tabulated Summary	☐	☐							

Section D. Nonclinical Study Report (As requested)									
1. **Table of Content**	☐	☐							
2. **Study Reports**									
2.1 Pharmacology									
2.1.1 Primary Pharmacodynamics	☐	☐							
2.1.2 Secondary Pharmacodynamics	☐	☐							
2.1.3 Safety Pharmacology	☐	☐							
2.1.4 Pharmacodynamic Drug Interactions	☐	☐							
2.2 Pharmacokinetics									
2.2.1 Analytical Methods and Validation Reports	☐	*☐							
2.2.2 Absorption	☐	*☐	*☐	*☐					
2.2.3 Distribution	☐	*☐	*☐	*☐					
2.2.4 Metabolism	☐	*☐	*☐	*☐					
2.2.5 Excretion	☐	*☐	*☐	*☐					
2.2.6 Pharmacokinetics Drug Interaction (non-clinical)	☐	*☐							
2.2.7 Other Pharmacokinetic Studies	☐	*☐	*☐						
2.3 Toxicology									
2.3.1 Single dose toxicity	☐	☐							
2.3.2 Repeat dose toxicity	☐	☐							
2.3.3 Genotoxicity	☐								
2.3.3.1 *In vitro*	☐								
2.3.3.2 *In vivo*	☐								
2.3.4 Carcinogenicity	☐	*☐							
2.3.4.1 Long-term studies	☐	*☐							
2.3.4.2 Short-or medium-term studies	☐	*☐							
2.3.4.3 Other studies	☐	*☐							

2.3.5 Reproductive and developmental toxicity	☐	☐							
2.3.5.1 Fertility and early embryonic development	☐	☐							
2.3.5.2 Embryo-fetal development	☐	☐							
2.3.5.3 Pre-natal and post-natal development	☐	☐							
2.3.5.4 Studies in which the offspring are dosed and/or further evaluated	☐	☐							
2.3.6 Local tolerance	*☐	*☐	*☐	*☐	*☐				
2.3.7 Other Toxicity Studies, if available	*☐	*☐	*☐	*☐	*☐				
2.3.7.1 Antigenicity									
2.3.7.2 Immunotoxicity									
2.3.7.3 Dependence									
2.3.7.4 Metabolites									
2.3.7.5 Impurities									
2.3.7.6 Other									
Section E. List of Key Literature References	☐	☐	*☐	*☐	*☐				

NCE - New chemical entity
Biotech - Biotechnology-derived product
MaV - Major variation *(Pharmaceutical product that have undergone variation affecting one or more of the following : the route of administration, strength and posology, indications. The submission of additional data is required and necessary to establish the quality, safety and efficacy of the new formulation resulting from the variation)*
RT - Route of administration
S / P - Strength and Posology
IND - Indication
MiV - Minor Variation *(Pharmaceutical product that have undergone variation affecting one or more of the following : route of administration, strength and posology, indications or active ingredient/s. The submission of additional data is required and necessary to establish the quality of the new formulation resulting from the variation)*
GP - Generic product
*☐ - Where applicable, i.e. change of route of administration due to change in formulation
**☐ - Generally inappropriate for biotechnology-derived products, however, product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and /or biological activity of the product (eg. Growth factors, immunosuppressive agents, etc

ANNEX 6.5

CHECKLIST FOR SUBMISSION OF APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS
PART IV REQUIREMENTS (CLINICAL DOCUMENT)

The table below provides as a checklist of information required for the application of registration of medicinal products for the various product classifications.

Product Name:		**Reference No.:**	

Section	Document	APPLICANT							DRU	DRU Remarks
		APPLICATION TYPE								
		NCE	BIOTECH	MaV			MiV	GP		
				RT	S/P	IND				
A	**Table of Contents**	☐	☐	☐	☐	☐				
B	**Clinical Overview**	☐	☐	☐	☐	☐				
	1. Product Development Rationale	☐	☐	☐	☐	☐				
	2. Overview of Biopharmaceutics	☐	☐	☐	☐	☐				
	3. Overview of Clinical Pharmacology	☐	☐	☐	☐	☐				
	4. Overview of Efficacy	☐	☐	☐	☐	☐				
	5. Overview of Safety	☐	☐	☐	☐	☐				
	6. Benefits and Risks Conclusions	☐	☐	☐	☐	☐				
C	**Clinical Summary**	☐	☐	☐	☐	☐				
	C1. Summary of Biopharmaceutic Studies and Associated Analytical Methods	☐	☐	☐	☐	☐				
	1.1 Background and Overview	☐	☐	☐	☐	☐				
	1.2 Summary of Results of Individual Studies	☐	☐	☐	☐	☐				
	1.3 Comparison and Analyses of Results Across Studies	☐	☐	☐	☐	☐				
	Appendix 1	☐	☐	☐	☐	☐				

Section	Document	APPLICANT							DRU	DRU Remarks
		APPLICATION TYPE								
		NCE	BIOTECH	MaV			MiV	GP		
				RT	S/P	IND				
	C2. Summary of Clinical Pharmacology Studies	☐	☐	☐	☐	☐				
	2.1 Background and Overview	☐	☐	☐	☐	☐				
	2.2 Summary of Results of Individual Studies	☐	☐	☐	☐	☐				
	2.3 Comparison and Analyses of Results Across Studies	☐	☐	☐	☐	☐				
	2.4 Special Studies	☐	☐	☐	☐	☐				
	Appendix 2	☐	☐	☐	☐	☐				
	C3. Summary of Clinical Efficacy	☐	☐	☐	☐	☐				
	3.1 Background and Overview of Clinical Efficacy	☐	☐	☐	☐	☐				
	3.2 Summary of Results of Individual Studies	☐	☐	☐	☐	☐				
	3.3 Comparison and Analyses of Results Across Studies	☐	☐	☐	☐	☐				
	3.4 Analysis of Clinical Information Relevant to Dosing Recommendations	☐	☐	☐	☐	☐				
	3.5 Persistence of Efficacy and/or Tolerance Effects	☐	☐	☐	☐	☐				
	Appendix 3	☐	☐	☐	☐	☐				
	C4. Summary of Clinical Safety	☐	☐	☐	☐	☐				
	4.1 Exposure to the Drug	☐	☐	☐	☐	☐				
	4.2 Adverse Events	☐	☐	☐	☐	☐				
	4.3 Clinical Laboratory Evaluations	☐	☐	☐	☐	☐				
	4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety	☐	☐	☐	☐	☐				
	4.5 Safety in Special Groups and Situations	☐	☐	☐	☐	☐				
	4.6 Post-marketing Data	☐	☐	☐	☐	☐				
	Appendix 4	☐	☐	☐	☐	☐				

