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1. INTRODUCTION

1.1 All medicinal products in Brunei Darussalam are controlled under the Medicines Order 2007 & Poisons Act 1956. As a preliminary step, the Department of Pharmaceutical Services (DPS) issues provisional registration of all medicinal products for human use prior to their use in Brunei Darussalam. All local manufacturers, wholesalers and importers of medicinal products must be licensed before they can conduct their businesses.

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

1.3 Meaning of ‘medicinal product’ and related expression as stated in the Medicines Order (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:-

(a) substances used in dental surgery for filling dental cavities;
(b) 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
(c) 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.

1.4 Provisional product registration certificate will be issued by the DPS for medicinal products that have been approved for registration in Brunei Darussalam. For provisional registration, only products that are registered in any of the DPS’s benchmark regulatory agencies i.e. Australia, Canada, Malaysia, Singapore, United Kingdom, and United States of America can be considered.

2. APPLICATION PROCEDURES FOR MEDICINAL PRODUCT REGISTRATION

2.1 The onus of applying for product registration rests with the firm responsible for the introduction of the product into the Brunei Darussalam market, i.e.:
2.1.1 In the case of an imported product, the manufacturer’s local representative or its appointed sole agent.

2.1.2 In the case of a locally manufactured product, the manufacturer of the product or the local product owner.

2.2 Applications for provisional product registration are to be made by submission of the letter of intent (refer to Annex 1 for the recommended model of the letter of intent) and by using the prescribed forms issued by the DPS. Application forms are charged at B$2.00 per set and 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

2.3 Applications must be duly completed and supported by all of the required documents i.e. Part I and Part II of the application dossier (Please see section 3 below on documents required for application for registration of medicinal products). The submitted application will be screened and validated for completeness within 14 days. Applications which are incomplete will not be accepted for evaluation.

2.4 Applications are to be submitted by the person responsible for the company 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

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

2.6 The processing fee of B$100.00 per product is payable at the point of submission of the application. Payment shall be made in the form of cash and it is non-refundable.

2.7 Upon acceptance of an application, an acknowledgement for the receipt of the application will be issued and a reference number will be generated. The reference number shown in this acknowledgement should be used in all subsequent correspondences relating to the application.

2.8 The flowchart on the procedure of application for provisional registration of medicinal products is as shown in Annex 2.

3. DOCUMENTS REQUIRED FOR APPLICATION FOR REGISTRATION OF MEDICINAL PRODUCTS

3.1 All applications for provisional 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. The application dossier required will consist of 4 parts which are as follows:

**PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION**

Section 1: Application Form (Form No: DPS/DRS/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, all applicants are advised to read the guidelines in the following annexes:

- **Annex 3.1** - Guide on How to Fill the Application Form for Registration of A Medicinal Product (Part I: Section 1)
- **Annex 3.2** - Guideline on Submission of Letter of Authorisation for Application of Registration of Medicinal Products (Part I: Section 2)
- **Annex 3.3** - Guideline on Submission of Certifications for Application of Registration of Medicinal Products (Part I: Section 3)
- **Annex 3.4** - Guideline on Submission of Product Labelling for Application of Registration of Medicinal Products (Part I: Section 4)
- **Annex 3.5** - 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: DPS/DRS/02/A)

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

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

- **Annex 4.1** - Guide on Submission of Quality Data for Application of Registration of Medicinal Products - Quality Requirements for Drug Substance (Part II – Section 1)
- **Annex 4.2** - Guide on Submission of Quality Data for Application of Registration of Medicinal Products - Quality Requirements for Drug Product (Part II – Section 2)
- **Annex 4.2.1** - Guidelines for Submission of Protocol of Analysis
- **Annex 4.2.2** - Minimum General Quality Control Specifications for Pharmaceutical Dosage Forms
Annex 4.2.3 - Guideline for Submission of Analytical Method Validation Forms

PART III: NON-CLINICAL (For a submission of New Chemical Entity, Biotechnological Products and some Major Variation Products only)

Section A: Table of Contents
Section B: Nonclinical Overview
Section C: Nonclinical Summary (Written and Tabulated)
Section D: Nonclinical Study Reports (As requested)
Section E: List of Key Literature References

Note:

- For guidance in the preparation of Part III of the application dossier, all applicants are advised to read the guidelines in the following annex:

  Annex 5 - Guide on Submission of Non-clinical Documents (Part III)

- For guidance in preparing the documents refer to Part III of The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use.

- Nonclinical 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.

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

PART IV: CLINICAL DOCUMENTS (For a submission of New Chemical Entity, Biotechnological Products and some Major Variation Products only)

Section A: Table of Contents
Section B: Clinical Overview
Section C: Clinical Summary
Section D: Tabular Listing of All Clinical Studies
Section E: Clinical Study Reports (If Applicable)
Section F: List of Key Literature References

Note:

- For guidance in the preparation of Part IV of the application dossier, all applicants are advised to read the guidelines in the following annex:
Annex 6 - Guide on Submission of Clinical Documents (Part IV)

- For guide in preparing the documents refer to Part IV of The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use.

- 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. Therefore, the authority who wishes to obtain such Clinical Study Reports should request for additional documentation.

- 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.

3.2 In addition to the hard copy, a soft copy of the application forms for administrative data and product information & quality requirements of the Drug Substance and the Drug Product can be obtained from the Drug Registration Unit. This will enable applicants to fill in the forms accordingly. For submission, a hard copy of the completed forms MUST be submitted.

3.3 The checklists for all the 4 parts above should be used to check against all the required items by Part I, Part II, Part III and Part IV of the application dossier. The completed checklists should be attached at the front of each part upon submission to the Drug Registration Unit.

4. PROCESSING OF APPLICATIONS

4.1 Review of application for provisional 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.

4.2 During product evaluation, the Drug Registration Unit 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 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.

4.3 The applicant will be informed of the decision of the Drug Registration Committee (Provisional) in writing as to whether the application has been approved or rejected.

4.4 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. A certificate of registration shall be issued for the registered product.
5. **REJECTION, CANCELLATION, SUSPENSION OF REGISTRATION**

5.1 The Drug Registration Committee 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.

5.2 Such products may not be imported and marketed in Brunei Darussalam. The holder of the registration certificate shall immediately surrender to the committee the registration certificate upon cancellation or suspension of registration of the product.

6. **APPEAL AGAINST DRUG REGISTRATION COMMITTEE DECISIONS**

6.1 For products that have been rejected for provisional registration by the Drug Registration Committee, applicant may make a written appeal to the Chairperson of the Committee by using the prescribed form (Form No: DPS/DRU/Appeal/01) issued by the DPS. All notice of appeals must be made within **THIRTY (30) calendar days** from the date of the committee’s notification. A soft copy of the application form can be obtained from the Drug Registration Unit. For submission, a hard copy of the completed form must be submitted. The Application form for appeal appears as Annex 7.

7. **MAINTENANCE OF REGISTRATION**

7.1 The conditions for registration of pharmaceutical products are as follows:-

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

7.1.2 The holder of the registration certificate must supply such documents, items, samples, particulars or information as the committee may require in relation to the registered product.

7.1.3 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 committee.

7.1.4 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 committee’s decision is made known to the applicant (for ‘existing’ products which are registered); and
- labelled **immediately** (for ‘new’ products which are registered).
7.1.5 The labels for the registered product must comply with all of the labelling requirements as specified by the Drug Registration Committee.

7.1.6 The registered product must only be indicated for use as approved by the Drug Registration Committee.

7.1.7 The holder of the registration certificate must inform the Drug Registration Committee of any adverse reactions or complaints on the registered product immediately after he/she receives notice of such adverse reactions or complaints.

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

7.2 The registration of a product shall be **valid for 3 years** or such period as specified in the registration certificate (unless sooner suspended or cancelled by the committee).

7.3 The **renewal** of product registration should be done **not later than a year** prior to expiry together with an appropriate fee.

8. **CHANGE IN PARTICULARS OF REGISTERED PRODUCTS**

8.1 The holder of a provisional product registration certificate must inform the DPS 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 DPS is required before the changes can be made, with the exception of some minor variations that require only notification to the DPS.

