GUIDELINE ON APPLICATION FOR VARIATION TO REGISTERED MEDICINAL PRODUCTS

1. Introduction

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

This guidance document is adopted from the ASEAN Variation Guideline for Pharmaceutical Products incorporating Brunei's specific requirements. This guideline should also be read in conjunction with the most updated ASEAN Variation Guideline for Pharmaceutical Products.

This guideline concerns the variation applications submitted by the Product Licence Holder for pharmaceutical products for human use only. Some of the variations are applicable for biotechnological products. However, more extensive data may be required.

2. Types of Variation

(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-PA & MiV-N)

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 5** shows the types of variation, conditions and supporting documents required.

3. Application Form

3.1 Application for variation to a registered medicinal product shall be made on prescribed form (Form ref. no. BDMCA/DPS/Vartn/02 for MaV and MiV-PA applications or BDMCA/DPS/Vartn/03 for MiV-N applications). The forms appear as **Annex 16 and Annex 17** respectively. In the event that MiV-N application is submitted together with other variation applications which require prior approval, applicant may submit the Form ref. no. BDMCA/DPS/Vartn/02 to the DRU.

3.2 The forms can be obtained from:

Drug Registration Unit
Product Regulation Section
2nd Floor, Department of Pharmaceutical Services
Ministry of Health
Spg 433, Kg Madaras, Mukim Gadong 'A'
Rimba Highway, BE4710
Brunei Darussalam

or can be downloaded at the following website:
http://www.moh.gov.bn/SitePages/Forms.aspx

4. Supporting Documents

4.1 The documents required to be submitted for the various types of variation are stated in **Appendix 5.**

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

4.3 Proof of approval status of the variation application in DPS's reference countries must be submitted.

4.4 Any variations not yet listed in Appendix 5 should be justified and decided by the BDMCA. Appropriate reference can be made to:

- EMA Classification Guidance on Minor Variations of Type IA, Minor Variations of Type IB and Major Variations of Type 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.
- 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.
- WHO Guidance on Variations to a Prequalified Product Dossier.

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

5. Application Submission

5.1 Applications must be submitted in **electronic format**. Applicants are required to adhere to the following requirements:

- Electronic copies of all documents are required to be saved into a **CD** in PDF format. Documents in the form of scanned data or image format (jpeg, png, etc.) will not be accepted.
- All documents must be organized clearly into named folders and subfolders and arranged according to the ACTD format.
- For application for variation to registered medicinal products with different strengths, applicant may submit one CD, provided that the changes across the different strengths are the same.
- For submissions with several variation applications, the variation application must be arranged in folders according to their respective variation code.
- The CD is required to be submitted in a CD sleeve and labelled in the recommended format which appears as **Annex 6.**

5.2 Certain documents which include original or notarized signatures and require proof of authenticity are required to be submitted in **hardcopy format**. The hardcopy requirements are detailed below:

Checklist	▪ Checklist for Submission of Documents for Application for Variation to Registered Medicinal Products
Log Forms	▪ Log for Application for Variation to Registered Medicinal Products ▪ Log for Application for Minor Variation Notification (MiV-N) to Registered Medicinal Products ▪ Log for Submission of Updated Documents for Application for Variation to Registered Medicinal Products
Application Forms	▪ Application Form for Variation to Registered Medicinal Products (BDMCA/DPS/Vartn/02) ▪ Application Form for Minor Variation to Registered Medicinal Products (BDMCA/DPS/Vartn/03)
Letters	▪ Letter of Intent ▪ Letter of Authorisation ▪ Declaration Letters including Stability Commitment Letters
Certification	▪ Certificate of Pharmaceutical Product (CPP)
Product Labelling	▪ Outer Carton Label, Blister Label, Inner Label (where applicable) ▪ Proposed Package Insert for Brunei

5.3 The Authority may request the hard copy of the supporting documents if deemed necessary. Applicants are required to ensure that the hardcopy documents are identical to the electronic copies submitted. Under Section 22(3) of Medicines Order, 2007, any person who when making an application for registration of medicinal product makes a statement which he knows or has reason to believe is false in a material particular is guilty of an offence.

5.4 Application form must be duly completed and supported by all of the required documents according to the variation code. Applicants may refer to Appendix 5 for the required documents. In order to ensure that the application is complete, checklists of the documents submitted for the respective variation code must be provided. An example of the checklist for the variation code MaV-1 appears as **Annex 20.** The completed checklists should be attached at the front of each variation application upon submission to the DRU.

5.5 Applications are to be submitted together with the Log for Application for Variation to Registered Medicinal Products which appears as **Annex 21**.

5.6 Failure to comply with the above requirements will lead to non-acceptance of the application.

5.7 Submission of the variation applications must be made by appointment with the DRU.

5.8 Application is to be submitted **at least 9 months in advance** from the actual implementation date to:

Drug Registration Unit
Product Regulation Section
2nd Floor, Department of Pharmaceutical Services
Ministry of Health
Spg 433, Kg Madaras, Mukim Gadong 'A'
Rimba Highway, BE4710
Brunei Darussalam

5.9 During evaluation of the variation application, the 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 **THIRTY (30) calendar days** from the **issuance of 1st query** and **additional THIRTY (30) calendar days after issuance of 2nd query**. The application will be rejected / closed if no response is received from applicant after the deadline given and a new application will have to be submitted.

5.10 Applicant may submit update to variation applications which have been submitted and are currently pending approval in Brunei Darussalam using the Log for Submission of Updated Documents for Application for Variation to Registered Medicinal Products, which appears as **Annex 22**.

6. Fees

Please refer to Section 8 Application Fees.

7. Timeline

Please refer to **Appendix 1**.

8. 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