	C5. Synopses of Individual Studies	☐	☐	☐	☐	☐				
D	**Tabular Listing of All Clinical Studies**	☐	☐	☐	☐	☐				
E	**Clinical Study Reports (if applicable)**	☐	☐	☐	☐	☐				
	E1. Reports of Biopharmaceutic Studies	☐	☐	☐	☐	☐				
	1.1 Bioavailability (BA) Study Reports	☐	☐	☐	☐	☐				
	1.2 Comparative BA or Bioequivalence (BE) Study Reports	☐	☐	☐	☐	☐				
	1.3 *In vitro-In vivo* Correlation Study Reports	☐	☐	☐	☐	☐				
	1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	☐	☐	☐	☐	☐				
	E2. Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	☐	☐	☐	☐	☐				
	2.1 Plasma Protein Binding Study Reports	☐	☐	☐	☐	☐				
	2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	☐	☐	☐	☐	☐				
	2.3 Reports of Studies Using Other Human Biomaterials	☐	☐	☐	☐	☐				
	E3. Reports of Human Pharmacokinetic (PK) Studies	☐	☐	☐	☐	☐				
	3.1 Healthy Subject PK and Initial Tolerability Study Reports	☐	☐	☐	☐	☐				
	3.2 Patient PK and Initial Tolerability Study Reports	☐	☐	☐	☐	☐				
	3.3 Population PK Study Reports	☐	☐	☐	☐	☐				
	E4. Reports of Human Pharmacodynamic (PD) Studies	☐	☐	☐	☐	☐				
	4.1 Healthy Subject PD and PK/PD Study Reports	☐	☐	☐	☐	☐				
	4.2 Patient PD and PK/PD Study Reports	☐	☐	☐	☐	☐				

	E5. Reports of Efficacy and Safety Studies	☐	☐	☐	☐	☐				
	5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	☐	☐	☐	☐	☐				
	5.2 Study Reports of Uncontrolled Clinical Studies	☐	☐	☐	☐	☐				
	5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses	☐	☐	☐	☐	☐				
	5.4 Other Clinical Study Reports	☐	☐	☐	☐	☐				
	E6. Reports of Post-Marketing Experience	☐	☐	☐	☐	☐				
	E7. Case Report Forms and Individual Patient Listing	☐	☐	☐	☐	☐				
F	**List of Key Literature References**	☐	☐	☐	☐	☐				

Legends:

NCE - New Chemical Entity
Biotech - Biotechnological Products
MaV - Major Variation *(Pharmaceutical product that have undergone variation affecting one or more of the following aspects : the route of administration, strength and posology, indications.*
RT - Route of Administration
S / P - Strength and Posology
IND - Indication
MiV - Minor Variation *(Pharmaceutical product that have undergone variation affecting one or more of the following aspects : route of administration, strength and posology, indications and active ingredient(s).*
GP - Generic Products

ANNEX 7

DEPARTMENT OF PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH
BRUNEI DARUSSALAM

APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS

ORGANISATION OF THE DOSSIER
PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

SECTION A: TABLE OF CONTENTS

Section 1: Application Form (Form No.: BDMCA/DPS/01)
All sections of the application form must be completed. All entries and documents must be in English and/or Malay.

Section 2: Letter of Authorisation
A copy of a letter of authorisation from the product owner / manufacturer to the applicant for application of registration of the medicinal product should be provided.

Section 3: Certifications
A copy of the following types of certificates should be provided for application of registration of medicinal products:

- For contract manufacturing –
  a. Licence of pharmaceutical industries and contract manufacturer
  b. Contract Manufacturing Agreement
  c. GMP Certificate of contract manufacturer (Original)

- For manufacturing "under-licence" –
  a. Licence of pharmaceutical industries
  b. GMP Certificate of the manufacturer
  c. Copy of "under-licence" agreement

- For locally manufactured products (excluding the above) –
  a. Licence of pharmaceutical industries
  b. GMP Certificate of the manufacturer

- For imported products –
  a. Licence of pharmaceutical industries / importer / wholesaler
  b. Certificate of Pharmaceutical Product (CPP) issued by the competent authority in the country of origin according to the current WHO format (Original) (Mandatory)
  c. Site Master File of manufacturer (Optional).

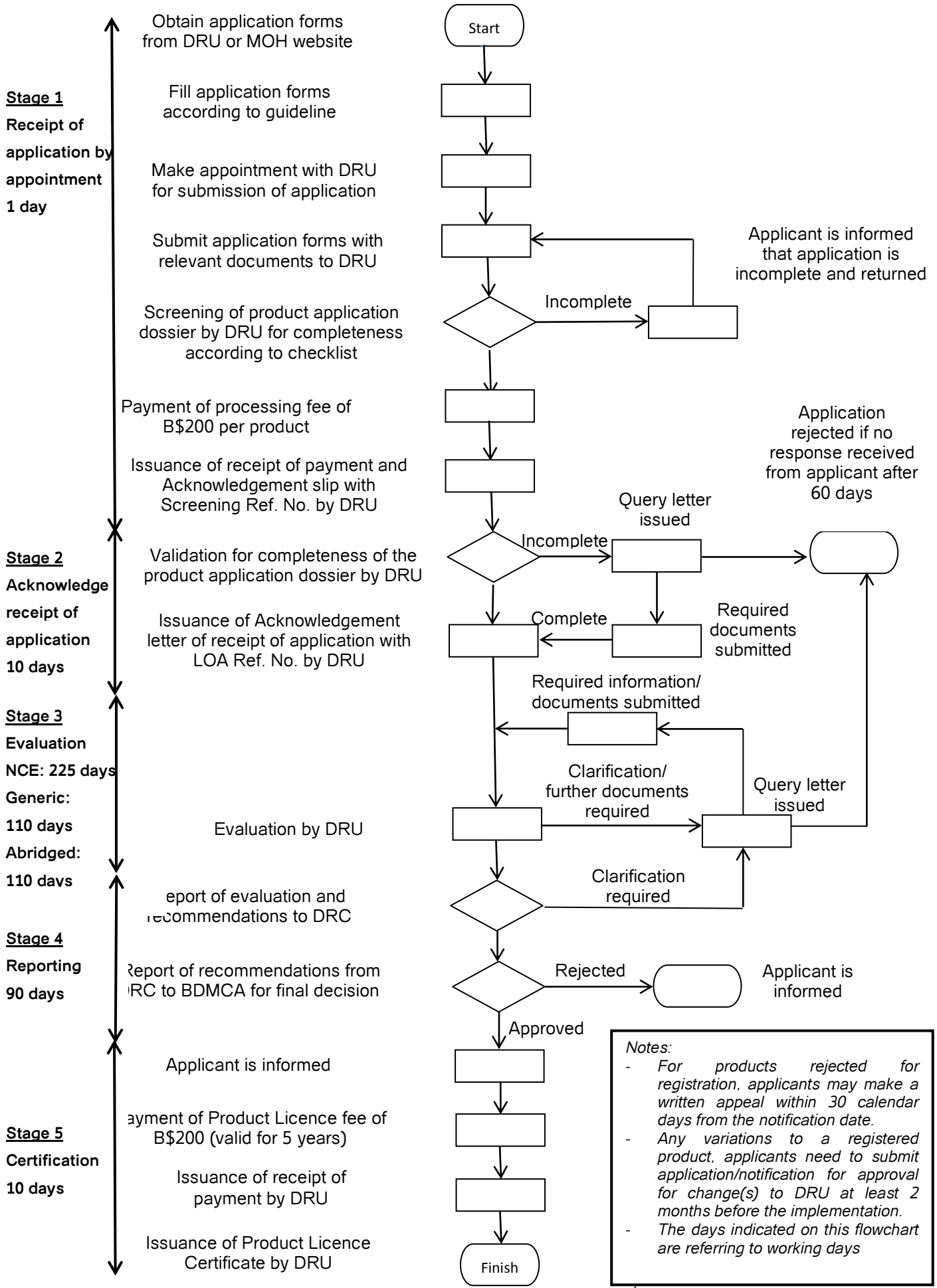
Section 4: Labelling
Samples / proposed drafts of product labelling should be submitted for unit cartons, inner labels and blister/strips (if applicable). This should be in English and/or Malay.