8.2 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 changes are made without prior approval from the DPS.

8.3 The application form (Form No: DPS/DRS/Vartn/01) and Guideline on Application for Variations to a Registered Medicinal Product appear as **Annex 8.1 and Annex 8.2** respectively. A soft copy of the application form can also be obtained from the Drug Registration Unit but for submission, a hard copy of the completed form **MUST** be submitted.
RECOMMENDED MODEL OF LETTER OF INTENT

COMPANY LETTERHEAD

ANNEX 1

APPLICANT’S COMPANY NAME AND ADDRESS

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 Provisional Product Registration

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

PRODUCT NAME
DOSAGE FORM AND STRENGTH

with the Drug Regulatory Authority in Brunei Darussalam. We enclose herewith the following documents as required, for your perusal:

Part I

Section I : Application Form (Form No: DPS/DRS/01)
Section II : Letter of Authorisation
Section III : (Please list the names of certificates enclosed as appropriate)
Section IV : Samples / Proposed Drafts of Product Labelling for unit carton, inner label & blister strips.
Section V : Samples / Proposed Drafts of 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: DPS/DRS/02/A)

Section II : Application Form for Quality requirements of the Drug Product
(Form No: DPS/DRS/02/B)

With regards,

[Applicant's signature]

[Applicant's Name & Designation]
FLOWCHART ON THE PROCEDURE OF APPLICATION FOR PROVISIONAL REGISTRATION OF MEDICINAL PRODUCTS

Application form obtained at B$2.00 per set from DRU

Application form filled according to guidelines

Appointment made with DRU for submission of application

Application form with relevant documents submitted to DRU

Documents screened and validated by DRU for completeness according to checklist

Receipt of applications acknowledged by DRU

Payment of processing fee of B$100 / product

Receipt of payment issued to applicant

Submitted documents checked for additional information and supporting documents

Evaluation

Committee Meeting

Rejected

Approved

Applicant informed

Certificate of Product Registration Issued

Finish

Incomplete

Application rejected if no response received from applicants after 60 days

Additional supporting documents submitted by applicant within 60 days

Applicant informed*

*Products rejected for registration, applicants may make a written appeal within 30 calendar days from the notification date.

Note:
Any variations to a registered product, applicants need to submit application/ notification for approval for change(s) to the Department of Pharmaceutical Services at least 2 months before the implementation.

March 2007
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, DPS/DRS/01 for all categories of pharmaceutical 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.

With EXCEPTION to injectables and peritoneal dialysis products, different packings (materials) or pack sizes (quantity/volume) of a product made by the same manufacturer to the same specifications, strength (content) of ingredients and dosage form, shall require only one application for product registration. The product registration shall be for the packings and pack sizes stated in the registration documents only. A separate application for registration MUST be submitted for different packing or pack sizes of injectable products and peritoneal dialysis products.

[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 registration certificate 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 according to the Guidelines on Registration and Post-registration Control of Medicinal Products Derived from Human Blood if a product contains ingredients derived from human blood. Please refer to Appendix 2 – Guidelines on Registration and Post-Registration Control of Medicinal Products Derived from Human Blood.

b) Ingredients Derived From Animals

Additional data needs to be provided according to the Guidelines for Minimising The Risk of Transmissible Spongiform Encephalopathy (TSE) Contamination in Human Medicinal Products if a product contains ingredients derived from animal source. Please refer to Appendix 3 - Guidelines for Minimising The Risk of Transmissible Spongiform Encephalopathy (TSE) Contamination in Human Medicinal Products.

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 4 – 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 DPS.
Should it be desired to include new indications, an application shall be filed with the DPS 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.

<table>
<thead>
<tr>
<th>Container Closure System</th>
<th>Quantity/Container</th>
<th>Shelf-Life</th>
<th>Storage Conditions</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Syringe</td>
<td>5ml/Syringe</td>
<td>24 months</td>
<td>2°C – 8°C</td>
<td>4 x 1’s</td>
</tr>
</tbody>
</table>

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 DPS 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) which is the object of the local application, should be provided.

<table>
<thead>
<tr>
<th>Country</th>
<th>Application status with details</th>
<th>Date</th>
<th>Approved forensic classification of the product</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. EU Centralised</td>
<td>Approved</td>
<td>1/1/2003</td>
<td>POM</td>
</tr>
</tbody>
</table>

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 DPS’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 DPS’s benchmark regulatory agencies for drug registration, to provide the expected date of submission.

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 Department of Pharmaceutical Services i.e. the authorities listed in the WHO ‘Certification Scheme On The Quality of Pharmaceutical Products Moving In International Commerce’.

If the product is being packed by a different company, copy of the GMP certificate of that company is also required.

All copies of 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 data sheet/Summary of Product Characteristics (SmPC) should be given on the certificate or be appended.

Details of quantitative composition are preferred but their provision is subject to the agreement of the product licence/registration holder.
**Note:** Enclose all certificates under Part I: Section 3 of Administrative Data & Product Information.

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 which is the object of the 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

6.1 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

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEROSOL</td>
<td>GRANULE, EFFERVESCENT, FOR SUSPENSION</td>
</tr>
<tr>
<td>AEROSOL, FOAM</td>
<td>GRANULE, FOR SOLUTION</td>
</tr>
<tr>
<td>AEROSOL, METERED</td>
<td>GRANULE, FOR SUSPENSION</td>
</tr>
<tr>
<td>AEROSOL, POWDER</td>
<td>GRANULE, FOR SUSPENSION, EXTENDED RELEASE</td>
</tr>
<tr>
<td>BEAD</td>
<td>GUM</td>
</tr>
<tr>
<td>BEAD, IMPLANT, EXTENDED RELEASE</td>
<td>GUM, CHEWING</td>
</tr>
<tr>
<td>CAPSULE</td>
<td>IMPLANT</td>
</tr>
<tr>
<td>CAPSULE, COATED</td>
<td>INHALANT</td>
</tr>
<tr>
<td>CAPSULE, COATED PELLETS</td>
<td>INJECTION</td>
</tr>
<tr>
<td>CAPSULE, COATED, EXTENDED RELEASE</td>
<td>INJECTION, EMULSION</td>
</tr>
<tr>
<td>CAPSULE, DELAYED RELEASE</td>
<td>INJECTION, LIPID COMPLEX</td>
</tr>
<tr>
<td>CAPSULE, DELAYED RELEASE PELLETS</td>
<td>INJECTION, POWDER FOR SUSPENSION</td>
</tr>
<tr>
<td>CAPSULE, EXTENDED RELEASE</td>
<td>INJECTION, POWDER FOR SUSPENSION, EXTENDED RELEASE</td>
</tr>
<tr>
<td>CAPSULE, FILM COATED, EXTENDED RELEASE</td>
<td>INJECTION, POWDER, LYOPHILISED, FOR SOLUTION</td>
</tr>
<tr>
<td>CAPSULE, GELATIN COATED</td>
<td>INJECTION, POWDER, LYOPHILISED, FOR SUSPENSION</td>
</tr>
<tr>
<td>CAPSULE, LIQUID FILLED</td>
<td>INJECTION, POWDER, LYOPHILISED, FOR SUSPENSION, EXTENDED RELEASE</td>
</tr>
<tr>
<td>CELL SUSPENSION</td>
<td>INJECTION, POWDER, LYOPHILISED, FOR LIPOSOMAL SUSPENSION</td>
</tr>
<tr>
<td>CEMENT</td>
<td>INJECTION, SOLUTION</td>
</tr>
<tr>
<td>COLLODION</td>
<td>INJECTION, SOLUTION, CONCENTRATE</td>
</tr>
<tr>
<td>CREAM</td>
<td>INJECTION, SUSPENSION</td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>INJECTION, SUSPENSION, EXTENDED RELEASE</td>
</tr>
<tr>
<td>DIAPHRAGM</td>
<td>INJECTION, SUSPENSION, LIPOSOMAL</td>
</tr>
<tr>
<td>DISC</td>
<td>INTRAUTERINE DEVICE</td>
</tr>
<tr>
<td>DOUCHE</td>
<td>IRRIGANT</td>
</tr>
<tr>
<td>ELIXIR</td>
<td>LINCTUS</td>
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<tr>
<td>EMULSION</td>
<td>LINIMENT</td>
</tr>
<tr>
<td>ENEMA</td>
<td>LIQUID</td>
</tr>
<tr>
<td>EXTRACT</td>
<td>LOTION</td>
</tr>
<tr>
<td>EYE/EAR/NOSE DROP</td>
<td>LOZENGE</td>
</tr>
<tr>
<td>FILM</td>
<td>MIXTURE</td>
</tr>
<tr>
<td>GAS</td>
<td>MOUTHWASH</td>
</tr>
<tr>
<td>GAUZE</td>
<td>OIL</td>
</tr>
<tr>
<td>GEL</td>
<td>OINTMENT</td>
</tr>
<tr>
<td>GEL, DENTIFRICE</td>
<td>PAD</td>
</tr>
<tr>
<td>GENERATOR</td>
<td>PAINT</td>
</tr>
<tr>
<td>GRAFT</td>
<td>PASTE</td>
</tr>
<tr>
<td>GRANULE</td>
<td>PASTE, DENTIFRICE</td>
</tr>
<tr>
<td>GRANULE, DELAYED RELEASE</td>
<td>PASTILLE</td>
</tr>
<tr>
<td>GRANULE, EFFERVESCENT FOR SOLUTION</td>
<td>PATCH</td>
</tr>
</tbody>
</table>
### LIST OF RECOGNISED DOSAGE FORMS – CONT’D