Section 5: Product Information
Samples / proposed drafts of product information should be provided in English and/or Malay. Product information consists of Summary of Product Characteristics (SmPC) or Package Inserts (for generic products), SmPC (for NCE and Biotechnology products) and Patient Information Leaflets (PIL) (for OTC products).

SECTION B: CHECKLIST

The checklist enclosed with the application form is to be used to check against all the required documents in Part I of the application dossier. It is to be completed and attached at the front of each application form upon submission to the Drug Registration Unit.

FLOWCHART ON THE PROCEDURE OF APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCT



Notes:

- *For products rejected for registration, applicants may make a written appeal within 30 calendar days from the notification date.*
- *Any variations to a registered product, applicants need to submit application/notification for approval for change(s) to DRU at least 2 months before the implementation.*
- *The days indicated on this flowchart are referring to working days*

ANNEX 9

APPEAL FOR REGISTRATION OF REJECTED MEDICINAL PRODUCTS
(Form No: BDMCA/DPS/Appeal/01)

To:
Chairperson of Brunei Darussalam Medicines Control Authority
Ministry of Health
Commonwealth Drive BB 3910
Bandar Seri Begawan
Brunei Darussalam

I wish to appeal for registration of the following medicinal product in Brunei Darussalam.

Date of Rejection	
Application No	L O A - P / / / S
Name of Product	
Active Ingredient(s)	
Proposed Indication(s)	
Proposed Dosage Regimen(s)	
Countries where product is registered with the above indication(s) and dosage regimen(s)	
Countries where product is rejected/withdrawn	
Reasons for appeal	
Documents submitted to support appeal	

Note: Only appeals accompanied by relevant new information or supporting documents <u>not</u> previously submitted will be considered. Appeal must be done within 30 calendar days from date of rejection, otherwise a new application is required to be submitted.

Name of applicant	
Designation	
Name and address of company	
Contact number	
Signature, date & company Stamp	

ANNEX 10

Form No. BDMCA/DPS/RN/01

DEPARTMENT OF PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH
BRUNEI DARUSSALAM

APPLICATION FOR RENEWAL OF REGISTRATION FOR MEDICINAL PRODUCT

L	O	A	-	P	/			/	S							

(Please use the Ref. No. from the original application)

PRODUCT LICENCE NO.:

B	R	U									P					

NO. OF RENEWAL: ……

VALIDITY OF PRODUCT REGISTRATION (FROM: …… TO: ……..)

Instructions:

1. *Only **ONE COPY** of the application form is to be submitted per product. Form must be **TYPED**.*
2. *Completed form is to be sent to the Drug Registration Unit, Drug Administration Section, Department of Pharmaceutical Services, Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium, Bandar Seri Begawan, BA 1111, Brunei Darussalam.*

1.0	**PRODUCT DETAILS**		
1.1	Proprietary Name:		
1.2	Dosage Form:		
1.3	Active Ingredient (Name and Strength) :		
1.4	Current Price (Optional): a) Wholesale Price: _____ b) Retail Price: _____		
2.0	**PRODUCT LICENCE HOLDER PARTICULARS**		
2.1	Name of Company:		
2.2	Address:		
2.3	Company Registration No.: *(Please enclose a copy of Company Registration Certificate)*		
2.4	Telephone no.:	2.5 Fax no.:	2.6 E-mail Address:

3.0	**MANUFACTURER 'S PARTICULARS** *Note: If more than 1 manufacturer, please write on a separate sheet of A4 paper*		
3.1	Name of Manufacturer :		
3.2	Address:		
3.3	Telephone no.:	3.4 Fax no.:	3.5 E-mail Address:
4.0	**IMPORTER'S PARTICULARS** *(For imported medicinal products only)*		
4.1	Name of Importer:		
4.2	Address:		
4.3	Telephone no.:	4.4 Fax no.:	4.5 E-mail address:

5.0 **POST-MARKETING SURVEILLANCE OF THE REGISTERED MEDICINAL PRODUCT**

5.1 **Monitoring of Adverse Drug Reaction (ADR) Report (local and overseas)**
Please list related reports received and actions taken:

a) Reporting by Consumers

Type of ADR	Date of Report	Reporter	Action / Date of Report Submitted to Drug Administration Section (DAS)

b) Reporting by DAS

Type of ADR	Date of Report	Action Taken	Date of Action Taken

5.2 **Monitoring of Product Complaints**

a) Complaints by Consumers

Type of Complaint	Date Received	Reporter	Action	Date of Complaint Submitted to DAS

b) Complaints that require investigation as instructed by DAS

Type of Complaint	Date Received	Reporter	Action	Date of Action Taken

5.3 **Monitoring of Product Quality (Post-Marketing)**

5.3.1 Has the product sample been taken for quality testing after registration? Yes / No

5.3.2 If yes, please fill in the following information:

a) Date Sample Taken: ……

b) Date of Any Product Deficiencies Reported (*if applicable*): …….
i.e. non-conformance to the registered product details such as **NO** package insert, registration no., product registration holder, different packaging, etc.

5.4 Punitive Action Against the Product

5.4.1 Any punitive action (including warning) against the product? Yes / No

5.4.2 If yes, please state the date, type of failure, type of action and follow-up action:

Date	Failure	Type of Action	Remedial Action

*Note: Please indicate as **"NONE"** if no punitive action is taken against the product.*

6.0	**VARIATIONS TO THE REGISTERED INFORMATION**

6.1 Please list down variations to the registered information that have been submitted to DAS with the date /references of approval

Type of Variations	Date of Application	Date Approved	Ref. No. from DAS

7.0 DECLARATION

I, on behalf of the company named in Section 2.1, hereby

7.1 Declare that all particulars given in this application form are true.

7.2 Undertake to abide to the laws and legislations stated in the Medicines Order 2007.

7.3 Undertake to notify the Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam of any change in the particulars submitted in this application and of any new safety information during the course of evaluation and as long as the product remains on the market.

7.4 Undertake to notify the Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam if a product is rejected for registration in any drug regulatory authority.

I understand that a wilfully false statement is an offence under the Medicines Order 2007 and that all documents submitted for evaluation are not returnable.

Name (in block letters)
Passport/ IC No.
Designation
Signature Company Stamp

Date

FOR OFFICIAL USE

PROCESSING FEE DETAILS

Receipt No: …….. Amount Paid: …….

Name of Payee: ……

Name & Signature of officer receiving the processing Fees:	**Received date:**
……	……

Notes:

ANNEX 11

GUIDE TO APPLICATION FOR RENEWAL OF MEDICINAL PRODUCT REGISTRATION

1) Applications for Renewal of Medicinal Product Registration shall be made on prescribed form, **Form No. BDMCA/DPS/RN/01.**

2) Only **ONE COPY** of the application form is to be submitted per product and form must be **TYPED**.

3) All entries must be made in English. Relevant information required in the form should be supplied accordingly. Otherwise, the incomplete form may result in an undue delay in the processing of the application.

4) A separate A4-size sheet may be attached to the application form if the space provided on the form is inadequate. The attached sheets should be numbered appropriately at the top right hand corner, where each of the numbers would correspond to that in the column of the application form.

5) Application for renewal of medicinal product registration should be submitted at least 1 year prior to expiry of the registration of the product.

6) Fee paid for the renewal of registration for medicinal product is non-refundable.

7) Applications are also required to submit the following documents:

   i) The original Certificate of a Pharmaceutical Product (CPP) from the country of manufacture. In cases where the CPP is not obtainable from the relevant regulatory agency because the product is manufactured solely for export, the product registration holder may submit a certified true copy of the manufacturer's GMP certificate or its equivalent in addition to a CPP from another country to which the same product is exported to and sold therein. CPP not more than **2 years** old (based on issue date) is required. Renewal may be withheld if the required fresh CPP is not submitted.

   ii) The latest Periodic Safety Update Report (PSUR) of the product.

8) The renewal of the product registration is based on the existing approved registration information. Product Licence holder is required to submit variation application separately if there is any change to the product information.

9) The completed application form together with the required supporting documents should be sent to:

DRUG ADMINISTRATION SECTION
Block 2G:8:03, 8th Floor,
Ong Sum Ping Condominium,
Bandar Seri Begawan BA1111
Brunei Darussalam

10) For application enquiries or more information, please contact the Drug Administration Section (DAS) officer at telephone/fax no: +673 2230001.

ANNEX 12

FORM NO.: BDMCA/DPS/Vartn/02

DEPARTMENT OF PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH
BRUNEI DARUSSALAM

APPLICATION FOR VARIATIONS TO A REGISTERED MEDICINAL PRODUCT

Variation Screening Ref. No. (for official use only): (……)/DRU/DRA.Variation/20……

Instruction:

1. Applicants are advised to refer to the "Guideline on application for variations to a registered medicinal product" for guidance before filling up application form.
2. Only **one original copy** of the application form is required to be submitted per product. Form must be typed.
3. Completed form is to be sent to the Drug Registration Unit, Drug Administration Section, Department of Pharmaceutical Services, Block 2G:8:04, 8th Floor, Ong Sum Ping Condominium, Bandar Seri Begawan, BA1111, Brunei Darussalam.

1.0	**DETAILS OF MEDICINAL PRODUCT REGISTRATION**		
1.1	Product Licence No. (s):	Expiry Date:	Application Ref. No.: LOA-P/……../S……..
1.2	Product Name and Strength:		
1.3	Active Ingredient(s):		

2. 0	**DETAILS OF PRODUCT LICENCE HOLDER**	
2.1	Name of Company : (in block letters)	
	Address:	Tel No.: Fax No.: Email No.:

3.0	**APPLICANT PARTICULARS**	
3.1	Person authorised to submit and handle application on behalf of the company:	
	Name (Mr/Ms/Mrs/Mdm/Dr):	Designation:

4.0	DECLARATION

I, on behalf of the company named in Section 2.1, hereby declare that

4.1 There are no other changes than those proposed on this application form;

4.2 All the conditions for the proposed changes are fulfilled;

4.3 The supporting documents required for the proposed changes have been submitted; and

4.4 All particulars given in this application form and the supporting documents attached to this form are true.

I understand that a wilfully false statement is an offence under the Medicines Order 2007 and that all documents submitted for evaluation are not returnable.

Name (in block letters):

Signature: Company Stamp:

Date:

AMENDMENT FEE DETAILS (For Official Use)	
Receipt No:	Amount Paid:
Name of Payee:	
Name & Signature of officer receiving the Amendment Fees:	Received date:
Notes:	

5.0 DETAILS OF PROPOSED CHANGE(S)						
Variation Code*	Current Product Details	Proposed Change(s)	Reasons for Change	Expected effective date	Variation Application Status in DPS's reference countries	Enclosures**

* Please refer to **Appendix 4 – Types of Variations** of the Guide to Application for Registration of Medicinal Products (3rd Edition) for the Variation Code e.g. MaV-1, MiV-PA1 etc.

** Please list and submit the documents required for each Variation Code as listed on **Appendix 4 – Types of Variations** and the supporting documents indicated in **Annex 13 (Item no. 4)** of the Guide to Application for Registration of Medicinal Products (3rd Edition)

ANNEX 13

GUIDELINE ON APPLICATION FOR VARIATIONS TO A REGISTERED MEDICINAL PRODUCT

1. Introduction

Product Licence holders are required to submit variation application to the Brunei Darussalam Medicine Control Authority (BDMCA) for approval before any changes to any aspect of a registered medicinal product for human use.

2. Types of Variations

The different types of variations are in accordance with the ASEAN Variation Guideline for Pharmaceutical Products.

(a) Major variation (MaV)
Variation to a registered medicinal product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

(b) Minor Variation (MiV-N & MiV-PA)
Variation to a registered medicinal product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

Note: **Appendix 4** shows the types of variations, conditions and supporting documents required.

3. Application Form

3.1 Application for variation of registered medicinal products shall be made on prescribed form, (form ref. no. BDMCA/DPS/Vartn/02) for all types of variations. The form appears as **Annex 10**.

3.2 The form can be obtained from:
Drug Registration Unit
Drug Administration Section
Department of Pharmaceutical Services
Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium
Bandar Seri Begawan, BA1111
Brunei Darussalam
Tel/Fax: +673 2230001 / +673 2230041

or can be downloaded at the following website:
http://www.moh.gov.bn/pharmacyservices/forms.htm

4. Supporting Documents

4.1 The documents that are required to be submitted for the various types of variations are stated in **Appendix 4**.

4.2 In addition to the documents required in Appendix 4, the followings **must** be submitted:

4.2.1 A declaration letter undersigned by the Head of Regulatory Officer that declares there is no other change except for the proposed variation.

4.2.2 Proof of approval status of the variation application in DPS's reference countries.

4.3 Any variations not yet listed in Appendix 4 should be justified and decided by the BDMCA. Appropriate reference can be made to:

i) EMA Classification Guidance on Minor Variations of Type IA, Minor Variations of Type IB And Major Variations of Type II.

ii) SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing And Controls, In Vitro Dissolution Testing, And In Vivo Bioequivalence Documentation.
iii) SUPAC-MR: Modified Release Solid, Oral Dosage Forms, Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation.
iv) WHO Guidance on Variations to a Prequalified Product Dossier.

4.4 The BDMCA reserves the right to request for additional information, when deemed necessary.

5. Application Submission

Application form must be duly completed and supported with the required documents. Application is to be submitted **at least 2 months in advance** from the actual implementation date to:

Drug Registration Unit
Drug Administration Section
Department of Pharmaceutical Services
Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium
Bandar Seri Begawan, BA1111
Brunei Darussalam
Tel/Fax: +673 2230001 / +673 2230041

6. Abbreviations:

C = Conditions to be fulfilled
D = Documents to be submitted
MaV = Major Variation
MiV-N = Minor Variation (Notification)
MiV-PA = Minor Variation (Prior Approval)

APPENDIX 4

TYPES OF VARIATIONS

A. MAJOR VARIATIONS (MaV)

Variation Code	Types of variations
MaV-1	Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product
MaV-2	Change of content of product labeling
MaV-3	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MaV-4	Addition or replacement of the manufacturing site of the drug product
MaV-5	Addition or replacement of the alternative site for the primary packaging (direct contact with drug product)
MaV-6	Change of the specification drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MaV-7	Change of batch size of sterile drug product
MaV-8	Change of batch size of non-sterile drug product
MaV-9	Major change in the manufacturing process for the drug product
MaV-10	Qualitative or quantitative change of excipient
MaV-11	Quantitative change in the coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form
MaV-12	Change in primary packaging material for sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material
MaV-13	Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for ~~a~~ sterile solid and liquid drug product
MaV-14	Inclusion or replacement of the solvent/diluent for the drug product
MaV-15	Extension of shelf-life of the drug product
MaV-16	Change of storage conditions of the drug product (Lowering from the current approved storage condition)