<table>
<thead>
<tr>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATCH, EXTENDED RELEASE</td>
</tr>
<tr>
<td>PELLET</td>
</tr>
<tr>
<td>PELLETS, COATED, EXTENDED RELEASE</td>
</tr>
<tr>
<td>PELLET, IMPLANTABLE</td>
</tr>
<tr>
<td>PESSARY</td>
</tr>
<tr>
<td>PILL</td>
</tr>
<tr>
<td>PLASTER</td>
</tr>
<tr>
<td>POULTICE</td>
</tr>
<tr>
<td>POWDER</td>
</tr>
<tr>
<td>POWDER, DENTIFRICE</td>
</tr>
<tr>
<td>POWDER, FOR SOLUTION</td>
</tr>
<tr>
<td>POWDER, FOR SUSPENSION</td>
</tr>
<tr>
<td>POWDER, METERED</td>
</tr>
<tr>
<td>SHAMPOO</td>
</tr>
<tr>
<td>SOAP</td>
</tr>
<tr>
<td>SOLUTION</td>
</tr>
<tr>
<td>SOLUTION, CONCENTRATE</td>
</tr>
<tr>
<td>SOLUTION, GEL FORMING, EXTENDED RELEASE</td>
</tr>
<tr>
<td>SPONGE</td>
</tr>
<tr>
<td>SPRAY</td>
</tr>
<tr>
<td>SPRAY, METERED</td>
</tr>
<tr>
<td>STICK</td>
</tr>
<tr>
<td>STRIP</td>
</tr>
<tr>
<td>SUPPOSITORY</td>
</tr>
<tr>
<td>SUPPOSITORY, EXTENDED RELEASE</td>
</tr>
<tr>
<td>SUSPENSION</td>
</tr>
<tr>
<td>SYRUP</td>
</tr>
<tr>
<td>TABLET</td>
</tr>
<tr>
<td>TABLET, CHEWABLE</td>
</tr>
<tr>
<td>TABLET, COATED</td>
</tr>
<tr>
<td>TABLET, DELAYED RELEASE</td>
</tr>
<tr>
<td>TABLET, DELAYED RELEASE PARTICLES</td>
</tr>
<tr>
<td>TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING</td>
</tr>
<tr>
<td>TABLET, EFFERVESCENT</td>
</tr>
<tr>
<td>TABLET, EFFERVESCENT, FOR SOLUTION</td>
</tr>
<tr>
<td>TABLET, EXTENDED RELEASE</td>
</tr>
<tr>
<td>TABLET, FILM COATED</td>
</tr>
<tr>
<td>TABLET, FILM COATED, EXTENDED RELEASE</td>
</tr>
<tr>
<td>TABLET, FOR SOLUTION</td>
</tr>
<tr>
<td>TABLET, FOR SUSPENSION</td>
</tr>
<tr>
<td>TABLET, MULTILAYER, EXTENDED RELEASE</td>
</tr>
<tr>
<td>TABLET, ORALLY DISINTEGRATING</td>
</tr>
<tr>
<td>TINCTURE</td>
</tr>
<tr>
<td>WAFER</td>
</tr>
<tr>
<td>OTHERS</td>
</tr>
</tbody>
</table>
APPENDIX 2 - GUIDELINES ON REGISTRATION AND POST-REGISTRATION CONTROL OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD

1. INTRODUCTION

Medicinal products containing components derived from human blood carry the risk of transmission of infectious agents. The safety of these products is assured through the registration control system, as described below.

This guideline is applicable to all medicinal products containing at least one ingredient (whether active or inactive) that is derived from human blood. This group of products is described as Human Blood-Derived Products (HBP) in this guideline.

2. REGISTRATION REQUIREMENTS

Safety of a HBP has to be supported by documentation in addition to the standard documentation required for registration of a medicinal product. The additional supporting documentation, which includes the control of donors, source materials, manufacturing processes and final product safety, are described below.

Certification to confirm compliance with the following criteria and supporting documentation are required to be submitted.

2.1 Control of Donors and Source Materials

2.1.1) Certification/confirmation that each donor of source material has undergone a proper screening procedure to ensure that all established health criteria (including viral risks requirements) are met. The criteria used must conform to the recommendations on suitability of blood and plasma donors as set out by the US FDA, the Council of Europe and the Australian TGA. Specifically, the following details need to be furnished:

a) Collection centres
   - Names and addresses of blood/plasma collection centres, including subcontractors and any separate site for testing of individual donations.
   - Audits:
     o Internal audits (frequency and date of last audit)
     o Audits by regulatory authority (frequency and date of last audit)

b) Data on epidemiology and blood-borne infections
   - Provide an assurance that there is a continuing evaluation of the epidemiology at collection centres.
   - Data should be reported as:
     o Incidence of confirmed seroconversion rates in regular donors (per number of donors and number of donations)
     o Prevalence of confirmed positives in new donors as well as in known donors

c) Selection/Exclusion criteria
- Characteristics of donation:
  o Identify whether plasma donor is renumerated or non-renumerated
  o Clarify the nature of any compensation for donation
  o Outline the nature of the examination and interview of donors

- Exclusion criteria for donors:
  o Confirm that centres do not collect blood/plasma from a population with a high prevalence of infections transmitted by blood (HIV, HCV, HBV etc.)
  o Confirm that there are measures taken to ensure viral safety for recipients with respect to major pathogenic agents
  o Compliance with those exclusion criteria specified in appropriate documents (Directives, Guidelines, Pharmacopoeial)

2.1.2) Certification/confirmation that each unit of the source material has been tested non-reactive for Hepatitis B surface antigen, antibody to HIV-1&2, and antibody to Hepatitis C Virus by tests approved for such use by the US FDA or an equivalent authority. There must be no pooling of plasma for testing purposes. Specifically, the following details need to be furnished:

- Screening tests for markers of infection
  o List of tests performed on individual donation
  o Test kit used for each test and licence number for each kit
  o Validation of these screening procedure methods
  o Details of any inventory hold/quarantine periods and procedures

2.1.3) Certification/confirmation that all steps in the processing of source material, including donor examination, blood collection, plasmapheresis, laboratory testing, labelling, storage, and issuing are performed in centres that have been licensed by the US FDA or equivalent authority for that purpose and that these conform to the requirements for the collection of source materials as specified in “The Collection, Fractionation, Quality Control, And Uses of Blood And Blood Products” published by the WHO. Specifically, the following details need to be furnished:

- System to trace the path of any donation
  o Confirm that there is a system in place that ensures traceability from the donation centre to finished product and vice versa.
  o Provide information on steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing.