B. MINOR VARIATION PRIOR APPROVAL (MiV-PA)

Variation Code	Types of variations
MiV-PA1	Change of drug product name
MiV-PA2	Change of product labeling (in accordance to country specific labeling requirement)
MiV-PA3	Addition or replacement of the company or party responsible for batch release
MiV-PA4	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
MiV-PA5	Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MiV-PA6	Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MiV-PA7	Change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MiV-PA8	Change of the specification of drug substance
MiV-PA9	Change of the test procedure of non-compendial drug substance
MiV-PA10	Change of shelf-life or retest period for drug substance
MiV-PA11	Change of storage condition for drug substance
MiV-PA12	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
MiV-PA13	Change of batch size of non-sterile drug product
MiV-PA14	Reduction or removal of overage

MiV-PA15	Qualitative or quantitative change of excipient
MiV-PA16	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral dosage form
MiV-PA17	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
MiV-PA18	Deletion of the solvent/diluent for the drug product
MiV-PA19	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)
MiV-PA20	Minor change of the manufacturing process for non-sterile product.
MiV-PA21	Change of specifications of an excipient
MiV-PA22	Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure
MiV-PA23	Change in the source of empty hard capsule
MiV-PA24	Change of release and shelf-life specifications of the drug product
MiV-PA25	Change of imprints, bossing or other markings on the tablets or printing on capsules including addition or change of inks used for product marking
MiV-PA26	Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass
MiV-PA27	Change in the test procedure of the drug product (including replacement or addition of a test procedure)
MiV-PA28	Change in primary packaging material for non-sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material
MiV-PA29	Addition or replacement of a manufacturer for secondary packaging
MiV-PA30	Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product
MiV-PA31	Change of outer carton pack sizes for a drug product
MiV-PA32	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)
MiV-PA33	Addition or replacement of measuring device for oral liquid dosage forms and other dosage form
MiV-PA34	Reduction of shelf-life of the drug product
MiV-PA35	Change of storage conditions of the drug product (Increasing from the current approved storage condition)

C. MINOR VARIATION NOTIFICATION (MiV-N)

Variation Code	Types of variations
MiV-N1	Change in name and/or address of the marketing authorization holder
MiV-N2	Change of product owner
MiV-N3	Change in ownership of manufacturer
MiV-N4	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product
MiV-N5	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release
MiV-N6	Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance
MiV-N7	Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)
MiV-N8	Renewal of European Pharmacopoeial Certificate of Suitability (CEP)
MiV-N9	Change of release and shelf-life specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium
MiV-N10	Deletion of pack size for a product

A. MAJOR VARIATION (MaV)

MaV- 1	Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed. 4. Clinical expert reports and/or clinical trial reports (where applicable). 5. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 6. Approval letters from reference countries or country of origin which have approved the new indication or dosing regimen (where applicable). 7. Clinical documents as per ASEAN Common Technical Dossier (ACTD) part IV (where applicable).
MaV-2	**Change of content of product labeling**
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a minor variation and not within the scope of MaV-1. 3. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed and supporting clinical documents when applicable. 4. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable).
MaV-3	**Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. Specifications of drug substances remain unchanged. 2. For Change and/or addition of alternative manufacturer/site of drug substance where European Pharmacopoeial Certificate of Suitability (CEP) is available, please refer to MiV-PA4.
D	1. Complete ACTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by the Drug Regulatory Authority. 2. Comparative tabulated format of the currently registered and revised drug substance manufacture information (where applicable). 3. Batch analysis data (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed manufacturing sites. 4. A letter of commitment from marketing authorization holder to conduct real time and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

MaV-4	Addition or replacement of the manufacturing site of the drug product
C	1. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. 2. For addition or replacement of the company or party responsible for batch release, please refer to MiV-PA3. 3. If there are changes to the manufacturing process, MaV-9 is also applicable.
D	1. Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. 2. Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action). 3. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 6. Comparative dissolution profile data manufactured in the currently approved and proposed manufacturing site for oral solid dosage forms as per compendium and validated dissolution test method. 7. Product formula. 8. Release and shelf-life specifications of drug product. 9. Batch numbering system (where applicable). 10. Specification of drug substance. 11. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 12. In case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable).
MaV-5	**Addition or replacement of alternative site for primary packaging (direct contact with drug product)**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product).
D	1. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned-such as a valid GMP Certificate and/or a CPP which covers GMP certification. 2. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 3. For sterile product, validation scheme and/or report on primary packaging processes as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 6. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable).

MaV-6	**Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]** **a) Specification limits are widened** **b) Deletion of test parameter and limits**
C	1. Test procedures remain the same, or changes in the test procedure are minor. 2. Not applicable to compendial drug substances/drug products. 3. Refer to MiV-PA12 if this change resulted in revision of CEP. 4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	**(a) <u>Specification limits are widened</u>** 1. Justification for change substantiated with scientific data to be provided. 2. Comparative tabulated format of the currently approved and revised specification of drug substance/drug product with changes highlighted. 3. Revised specification of drug substance / drug product. 4. Batch analysis data of the drug substance/drug product for all tests in the new specification for two pilot or production scale batches. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). **(b) <u>Deletion of test parameter and limits</u>** In addition to the above documents except D5, 6. Certificate of analysis of the drug substance/drug product for all tests with the new specification.
MaV-7	**Change of batch size of sterile drug product**
C	1. The change does not affect consistency of production. 2. Release and shelf-life specifications of drug product remain unchanged. 3. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. The product formulation remains unchanged.
D	1. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size should be provided upon submission. 2. Comparative tabulated format of proposed and currently approved batch manufacturing formula. 3. Batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to currently approved and proposed batch sizes. 4. Release and shelf-life specifications of the drug product. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-8	Change of batch size of non-sterile drug product
C	1. This is applicable to change of batch size more than 10-fold compared to the currently registered batch size. For change of batch size up to 10-fold compared to the currently registered batch size, please refer MiV-PA13. 2. The change does not affect consistency of production. 3. Release and shelf-life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration.
D	1. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration the proposed batch size should be provided upon submission. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. Batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to currently approved and proposed batch sizes and letter of undertaking to submit batch data on the next one full production batch. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 5. Release and shelf-life specifications of the drug product. 6. For oral solid dosage forms, comparative dissolution profile for at least one production batch (where applicable).
MaV-9	**Major change in the manufacturing process for drug product**
C	1. The same currently approved manufacturing site. If there is a change in manufacturing site, MaV-4 is also applicable. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA20.
D	1. Description of the new manufacturing process and technical justification for the change. 2. Validation scheme and/or report of the proposed manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 3. Copy of currently approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the new process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 4. Comparative batch analysis data of drug product for a minimum of one production batch manufactured according to currently registered and proposed processes. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 6. Comparative dissolution profile data between the products manufactured with the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validated dissolution test method. 7. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-10	**Qualitative or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)** **b) For modified release oral dosage forms** **c) For other critical dosage forms such as sterile preparations.**
C	1. Change will need to comply with the finished product specifications for example release and shelf-life specifications of the drug product remain the same, excluding product description. 2. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed new product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Replacement of an excipient with a comparable excipient of the same functional characteristics. 5. For other qualitative or quantitative changes of excipient for immediate release oral dosage forms and other non-critical dosage forms, please refer to MiV-PA15.
D	1. Justification for the change must be given by appropriate development of pharmaceutics. 2. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 3. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation (where applicable). 4. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 5. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 6. Drug product release and shelf-life specifications. 7. Batch analysis data (in a comparative tabulated format) of drug product on at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 11. Revised batch manufacturing formula. 12. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission. 13. Revised ACTD Section P3.1 to P3.4 (where applicable).