2.1.4) Certification/confirmation that all source materials are collected by aseptic techniques designed to assure the integrity and to minimise the risk of contamination of the source material and that the closure of the container used maintains a hermetic seal. Specifically, the following details need to be furnished:

A) Blood bags
   - Information on the name of bag, manufacturer, anticoagulant solution, composition, specification
   - Indication of conformance to a particular standard e.g. WHO, EP
B) Plasma quality
- Information on storage conditions and maximum storage time with indication on how conditions are maintained from collection centre to the manufacturer
- Confirmation of compliance with appropriate standard

C) Plasma specification
- Information on specification(s) and confirm compliance to specification(s)
- Information on in-process tests on plasma pool, if any

2.1.5) Certification to confirm that the source materials do not contain an additive other than citrate or acid citrate dextrose anticoagulant solution unless it has been shown that the processing method yields a final product free of the additive to such an extent that the continued safety, purity, potency, and effectiveness of the final product is not adversely affected.

2.2 Manufacturing Processes / QC Procedures

2.2.1) A specimen of the standard contract between the fractionator/manufacturer and donation centres or organisation responsible for collecting plasma with agreement to comply with GMP and its procedures.

2.2.2) Manufacturer’s letter of commitment stating that:
   a) All collection centres have signed the contract.
   b) The national authority will be notified in the event of a serious failure of a blood collection centre.

2.2.3) Certification/documentation to confirm that all steps in the manufacture of the final product are conducted in establishments that have been licensed by the US FDA or equivalent authority for that purpose. All handling and processing techniques employed conform with GMP of the US FDA, the Australian TGA, the EC or WHO’s guidelines on GMP for Biological Products.

2.2.4) Certification/documentation to confirm that each batch of source material intended for manufacture has been tested for Hepatitis B surface antigen, antibody to HIV-1&2 and antibody to Hepatitis C Virus by tests approved for such use by the US FDA or an equivalent authority. Each batch of source material must also be tested for HCV RNA by genomic amplification testing. Specifically, the following details need to be furnished:
   a) Plasma pooling
      - Information on the number of individual plasma units pooled together
      - List of tests performed on these plasma pools
      - Test kit used for each test and licence number for each kit

2.2.5) Certification/documentation to confirm that the processing method used does not affect the integrity of the product and has been demonstrated to consistently yield a product that is safe for use in humans. Processing methods used for the manufacture of products intended for intravenous use should have been shown to consistently yield a product that is safe for intravenous injection.

2.2.6) Certification/documentation to confirm that processing steps are conducted in a manner to minimise risk of contamination from microorganisms, pyrogens, or other
impurities. Preservatives to inhibit growth of microorganisms are not used or added to the product at any stage of processing. Specifically, the following details need to be furnished:

a) Manufacturing process
   - A detailed description of the manufacturing process and controls to demonstrate proper quality control or prevention of possible contamination with adventitious agents.
     - Starting materials: Information on raw materials, intermediate products, reagents and auxiliary materials with specifications or statements of quality of each.
     - Flowchart: A complete visual representation of the manufacturing process flow. This flow should show the steps in production, equipment, and materials used, and a complete list of the in-process controls and tests performed on the product at each step. This diagram should also include information on the methods used to transfer the product between steps.
     - Detailed description: A detailed description of the fractionation, formulation, sterilisation, aseptic processes and purification. This should include a rationale for the chosen methods, and the precautions taken to assure containment and prevention of contamination or cross-contamination. In-process bioburden and endotoxin limits should be specified where appropriate. Any reprocessing or related method should be fully validated and described. The allowable conditions for reprocessing of all or parts of any batch should be described.
     - Batch record: A complete batch record of the process of production of the biologic product should be included.

b) Process control
   - A description of the control checks performed at various stages of the manufacture, processing and packaging of the product.
   - A description of the in-process and final controls, including analytical tests and appropriate data to support the specifications.
   - Validation data
     - A description of the validation studies which identify and establish acceptable limits for critical parameters to be used as in-process controls, to assure the success of routine production.
     - Validation studies for the purification process: a description of the validation of the purification process to demonstrate adequate removal of extraneous substances such as chemicals used in purification, column contaminants, endotoxin, antibiotics, residual plasma proteins, non-viable particulates and viruses.
     - Validation studies for all sterilisation and aseptic processes (e.g. formulation through filling and sealing).

c) Special notes:
   - Albumin (Human Solution and Plasma Protein Fraction [Human] Solution):
     - The product must have undergone heat treatment or other established viral inactivation procedures. Heat treatment should be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of 60±0.5°C.
- Clotting Factor Concentrate, Intravenous Immunoglobulin and Intramuscular Immunoglobulin:
  - The product must have undergone processing methods that include established and validated specific viral inactivation capable of inactivating at least $10^5$ infectious particles of HIV per ml of solution (that is, a $5 \log_{10}$ reduction in concentration of viable virus), and not to transmit viral hepatitis.

2.3 Tests on Final Product

2.3.1) The physical, chemical and pharmaceutical properties of the finished products must comply with the relevant United States, British or European Pharmacopoeial requirements. Specifically, the following details need to be furnished:

a) Product testing
   - Specifications and analytical methods used for release testing and expiration dating, sufficient to assure product identity, purity, strength, or potency and lot-to-lot consistency.
   - Validation protocol and results for non-compendial analytical systems to demonstrate system suitability.
   - Lot release protocols, including specification ranges of representative lots of the product. Specifications may include, but not limited to, biochemical purity, safety, appearance, pH, residual moisture, excipients, endotoxins, and sterility.
   - Methods and standards of acceptance, including the sampling plan and the accuracy and precision of the analytical methods in sufficient details to permit duplication and verification.

b) Container closure system/shipping containers
   - A description of the container and closure system with information on its compatibility with the biological substance.
   - Evidence of container and closure integrity.

c) Stability
   - Stability data for the biological product as packaged in the container in which it is to be marketed.
   - A description of the storage conditions, study protocols and results supporting the stability of the biological product and any intermediates that are stored.
   - An expiration dating period supported by the results of the stability study.

2.4 Conditions for Marketing Approval

If approved for registration, the product registration certificate issued for a HBP will have the following conditions imposed:

2.4.1) The import and sale of the product to which the licence relates must be accompanied by a batch certification, which should contain the following information:

a) The name and country of source plasma collection centre;

b) Confirmation that each donor of the source material has been tested negative
for Hepatitis B surface antigen, antibody to HIV-1&2 and antibody to Hepatitis C virus;

c) Confirmation that the source material used in the manufacture of the batch of product has been tested negative for Hepatitis B surface antigen, antibodies to HIV-1&2 and antibody to Hepatitis C virus/HCV RNA; and

d) Confirmation that the product has undergone manufacturing processes that include established specific viral inactivation procedures.

2.4.2) The batch certification and product movement records shall be maintained for 10 years from the date of importation and be made available for inspection by the registration authority when required.

3. **POST-REGISTRATION CONTROLS**

The post-registration for HBP are as follows:

3.1. **Compliance with Standard Provisions for Product Registration**

Product registration holders are required to comply with the standard provisions stipulated in the Medicines Regulations.

3.2. **Amendments**

The product registration holder is responsible for ensuring that the product imported for local sale and supply is identical, in all aspects, to that approved by the DPS. The registration holder should notify the DPS of any minor variations and obtain approval from the DPS before implementing major variations (for example, change of source plasma).

3.3. **Requirements for Dealers**

3.3.1) Importers and distributors of HBP are required to be licensed under the Poisons Act. The dealers must:

   a) Ensure that only qualified personnel, for example, pharmacists, handle the importation and distribution of these products;

   b) Maintain batch certification and proper product movement records for each batch of product imported into Brunei Darussalam. These records must be kept for at least 10 years from the date of importation/distribution and be made available for inspection by the DPS when required.