MaV-11	**Quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The product release and shelf-life specifications have only been updated in respect of product description (where applicable). 3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA16.
D	1. Comparative dissolution profile data of at least one pilot/production batch of the drug product between the currently approved and proposed composition. 2. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 3. Revised release and shelf-life specifications of the drug product. 4. A declaration that the change does not interfere with the drug product release and shelf-life specifications test method. 5. Current and proposed product and batch manufacturing formula. 6. Revised draft of product label incorporating the proposed change (where applicable). 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-12	**Change in primary packaging material for sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA28.
D	1. Validation scheme and/or report of the manufacturing and sterilization process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in primary packaging material should be provided upon submission. 2. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Comparative tabulated format of specifications of the proposed and current primary packaging material. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 6. Revised ACTD Sections P3 and/or P7 (where applicable). 7. Appropriate scientific data on new packaging (comparative data on permeability, e.g. moisture, O_2, CO_2).

MaV-13	Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product
C	1. Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. The packaging material remains the same. 4. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile drug product, please refer to MiV-PA30.
D	1. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 3. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MaV-14	**Inclusion or replacement of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2. For deletion of the solvent/diluent, please refer to MiV-PA18. 3. For change of shelf-life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please also refer to MaV-15/MiV-PA34 and/or MaV-16/MiV-PA35 (where applicable)
D	1. In addition to section P for the solvent/diluent and reconstitution stability data, section S is required (where applicable). 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. Batch numbering system (where applicable). 4. A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/diluent (where applicable). 5. Revised artworks for the drug product labels incorporating the changes. 6. A declaration from the marketing authorization holder that the release and shelf-life specifications of drug product are not affected.

MaV-15	**Extension of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c)–The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For reduction of shelf-life, please refer to MiV-PA34.
D	1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf-life of the drug product (where applicable). 4. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).
MaV-16	**Change of storage conditions of the drug product (Lowering from the current approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For change of storage condition (Increasing from the current approved storage condition), please refer to MiV-PA35.
D	1. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Technical justification for the change.

C. MINOR VARIATION PRIOR APPROVAL (MiV-PA)

MiV- PA1	Change of drug product name
C	1. There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the product name change. 2. No confusion with another drug product either when spoken or written. 3. The new name does not (i) suggest greater safety or efficacy than supported by clinical data (ii) imply a therapeutic use (iii) imply superiority over another similar product and (iv) imply the presence of substance(s) not present in the product.
D	1. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 2. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change. 3. Revised draft package insert and labeling incorporating the proposed variation. 4. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 5. Trademark certificate (where applicable).
MiV- PA2	**Change of product labeling (in accordance to country specific labeling requirement)** Includes: a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication. c) Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labelling. d) Tightening of product's target population. e) Deletion of indication. f) Change of distributor's details.
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a MaV and does not contain promotional information. For major change in product labelling, please refer to MaV-2.
D	1. Current approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change. 4. Relevant document/reference to support the changes (where applicable).
MiV- PA3	**Addition or replacement of the company or party responsible for batch release**
C	1. Only applicable for batch release. 2. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed. 3. The manufacturer of the drug product remains the same.
D	1. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable). 2. Proof that the proposed site is appropriately authorized (accredited by the authority) to be responsible for batch release such as a valid GMP certificate or CPP which covers the GMP certification. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

MiV- PA4	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
C	1. Specifications of drug substances remain unchanged. 2. For change and/or addition of alternative manufacturer/site of drug substance where CEP is not available, please refer to MaV-3.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by the European Directorate for the Quality of medicines (EDQM). 2. Batch analysis data (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed manufacturing sites. 3. If the re-test period is not stated in the CEP, real time and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided. 4. A letter of commitment from marketing authorization holder to conduct real time and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
MiV- PA5	**Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. The change does not affect the reproducibility of the process. 2. Specifications of drug substance remain unchanged. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Comparative batch analysis data with specification and results (in a comparative tabulated format) on a minimum of one production or pilot batch manufactured to both the currently approved and proposed batch sizes. Batch data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 2. A letter of declaration from marketing authorized holder that the specifications of drug substance have not changed and the reproducibility of the process has not been affected. 3. Amended relevant ACTD Section S (where applicable).
MiV-PA 6	**Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. In-process limits are tightened or addition of new tests. 2. Refer to MiV-PA12 if this change resulted in revision of CEP. 3. The change is not a consequence of any commitment from previous assessments to review specification limits. 4. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable). 2. Comparative tabulated format of the proposed and current in-process controls and the relevant changes. 3. Comparative batch analysis data of two production batches of the drug substance for all tests in the proposed specification (where applicable).

MiV- PA7	Change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. Specifications and stability performance of drug substance remain unchanged. 3. The synthetic route remains the same (for example, intermediates remain the same). 4. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 5. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 6. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Drug Master File (DMF), or relevant updated drug substance (DS) section or equivalent/audit document. 2. Comparative tabulated format of the currently approved and new processes with changes highlighted (where available). 3. Certificate of analysis for two batches of the drug substance. 4. Batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the currently approved and proposed processes. 5. A letter of declaration from marketing authorization holder stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies. 6. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed or if there is any change to the specification (for example, tightening), the texts of the currently approved and proposed specifications should be provided (in a comparative tabulated format where possible). 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. For sterile drug substance, process validation report (where applicable).

MiV- PA8	**Change of the specification of drug substance** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. This is only applicable for drug substances which are non-compendial and generic drug substances without European Pharmacopoeial Certificate of Suitability (CEP) 2. For (b) - applicable to non-compendial method only. 3. Refer to MiV-PA12 if this change resulted in revision of CEP. 4. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-6. 5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 6. Test procedures remain the same, or changes in the test procedure are minor.
D	**(a) Specification limits are tightened** 1. Comparative tabulated format of the currently approved and revised specification of drug substance with changes highlighted. 2. Comparative batch analysis data of the drug substance for all tests in the new specification for two pilot or production scale batches. 3. Technical justification for the change. **(b) Addition of new test parameter and limits** In addition to the above documents, 4. Description of any new analytical method and summary of the validation data.

MiV- PA9	**Change of the test procedure of non-compendial drug substance**
C	1. Results of method validation show new test procedure to be at least equivalent to the former procedure. 2. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Description of the analytical methodology, a summary of validation data, and comparative analytical results between the currently approved and proposed test (where applicable). 2. Specification of the drug substance.

MiV-PA 10	Change of shelf-life or re-test period for drug substance
C	1. The stability studies must show compliance with specification. 2. No change in storage condition. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested shelf-life or retest period. 2. Specifications of the drug substance.

MiV-PA 11	Change of storage condition for drug substance
C	1. The stability studies must show compliance with specification. 2. No change in shelf-life/retest period. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested storage condition. 2. Specifications of the drug substance.