3.3.2) Companies dealing in medicinal products derived from human have to be vigilant in the checking of documentation and maintenance of records. Companies who receive reports of possible product contamination should immediately check their records for any importation or distribution of the product. Information on importation or distribution of possibly contaminated products and the proposed recall plan should be submitted to the DPS without delay. A crisis management plan should be put in place for this purpose.

3.4. **Inspection**

The DPS will conduct inspections on local importers and product registration holders to check for compliance with the above requirements.
APPENDIX 3 - GUIDELINES FOR MINIMISING THE RISK OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY (TSE) CONTAMINATION IN HUMAN MEDICINAL PRODUCTS

1. INTRODUCTION

Transmissible Spongiform Encephalopathy (TSE) includes scrapie in sheeps and goats, chronic wasting disease in mule, deer and elk, bovine spongiform encephalopathy (BSE) in cattle, as well as Kuru and Creutzfeldt-Jakob Disease (CJD) in humans. Agents causing these diseases replicate in infected individuals generally without evidence of infection detectable by currently available diagnostic tests. It is believed that these agents may have incubation periods of up to several years before causing observable disease (usually neurological disorder) and eventually death. No means of therapy is known.

BSE was first recognised in the United Kingdom in 1986. A large number of cattle and individual herds have since been affected. BSE is a food borne infection and there is evidence suggesting that the new variant of human Creutzfeldt-Jakob Disease (vCJD) may be caused by the same agent that is responsible for BSE in cattle.

The discovery of vCJD has raised concerns that the BSE can be transmitted to man. Caution is therefore warranted if biological materials from species known to be affected by TSE, are used for the manufacture of medicinal products. This guideline provides recommendations that should be followed to minimise the risk of TSE agent contamination in human medicines.

This guideline is applicable to all materials of animal origin that are used in the preparation of both active (e.g. insulin) and inactive ingredients (e.g. gelatin, cell culture medium), and other reagent that may come into contact with a pharmaceutical product during its manufacturing process (e.g. cell culture serum and enzymes). For human blood-derived ingredients, please refer to the "Guidelines on registration and post-registration control of medicinal products derived from human blood".

2. REGISTRATION REQUIREMENTS

The risk of transmission of infectious agents can be greatly reduced, by controlling a number of parameters. These parameters include the source of animals, the nature of animal tissue used in manufacturing and the production process. Detailed information as listed below must be submitted to support the registration of any pharmaceutical product that contains animal derived ingredients.

2.1 Source of animals

2.1.1) The most satisfactory source of materials is from countries without any reported case of BSE (please refer to the updated statistics for BSE positive countries provided by Office International Des Episooties (OIE), http://www.oie.int/eng/info/en_esbmonde.htm). A compulsory notification of BSE cases in the country of origin and a compulsory clinical and laboratory verification of suspected cases are required for product application.
2.1.2) Material sourced from countries where a positive number of indigenous cases have occurred should not be accepted for product application unless there is proper justification.

2.2 Nature of animal tissue used in manufacturing

2.2.1) In a BSE infected animal, different organs and secretions have different levels of infectivity. On the basis of data on natural scrapie, organs, tissues, and fluids have been classified into four main groups bearing different potential risks, as shown below:

a) **Category I (High Infectivity):** brain, spinal cord, eye

b) **Category II (Medium Infectivity):** ileum, lymph nodes, proximal colon, spleen, tonsil, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary, adrenal

c) **Category III (Low Infectivity):** distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus

d) **Category IV (No detectable Infectivity):** blood clots, faeces, heart, kidney mammary gland, milk ovary, saliva, salivary gland, seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, foetal tissue, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine

2.2.2) In certain situations there could be cross-contamination of tissues from different categories of infectivity e.g. direct contact between different materials, or the use of penetrative brain stunning as a method of slaughtering the animals.

2.2.3) For product applications, the applicants should provide detailed information on the nature and quantity of each animal derived material.

- Used in the manufacturing process (whether or not this is present in the final product); and
- Present in the final product formulation.

2.3 Production process

2.3.1) Controlled sourcing is the most important criterion in achieving acceptable safety of the product due to the documented resistance of TSE agents to most inactivation procedures. The production process, wherever possible, should be designed to take into consideration all available information on methods that are thought to inactivate or remove TSE agents.

2.3.2) If claims are made that inactivation of TSE agents occurs during the manufacturing process, relevant information on the process should be submitted for evaluation.

2.4 Assessment report for the risk of TSE

2.4.1) The applicant should submit an assessment report on the risk of TSE in relation to the product submitted for registration.
2.4.2) The scope of this report should cover sections 2.1, 2.2 and 2.3 above, as well as the risk factors associated with the route of administration and the maximum therapeutic dosage (daily dosage and duration of treatment) of the product.

2.5 Certificate of Suitability

2.5.1) Preference is accorded to animal-derived materials that have been awarded Certificates of Suitability by the European Directorate for the Quality of Medicines (EDQM). Pharmaceutical manufacturers should submit these Certificates of Suitability, in lieu of the documents stipulated under paragraphs 2.1 to 2.4 above, to support the registration of their products.

2.5.2) Applicant may refer to Ph.Eur. and the EDQM website (http://www.pheur.org) for more information on TSE and the Certificate of Suitability.

3. POST-REGISTRATION REQUIREMENTS

3.1 Compliance with standard provisions for product registration

Product registration holders are required to comply with the standard provisions stipulated in the Medicines Regulations.

3.2 Amendments

The product registration holder is responsible for ensuring that the product imported for local sale and supply is identical, in all aspects, to that approved by the DPS. The registration holder should notify the DPS of any variations and obtain approval from the DPS before implementing the variation if necessary (for example, change of source materials for manufacturing).

3.3 Requirements for Dealers

Applicants dealing in medicinal products containing ingredients derived from animal sources have to be vigilant in the checking of documentation and maintenance of records. Applicants that receive reports on possible product contamination by infective agents such as TSE should immediately check their records for any importation or distribution of the product. The dealer for any animal-sourced medicinal product should put in place a recall plan and a crisis management plan.

4. CONCLUSION

The acceptability of a particular medicinal product containing animal source ingredients, or which as a result of manufacture could contain these materials, will be influenced by a number of factors, including:

- Documented and recorded source of animals
- Nature of animal tissue used in the manufacture
- Production process
- Route of administration
- Quantity of tissue used in the medicinal products
- Maximum therapeutic dosage
- Intended use of the blood

The above guidelines only serve as a guidance. Pharmaceutical manufacturers and owners are required to observe international best practices at all times and to comply with the requirements
of the EU, USA, Australia, Canada, in particular, the requirements as set down in the following documents:

a) CPMP & CVMP’s Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01.


c) Ph.Eur, general monograph on “Product with risk of transmitting agents of animal spongiform encephalopathies”.

## APPENDIX 4 - LIST OF RECOGNISED ROUTES OF ADMINISTRATION

<table>
<thead>
<tr>
<th>Buccal</th>
<th>Rectal</th>
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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 pharmaceutical product

Product Name
Dosage Form and Strength

with the Drug Regulatory Authority in Brunei Darussalam on our behalf. They will be the marketing authorisation holder of the registration certificate and be responsible for all matters pertaining to the regulation of this product.

Signature: ________________________________

Name: ________________________________

Designation: ________________________________

Date: ________________________________
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

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) and amount(s) per unit dose:

_____________________________________________________

_____________________________________________________

For complete qualitative composition including excipients, see attached

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

□ 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.

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

_____________________________________________________

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

Name : ____________________________________________

Address : _________________________________________

2A.3 Status of product licence holder:
2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are:

Name: ________________________________
Address: ________________________________

2A.4 Summary Basis of Approval appended?  
- □ Yes
- □ No

2A.5 Is the attached, officially approved product information complete and consonant with the licence?  
- □ Yes
- □ No
- □ Not provided

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

Name: ________________________________
Address: ________________________________

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

Name: ________________________________
Address: ________________________________

2B.2 Status of applicant:  
- □ a
- □ b
- □ c

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

Name: ________________________________
Address: ________________________________

2B.3 Why is marketing authorisation lacking?  
- □ not required
- □ under consideration
- □ not requested
- □ refused

2B.4 Remarks:  
______________________________

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

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

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 none 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 3.4

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)
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 Department of Pharmaceutical Services (DPS) of Ministry of Health, Brunei Darussalam for registration i.e. 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
GUIDE ON SUBMISSION OF QUALITY DATA FOR APPLICATION OF REGISTRATION OF MEDICINAL PRODUCTS - QUALITY REQUIREMENTS FOR DRUG SUBSTANCE

(PART II: SECTION 1)

INTRODUCTION

This section caters for medicinal products containing certain categories of active ingredients only. Full particulars are required for the following:

- Medicinal products containing new drug substances or combination of new drug substances.
- Medicinal products containing new drug substances in combination with well established ingredients. (it is required for new drug substances only. Effects of the combination on the properties of the new drug substances and well established ingredients, if any, should be included)
- Medicinal products containing little-known ingredients or non-pharmacopoeial substances – poorly documented in the literature.
- Medicinal products containing pharmacopoeial substances when there is reason to doubt the validity of the specifications, for example, when obtained from a new source, different method of manufacture / synthesis, giving rise to different impurities, etc.

Full particulars are not required for products containing simple, widely used, well-documented ingredients, especially those which are subjects of current pharmacopoeias. Only a clear and concise, but as far as possible, complete summary of necessary data and particulars of relevant active ingredients, need to be submitted with the application form, DPS/DRS/02/A. Details of data and supporting documents shall be kept by the applicant and submitted to the Drug Quality Control Section immediately on request.

SECTION A: TABLE OF CONTENTS

A table of contents for the filed application should be provided.
### SECTION B: QUALITY OVERALL SUMMARY

The tabulated information below can be used as a checklist to which information is required for the registration of the medicinal product concerned.

<table>
<thead>
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<th>PARAMETERS</th>
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<td>1.3 General Properties</td>
<td>- Physico-chemical properties.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biological activity.</td>
<td>✓</td>
</tr>
<tr>
<td>S2</td>
<td>Manufacture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1 Manufacturer(s)</td>
<td>- Name and address of manufacturer(s)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>2.2 Description of Manufacturing Process and Process Controls</td>
<td>- The description of the drug substance manufacturing process and process control that represents the applicant’s commitment for the manufacture of the drug substances.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Information on manufacturing process that typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>2.3 Control of Materials</td>
<td>- Specifications of starting materials, solvents, reagents, catalysts, and any other materials used in the manufacturing process of the drug substance indicating where each material is used in the process. Tests and acceptance criteria of these materials.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Control of source and starting materials of biological origin.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Source, history and generation of cell substrate.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cell banking system, characterisation and testing.</td>
<td>✓</td>
</tr>
<tr>
<td>No.</td>
<td>PARAMETERS</td>
<td>COMPONENTS</td>
<td>REQUIREMENTS</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
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</tr>
<tr>
<td></td>
<td><strong>2.4 Controls of Critical Steps and Intermediates</strong></td>
<td>- Viral safety evaluation.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Critical Steps: Tests and acceptance criteria, with justification</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>including experimental data, performed at critical steps of the</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>manufacturing process.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Intermediates: Specifications and analytical procedure, if any, for</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intermediates isolated during the manufacturing process.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Stability data supporting storage conditions.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Process validation and/or evaluation studies for aseptic processing and</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sterilisation.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td><strong>2.5 Process Validation and/or Evaluation</strong></td>
<td>- Description and discussion of significant changes made to the</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>manufacturing process and/or manufacturing site of the drug</td>
<td>✓</td>
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<tr>
<td></td>
<td></td>
<td>substance used in producing non-clinical, clinical, scale-up, pilot and</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>if available, production scale batches.</td>
<td>✓</td>
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<tr>
<td></td>
<td></td>
<td>- Development history of the manufacturing process as described in S2.2.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td><strong>2.6 Manufacturing Process Development</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3</td>
<td><strong>Characterisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**3.1 Elucidation of Structure and other</td>
<td>- Evidence of chemical structure based on e.g. synthetic route and</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Characteristics**</td>
<td>spectral analyses.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Compendial requirements or equivalent information from the</td>
<td>✓</td>
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<tr>
<td></td>
<td></td>
<td>manufacturer.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Details on primary, secondary and higher-order structure and</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>information on biological activity, purity and immunochemical</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>properties (when relevant).</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>3.2 Impurities</strong></td>
<td>- Summary of impurities monitored or tested for during and after</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>manufacture of drug substance.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compendial requirements or equivalent information from the</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>manufacturer.</td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td><strong>Control of Drug Substance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>4.1 Specification</strong></td>
<td>- Detailed specification, tests and acceptance criteria.</td>
<td>✓</td>
</tr>
<tr>
<td>No.</td>
<td>PARAMETERS</td>
<td>COMPONENTS</td>
<td>REQUIREMENTS</td>
</tr>
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<td>---------------------------------------------------------------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Compendial specifications or equivalent information from the manufacturer.</td>
<td>NCE Biotech</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Specify source, including as appropriate species of animal, type of microorganism etc.</td>
<td>MaV MiV G</td>
</tr>
<tr>
<td>4.2</td>
<td>Analytical Procedures</td>
<td>- The analytical procedures used for testing of drug substance.</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compendial methods or equivalent information from the manufacturer.</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance.</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>4.3</td>
<td>Validation of Analytical Procedures</td>
<td>- Description of recent batches and results of the analysis to establish the specification.</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Justification for drug substance specification.</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>S5</td>
<td>Reference Standards or Materials</td>
<td>- Information on the reference standards or reference materials used for testing of the drug substance.</td>
<td>✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compendial requirements or equivalent information from the manufacturer.</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>S6</td>
<td>Container Closure System</td>
<td>- Description of the container closure systems (S6.1 – S6.3).</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>S7</td>
<td>Stability</td>
<td>- Stability studies summary and conclusion (S7.1 – S7.3).</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Stability data from manufacturer or equivalent.</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>S8</td>
<td>Other data, if any</td>
<td>- Summary reports of other relevant data.</td>
<td>✓ ✓ ✓</td>
</tr>
</tbody>
</table>

**Key**

* : if required

**NCE**: New Chemical Entity

**Biotech**: Biotechnological Products

**MaV**: Major Variation

**MiV**: Minor Variation

**G**: Generics
SECTION C: BODY OF QUALITY DATA ON DRUG SUBSTANCE

The contents for the filed application should consist of information addressing the requirements arranged according to the format provided below.

S1. IDENTITY OF DRUG SUBSTANCE

S1.1 Nomenclature

Information provided should include the following:

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, if any

S1.1.4 Laboratory code (if applicable)

S1.1.5 Chemical Name according to International Union of Pure and Applied Chemistry (IUPAC)

S1.2 Structural Formula

The structural formula should be given diagrammatically along with the molecular weight of the drug substance. Molecular weight of base or acid should be given when as salt. For natural products, the active components and structural details should be clearly stated. For the less well-defined substance, a detailed description of the nature of substance should be given.

S1.2.1 Structural Formula

Structural formula should be given for NCE and generic products only.

S1.2.2 Molecular Formula

Molecular formula should be given for NCE and generic products only.

S1.2.3 Relative Molecular Mass

Relative molecular mass should be given for NCE, biotechnological and generic products.

S1.2.4 Schematic Amino Acid Sequence

Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications should be given for biotechnological products only.

S1.3 General Properties

S1.3.1 Physicochemical Properties
List of physicochemical and other relevant properties of the drug substance are required to be provided, where applicable, such as, colour; physical state (powder, amorphous, liquid, etc), odour; taste; solubility in water; common solvents (chloroform, ether, alcohol, etc), melting points, hygroscopicity; $pK_a$, $pH$ values and other characteristics.

S1.3.2 Biological Properties

Biological properties are required for biotechnological products.

References

**NCE Products**
- ICH Guidelines Q6A

**Biotech Products**
- ICH Guidelines Q6B

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**S2. MANUFACTURE OF DRUG SUBSTANCE**

**S2.1 Name and Address of Manufacturer(s)**

Name and full address of manufacturer(s) of the drug substance including the city and country of the manufacturer(s) should be provided.