MiV-PA 12	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
C	None
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. Specifications of drug substance (where applicable). 3. Results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP (where applicable). 4. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc), if applicable. 5. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). *If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.

MiV-PA13	Change of batch size of non-sterile drug product
C	1. This is applicable to change of batch size up to 10-fold compared to the currently registered batch size. 2. The change does not affect consistency of production. 3. Release and end-of-shelf-life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches at the proposed new batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 5. For change of batch size for sterile products, please refer to MaV-7 and for change of batch size more than 10-fold compared to the currently registered batch size, please refer MaV-8.
D	1. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed batch size should be provided upon submission. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. Batch analysis data (in a comparative table) of drug production a minimum of one production batch–according to currently approved and proposed batch sizes and a letter of undertaking to submit batch data on the next full production batch. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 5. Release and shelf-life specifications of the drug product. 6. Revised ACTD Section P3.1-3.4 (where applicable).
MiV-PA14	**Reduction or removal of overage**
C	1. Changes of previously approved manufacturing overages of drug substance only. 2. Release and end-of-shelf-life specifications of drug product remain unchanged.
D	1. Justification for the change. 2. Comparative tabulated format of currently approved and proposed batch manufacturing formula. 3. Certificate of analysis for two batches of the finished product. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV–PA15	**Qualitative and/or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)** **b) For other non-critical dosage forms eg. oral liquid, external preparation.**
C	1. Release and shelf-life specifications of the drug product remain unchanged 2. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Replacement of an excipient with a comparable excipient of the same functional characteristics (where applicable). 5. For qualitative or quantitative change of excipient for immediate release and modified release oral dosage forms and other critical dosage forms, please refer to MaV-10.
D	1. Justification for the change must be given by appropriate development of pharmaceutics. 2. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 3. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation. 4. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies. 5. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 6. Release and shelf-life specifications. 7. Batch analysis data (in a comparative tabulated format) of drug product of at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 11. Revised batch manufacturing formula. 12. A declaration that the new excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 13. Revised ACTD Section P3.1-3.4 (where applicable). 14. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission (where applicable).

MiV–PA16	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage form
C	1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The product release and end-of-shelf-life specifications of the drug product remain unchanged except for the weight and/or size. 3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral solid dosage forms please refer to MaV-11.
D	1. Comparative dissolution profile data of at least one pilot/production batch of the drug product between the currently approved and proposed composition. 2. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 3. Revised release and shelf-life specifications of the drug product. 4. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 5. Comparative tabulated format of current and proposed product and batch manufacturing formula. 6. Revised draft of product label incorporating the proposed change (where applicable). 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). Except for the change in weight and/or size of capsule shell, a letter of declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline on Stability Study of Drug Product have been started will suffice.

MiV- PA17	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring/flavouring agents must not have been rejected for pharmaceutical use. 3. The release and shelf-life specifications of the drug product remain unchanged except for the change in colour/flavour.
D	1. Qualitative and quantitative information of the current and proposed colouring/flavouring agent in a comparative table. 2. Revised product formulation and batch manufacturing formula. 3. Revised release and shelf-life specifications of the drug product. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 6. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant veterinary authority of the issuing country (where applicable). 7. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 8. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).
MiV- PA18	**Deletion of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	1. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Amended relevant ACTD Section P (where applicable).

MiV-PA19	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)
C	1. Release and shelf-life specifications of drug product remain unchanged. 2. The change is not a consequence of any commitment from previous assessments to review specification limits. 3. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	1. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 2. Revised in-process specifications together with justification and relevant process validation data. 3. Comparative batch analysis data of drug product of at least two production/pilot batches. 4. Comparative tabulated format-change of the in-process controls.
MiV- PA20	**Minor change of the manufacturing process for non-sterile product**
C	1. The same currently approved manufacturing site. 2. The overall manufacturing principle remains the same. 3. The change does not cause negative impact on the quality, safety and efficacy of the drug product. 4. Release and end-of-shelf-life specifications of drug product remain unchanged. 5. The dissolution profile of the proposed product is comparable to that of the current approved product. 6. For major change in the manufacturing process for drug product, please refer to MaV-9.
D	1. Description of the new manufacturing process and technical justification for the change. 2. For semi solid and suspension products, validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 3. For solid oral dosage forms, comparative dissolution profile data of at least one representative production batch of the drug product between the currently approved and proposed solid oral dosage forms formulation. 4. Copy of currently approved release and shelf-life specifications. Or, alternately, copy of revised release and shelf-life specifications that supports that the new process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 5. Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance (where applicable). 6. Batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the currently approved and the proposed process; batch data on the next two full production batches should be made available upon request. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action)." 8. Comparative tabulated format of present and proposed process with changes highlighted.

MiV-PA21	**Change of specifications of an excipient** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Applicable to non compendial excipients. For compendial excipients, please refer to MiV-N9. 2. Release and end-of-shelf-life specifications of drug product remain unchanged. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	1. Comparative tabulated format of the current and revised specification of the excipient with changes highlighted. 2. Batch analysis data of the excipient for all tests in the new specification. 3. Description of new method and summary of analytical validation (applicable for addition of new parameter).
MiV-PA22	**Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure**
C	1. Appropriate method validation studies have been performed in accordance with the ASEAN Guidelines For Validation of Analytical Procedures. 2. Results of method validation show new test procedure to be at least equivalent to the former procedure. 3. There have been no changes of the total impurity limits. 4. Only applicable to the currently approved test parameters. 5. No new unqualified impurities are detected. 6. This applies for non-compendial excipient.
D	1. Description of the analytical methodology with a comparative tabulation of the changes. 2. For quantitative test change, comparative analytical validation results showing that the current and proposed tests are equivalent.

MiV-PA23	**Change in the source of empty hard capsule**
C	1. From TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 2. No change in the formulation and manufacturing process of drug product. 3. Not applicable to change from hard capsule to soft gel. 4. Excipient and finished product release and end of shelf-life specifications remain unchanged.
D	1. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product using hard capsule between the two sources (where applicable). 2. Certificate of Analysis of the empty hard capsule of the proposed new source. 3. Technical specifications and composition of the empty hard capsule of the new source. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 5. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued by a competent authority of the issuing country. 6. A letter of declaration from the manufacturer or the marketing authorization holder of the material that it is purely of vegetable, animal or synthetic origin.
MiV-PA24	**Change of release and shelf-life specifications of the drug product** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Applicable to non-compendial method. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. The test methods remain the same or changes in the test methods are minor. 4. If there are changes to the test procedure, MiV-PA27 is also applicable. 5. For widening of specification limits and deletion of test parameter and limits of drug product, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Comparative tabulated format of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 2. Comparative batch analysis of the drug product for all tests in the new specification of at least two batches. 3. Technical justification for the change. **(b) Addition of new test parameter and limits** In addition to the above documents: 4. Description of any new method and summary of analytical validation data for non-compendial method. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). (where applicable).

MiV-PA25	Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking
C	**(a) Except score/break-line** 1. New markings do not cause confusion with other registered products. 2. Any ink proposed must comply to relevant pharmaceutical legislation or of food grade and not a listed banned substance. 3. Release and shelf-life specifications of the drug product remain unchanged except for appearance. **(b) On score/break-line** In addition to the above conditions, 4. Score/break-line is not meant for cosmetic purpose. 5. Applicable to addition or removal of score/break-line.
D	**(a) Except score/break-line** 1. Details and specifications of the proposed new inks (where applicable). 2. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 3. Detailed drawing or written description of the current and proposed imprint/bossing/markings. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Release and shelf-life specifications of the drug product with the new product description. 6. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). **(b) On score/break-line** In addition to the above documents, 7. Justification for the change (i.e. change in dosing regimen). 8. Certificate of analysis of two production/pilot scale batches. 9. Data on test of content uniformity of the subdivided parts of the tablets at release should be submitted.