**S2.2 Description of Manufacturing Process and Process Controls**

An adequate description of the manufacturing process and process controls of the drug substance should be provided as required by each product category below. Each stage of manufacturing process, isolation and purification steps should be described.

- **NCE Product**

  Information required is as follows:

  - A schematic flow diagram of the synthetic process(es) that includes molecular formulae, weights and yields, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents;

  - A sequential procedural narrative of the manufacturing process that provides quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale, and includes process controls, equipment and operating conditions, such as temperature, pressure, $pH$, time etc;

  - Explanation of alternative steps or process that is described with the same level of details as the primary process. Reprocessing steps should be identified and justified.

  - Alternative chemicals and solvents used in the manufacture of the drug substance should be clearly indicated. Circumstances under which such alternatives will be used shall be clearly stated.

- **Biotechnological Product**

  - Information on the manufacturing process, which typically starts with a vial(s) of the cell bank and includes cell culture, harvest(s), purification and modification reaction, filling storage and shipping conditions.
If the manufacturing process involves the use of antibiotics as intermediates, information on the methods of removing the residual quantities must be provided. Evidence to show that the final product is free from their contaminants is required.

**Bibliography of Manufacturing Process and Process Control**

List of papers, reports, articles, references and any other form of documentation pertaining to route of synthesis; chemical reactions; biological reactions and flow chart for synthesis / manufacture.

**References**

*Biotech Products*
- ICH Guidelines Q5A, Q5B and Q6B

**S2.3 Quality Control of Starting Materials**

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

Specifications for starting materials used in the manufacture of drug substance should be stated. This includes raw materials, solvents, reagents, catalysts, identifying where each material is used in the manufacturing process regardless at the start of manufacture or added at various stages of the manufacturing process. If materials are of Analar® grade or subject of current pharmacopoeias, it is sufficient to make appropriate references.

Specifications that are routinely tested should be indicated. If not routinely tested, the frequency and circumstances under which the test is done should also be indicated. Detailed analytical methods and test protocols should be submitted.

Information provided should demonstrate that materials including biologically-sourced materials, for example, media components, monoclonal antibodies, enzymes, meet standards appropriate for their intended use including the clearance or control of adventitious agents. For biologically-sourced materials, this can include information on the source such as species of animals or the microorganism used in the preparation of the bulk drug substance method, manufacture, and characterisation.

For **biotechnological products**, information should include the following:

- Control of source and starting materials of biological origin.
- Summaries of viral safety information for biologically-sourced materials.
- Source, history and generation of the cell substrate.
- Source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in ICH Q5B and ICH Q5D.
- Cell banking system, characterisation and testing.

Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in ICH Q5B and ICH Q5D.
S2.3.2 Criteria for Acceptance or Rejection

Criteria for accepting or rejecting batches of the starting materials should be stated.

References

Biotech Products
- ICH Guidelines Q5A, Q5B, Q5C and Q5D

S2.4 Control of Critical Steps and Intermediates

S2.4.1 Critical Steps

Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process should be provided to ensure that the process is controlled.

S2.4.2 Intermediates

Quality control checks carried out, if any, at each stage of manufacturing should be briefly stated. Details of specifications and analytical procedures or intermediates isolated during the manufacturing process should be provided, if any.

For biotechnological products, stability data supporting storage conditions is required.

References

All Products
- ICH Guidelines Q5C, Q6A and Q6B

S2.5 Process Validation and/or Evaluation

This section requires validation and/or evaluation studies for aseptic processing and sterilisation.

- Biotechnological Products
  Sufficient information on validation and/or evaluation studies is required on this product class due to the following:

  - To demonstrate the manufacturing process including reprocessing steps is suitable for its intended purpose.
  - To substantiate selection of critical process controls (operational parameters and in-process test) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification).

  Information should include a description of the plan for conducting the study and the results, analysis and conclusions from the executed study(ies). The validation of corresponding assay and analytical methods should be cross-referenced or provided as part of justifying the selection of critical process controls and limits.
For manufacturing steps intended to remove or inactivate viral contaminants, information from evaluation studies should be provided.

References

**All Products**
- ICH Guidelines Q5A, Q5D and Q6B

S2.6 Manufacturing Process Development

- **NCE Products**
  Description and discussion of significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing non-clinical, clinical scale-up, pilot and if available, production scale batches.

- **Biotechnological Products**
  Information required for this section includes the following:
  - Developmental history of the manufacturing process, as described by item S2.2 should be provided.
  - Description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. non-clinical or clinical studies) including for example, changes to the process or critical equipment. Justification of the change should also be explained.
  - Relevant information on drug substance batches manufactured during development, such as batch number, manufacturing scale and use, for example, stability and non-clinical reference material in relation to the change.
  - Assessment of the significance of change by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For changes in manufacturing that are considered significant, data from comparative analytical testing on relevant drug substance is required. A discussion of the data including a justification for selection of the test and assessment of results should be included.
  - Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) which may also include non-clinical and clinical studies in other modules of the submission should be included.

References

**NCE Products**
- ICH Guidelines Q3A

**Biotech Products**
- ICH Guidelines Q6B

S3. CHARACTERISATION

S3.1 Elucidation of Structure and Characteristics

S3.1.1 Structure of Drug Substance

Evidence of chemical structure, configuration, conformation, potential isomerism and potential for forming polymorphism should be provided, where applicable, supported by infra-red spectra with interpretation, UV characteristics including acid-alkali shifts, NMR spectra with interpretation, mass spectra with interpretation, diagnostic chemical reaction, elemental analysis, X-ray crystallography with interpretation, optical rotation and purity, and synthetic routes.
S3.1.2 Characteristics of Drug Substance

A summary on the development programmes undertaken to investigate the chemical and physicochemical properties or biological activities of the drug substance should be provided.

S3.1.3 Bibliography

List of papers, reports, articles, references and any other form of documentation pertaining to:

- Structure of the drug substance.
- Characteristics of the drug substance.

For NCE products, confirmation of structure based on synthetic route and spectral analysis. Information on the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorph should also be included.

For biotechnological products, details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant) should be provided.

For major variation, minor variation and generic products, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

Spectra and other diagrams submitted should be completely legible, well annotated with parameters for determination of specific characteristics.

References

NCE Products
- ICH Guidelines Q6A

Biotech Products
- ICH Guidelines Q6B

S3.2 Impurities

S3.2.1 Research and Development Studies

A list of impurities considered and studied during research and development of drug substance and their levels detected from the manufacturing process should be provided. Studies showing that analytical methods used for impurity control in the drug substance specifications are valid and sensitive should be included.

Criteria for selecting limits and methods for impurity control such as sensitivity and detection limits, specificity for impurity detected, method of detection, etc., should be discussed. Visual evidence of chromatogram spectra and tabulation of results obtained with samples of material should be included. Negative results (impurities tested for but not found) and methods which have been tried but have proved unsuccessful for detection of impurities are also important.

S3.2.2 Routine Impurities Control

A summary of impurities monitored or tested for during and after manufacture of drug substance, as routine batch to batch impurities control should be given. The analytical methods used for detection and quantitation of the impurities, for
example, HPLC and atomic absorption, and the specification limits (levels of acceptance) of these impurities should be briefly stated.

S3.2.3 Bibliography

List of papers, reports, articles, references and any other form of documentation pertaining to:
- Research and development studies on impurities.
- Research control of impurities.

For **generic products**, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

References

*NCE Products / Biotech Products*
- ICH Guidelines Q3A, Q3C, Q5C, Q6A and Q6B

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**S4. QUALITY CONTROL OF DRUG SUBSTANCE**

This section should provide the quality control measures taken during and after manufacture of the drug substance by which batch-to-batch uniformity of the drug substance is controlled and its quality maintained.