MiV- PA26	**Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass** **a) Immediate release oral solid dosage form, suppositories and pessaries** **b) Other than immediate release oral solid dosage forms, suppositories and pessaries.**
C	1. If appropriate, the dissolution profile of the proposed product is comparable to that of the current approved product. 2. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape.
D	**(a) Immediate release oral solid dosage form, suppositories and pessaries** 1. Detailed drawing or written description of the current and proposed appearance. 2. Release and shelf-life specifications of the drug product. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Comparative dissolution data on at least one pilot/production batch of the currently approved and proposed dimensions. 5. Data on test of content uniformity of the subdivided parts of tablets at release as conformed to compendial requirement should be submitted (only applicable for drug product with score/break-line). **(b) Other than immediate release oral solid dosage forms, suppositories and pessaries** In addition to the above condition, 6. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA27	**Change in the test procedure of the drug product (including replacement or addition of a test procedure)**
C	1. Drug product specifications are not adversely affected unless the specifications are tightened. 2. Results of method verification/validation show new test procedure to be at least equivalent to the former procedure. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	1. Description of the analytical methodology. 2. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test. 3. Certificate of analysis of the finished product of two production batches when made available. 4. Justification for the proposed change. 5. Comparative tabulated format-of the currently approved and proposed release and shelf-life specifications of the drug product.
MiV-PA28	**Change in primary packaging material for non-sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. Release and end-of-shelf-life specifications of drug product remain unchanged. 2. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 3. The change only concerns the same packaging type (for example from blister to blister). 4. For change in the primary packaging material for sterile drug product, please refer to MaV-12.
D	1. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 2. For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). 3. Comparative tabulated format of the currently approved and proposed specifications of the primary packaging material (where applicable). 4. Revised drafts of the package insert incorporating the proposed variation (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA 29	Addition or replacement of a manufacturer for secondary packaging
C	None
D	1. Proof that the proposed site is appropriately authorized (accredited by the authority) for the packaging activity concerned such as a valid GMP certificate and/or CPP which covers the GMP certification. 2. Official letter from product owner authorizing the new manufacture or packager to perform secondary packaging (where applicable). 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV-PA30	**Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. The new size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Change in the dimension of the primary packaging material (where applicable). 4. For change of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product, please refer to MaV-13. 5. The change only concerns the same packaging type and material.
D	1. Justification for the proposed pack size. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).
MiV- PA31	**Change of outer carton pack sizes for a drug product**
C	1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a drug product. 3. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the marketing authorization holder stating that no other changes except for the change of outer carton pack sizes for a drug product.

MiV-PA 32	**Change in any part of the (primary) packaging material not in contact with the finished product formulation such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)**
C	1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
D	1. Amendment of the relevant section(s) of the dossier (presented in the ACTD format), including revised product labeling as appropriate.

MiV-PA33	**Addition or replacement of measuring device for oral liquid dosage forms and other dosage form**
C	1. The size and where applicable, the accuracy of the proposed measuring device must be compatible with the approved posology. 2. The new device is compatible with the drug product.
D	1. Description of the device (including a drawing; where applicable). 2. The composition of the device material. Where applicable the materials should comply with the pharmacopoeia. 3. Justification that size and accuracy of the device are adequate for the posology as is approved in the product labeling. 4. Revised draft of the package insert and labeling incorporating the proposed variation (where applicable).

MiV-PA34	**Reduction of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For extension of shelf-life, please refer to MaV-15.
D	1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf-life of the drug product (where applicable). 4. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).

MiV-PA35	**Change of storage conditions of the drug product (Increasing from the current approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For change of storage condition (lowering from the current approved storage condition), please refer to MaV-16..
D	1. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Technical justification for the change of storage condition.

C. MINOR VARIATION NOTIFICATION (MiV-N)

MiV-N1	**Change in name and/or address (for example: postal code, street name) of the marketing authorization holder** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The name change refers to the renaming of a company or organization. 2. The change does not include transfer of marketing authorization to another company. 3. For change on the part of marketing authorization holder in product labelling only. Please refer to MaV-2 and MiV-PA3 if other parts are involved.
D	1. Letter by the product owner authorizing the new name of marketing authorization holder to hold the product license. 2. Official document from the relevant authority confirming the change with the new name and/or address. 3. Revised draft package insert and labeling incorporating the proposed variation (where applicable).
MiV- N2	**Change of product owner**
C	1. The marketing authorization holder remains the same. 2. The manufacturing site remains the same.
D	1. Declaration on the transfer of ownership between old product owner and new owner. 2. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 3. If the new product owner is not the manufacturer of the drug product, an official letter by the new product owner authorizing the manufacturer to manufacture the drug product on its behalf. 4. If the new product owner is not the manufacturer of the drug product, letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

MiV- N3	**Change in ownership of manufacturer** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturing site remains unchanged. 2. No other changes except for the change in ownership of manufacturer.
D	1. Letter of justification on the transfer of ownership such as a valid GMP certificate. 2. Official letter stating the transfer of ownership from old manufacturer to new manufacturer (where applicable). 3. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the new manufacturer to manufacture the drug products on its behalf. 4. In case of a contract manufacturer, letter of acceptance from the new manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- N4	**Change of the name or address (for example: postal code, street name) of the manufacturer of drug product** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturing site remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3. 3. No other changes except for the change of the name and/or address of a manufacturer of the drug product.
D	1. Official letter from product owner authorizing the manufacturer with new name/address to manufacture the drug product. 2. A valid GMP certificate, CPP which covers the GMP certification or official document from relevant authority confirming the new name and/or address. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

MiV-N5	**Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturer of the drug product remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3. 3. The batch release site remains the same.
D	1. Official letter from product owner authorizing company/manufacturer with new name/address responsible for batch release. 2. A valid GMP certificate CPP which covers the GMP certification or official document from relevant authority confirming the new name or address (where applicable). 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. A declaration from the marketing authorization holder that the change does not involve ~~a~~ change of batch release site.
MiV-N6	**Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance**
C	1. The manufacturing site of the drug substance remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug substance.
D	1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence when required.
MiV-N7	**Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)**
C	1. An alternative manufacturer is registered.
D	1. Reason for withdrawal/deletion.

MiV-N8	Renewal of European Pharmacopoeial Certificate of Suitability (CEP)
C	1. Only applicable if the renewal of CEP does not involve any variation.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM.
MiV-N9	**Change of release and shelf-life specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium**
C	1. Applicable to compendial specifications only. 2. Change is made exclusively to comply with an update of the relevant monograph of the compendium.
D	1. Tabulation of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 2. Batch analysis of the drug product for all tests in the new specification of at least two batches. 3. Revised release and shelf-life specifications.
MiV-N10	**Deletion of pack size for a product**
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling. 2. For addition of pack size for sterile and non-sterile products, please refer to MaV-13 and MiV-PA30 respectively. For change in the outer carton pack size, please refer to MiV-PA31.
D	1. Reason for deletion. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).