**S4.1 Specifications**

**S4.1.1 Tests and Specifications**
(Release Specifications)

Quality control specifications are required for each batch of the drug substance that includes listing of the following:

- Tests for identity and assay of drug substance with criteria that should include, at least the following:
  - Appearance, colour, odour, taste, crystallinity and texture.
  - Identity tests involving UV, IR, melting point, etc.
  - Physico-chemical tests on solubility, pH, moisture loss on drying, particle size, optical rotation and polymorphism.
  - Purity tests indicated by chromatography, ash values, heavy metals, trace elements, residual solvents, reagents and bases.
  - Assay method that is specific and sensitive.

- References to analytical procedures or test protocol used;
- Appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

The listed acceptance criteria established for the drug substance should conform to specifications considered acceptable for its intended use whether they are from compendial references such as the BP, USP, EP or the manufacturer.

References

ICH Guidelines Q6A
S4.1.2 Source of Drug Substance (for biotechnological products only)

Source of material should be stated such as species of animals, type of microorganisms, etc. Its manufacture and country of origin should also be included. The name of compendial reference used, its edition and page should be clearly stated. Otherwise, source of monographs and test protocols that include full details of specifications and acceptance limits used would need to be indicated.

References

ICH Guidelines Q6B

For major variation, minor variation and generic products, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

There should be an indication on the following:

- Which specifications are tested routinely on the batch at the time of manufacture.
- Tests which are done on every batch by stating the frequency of circumstances in which they are applied.

S4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory. It should also be clearly indicated when the active ingredients are bought to a purchase specification with a certificate of analysis, or tested by the manufacturer (or on his behalf) for compliance of specifications.

For major variation, minor variation and generic products, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

References

NCE Products
- ICH Guidelines Q2A

Biotech Products
- ICH Guidelines Q6B

S4.3 Validation of Analytical Procedures

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended use. Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered include:

- Selectivity,
- Precision (repeatability, intermediate precision and reproducibility),
- Accuracy,
- Linearity,
- Range,
- Limit of quantitation,
- Limit of detection,
- Robustness,
- System suitability.
For **major variation, minor variation** and **generic products**, validation of analytical procedures is required for non-compendial method only.

**References**

*NCE Products*
- ICH Guidelines Q2A and Q2B

*Biotech Products*
- ICH Guidelines Q6B

*MaV, MiV and Generics*
- ASEAN Guideline for Validation of Analytical Procedures

**S4.4 Batch Analyses**

Analytical reports of recent batches of drug substance (about 3 batches) representative of drug substance used in the manufacture of the drug product seeking registration should be provided.

Analytical reports for batches used for toxicity tests and clinical work submitted in support of the drug registration application, if different, should be included.

These reports should include date of manufacture, batch size and number, place of manufacture of drug substance, analytical method and results of analytical tests. Apparent inconsistent or anomalous results should be explained.

**References**

*NCE Products*
- ICH Guidelines Q3A, Q3C and Q6A

*Biotech Products*
- ICH Guidelines Q6B

**S4.5 Justification of Specification**

Justification for the drug substance specification should be provided. It should be presented for each procedure and each acceptance criterion included in the specification. It should refer to the following consideration:

- Relevant development data;
- Pharmacopoeial standards;
- Test data for drug substance used in toxicology and clinical studies;
- Results from accelerated and long-term stability studies; and
- A reasonable range of expected analytical and manufacturing variability.

Presentation of test results in graphic format could be used to justify individual acceptance criteria, particularly for assay values and impurity levels. Justification for proposing exclusion of a test from the specification should be based on development data and on process validation data.

For **major variation, minor variation** and **generic products**, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

**References**

*NCE Products*
- ICH Guidelines Q6A

*Biotech Products*
S5. REFERENCE STANDARDS OR MATERIALS

Quality information of reference standard or material used in any of the tests conducted on the drug substance should be provided. This includes a full characterisation of the reference standard with relevant visual evidence of spectra of chromatogram, where applicable and analytical results. Sufficient sample of the reference standard should be made available to the Drug Quality Control Section immediately on request.

For major variation, minor variation and generic products, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

References

NCE Products
- ICH Guidelines Q6A
- ICH Guidelines Q6B

S6. CONTAINER CLOSURE SYSTEM

For NCE and biotechnological products, the following requirements are essential:

S6.1 Immediate Container Closure System / Packaging

Description of container closure system of primary packaging which should include the following:

- Identity of materials of construction of each packaging component;
- Specifications of each packaging component that should encompass description and identification as well as critical dimensions with drawings where appropriate. Non-compendial methods (with validations) should be included where appropriate.

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

Description of container closure system of secondary packaging which should include the following:

- Identity of materials of construction of each packaging component;
- Specifications of each packaging component that should encompass description and identification as well as critical dimensions with drawings where appropriate. Non-compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components, for example, those that do not provide additional protection nor serve to deliver the product, only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

S6.3 Suitability of Packagings

Suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug
substance, including sorption to container and leaching, and/or safety of materials of construction.

S7. STABILITY

Stability studies on the drug substance should be designed to determine the inherent stability characteristics of the molecule under all the various possible conditions of storage and use such as during the processes of manufacture of the drug product containing the drug substance.

S7.1 Stability Studies Summary and Conclusion

The types of stability studies conducted and protocols used should be summarised. The summary should include results and conclusions of each study, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

References

NCE Products
- ICH Guidelines Q1A (R2), Q1B and Q5C

S7.2 Post-approval Stability Protocol and Stability Commitment

When available real-time stability data on primary batches do not cover the shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf-life.

The types of stability commitment recommended are found in ICH Q1A (R2) and the ASEAN Guideline on Stability Study of Drug Product. The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

A post-approval stability protocol and stability commitment report should be provided if the stability study submitted for the drug substance has been conducted under different storage conditions and it cannot be demonstrated that the drug substance will remain within its acceptance criteria.

An outline on the on-going or proposed post-approval stability studies performed on commitment batches should be provided that briefly describes the study protocols, conditions and parameters, monitoring of changes in characteristics of ingredients and degradation products, expected date of completion and/or proposed date of commencing the studies.

Details of the on-going stability studies including protocols and analytical methods used in the studies should be enclosed. Results and conclusions of the post-approval stability studies should be submitted to the Department of Pharmaceutical Services upon completion.

References

All Products
- ICH Guidelines Q1A (R2) and Q5C

S7.3 Stability Data

Detailed reports of stability studies should provide the following information:
• **Batches examined** that includes the number of batches, size of batches and batch numbers; a minimum of two batches required.

• **Conditions of storage** during the study such as temperature, humidity, light, acid, alkali and oxygen.

• **Containers and packaging** during the study where in the event the drug substance was not in its final containers, evidence that results would not differ significantly need to be shown.

• **Duration of study.**

• **Monitoring of changes in characteristics of ingredients and degradation products** includes changes in the content and potency of active ingredients and degradation products as well as changes in the characteristics of the drug substance such as appearance, colour, odour, moisture content, etc. Other changes monitored include changes due to interaction between drug substance and its container closure system such as leaching and sorption. Degradation products of ingredients should be identified and estimated, and their non-toxicity levels during the drug substance shelf-life should be established.

• **Analytical methods** used during the tests and studies should be sufficiently specific and sensitive to changes monitored.

• **Results of stability studies** should be presented in an appropriate format, for example, tabular, graphical and narrative. Information on analytical procedures used to generate the data and validation of these procedures should be included. Any changes in trends during the study should be noted.

• **Conclusions** should encompass discussion of results and when drawn from the studies including suitability of study protocol and analytical methods in determining stability of the drug substance; stability of the drug substance and deductions there from on the storage conditions and shelf-life; significance of amounts of degradation products detected since there is necessity for toxicity tests of stored materials; significance of loss of potency; or other changes observed.

All data generated and results provided should be duly signed by a responsible person i.e. QC officer.

For major variation, minor variation and generic products, provision of stability data from the manufacturer or equivalent information is sufficient.

**References**

**All Products**

• ICH Guidelines Q1A (R2) , Q1B, Q2A, Q2B and Q5C

---

**SECTION D: KEY LITERATURE REFERENCES**

**Summary of Other Data**

A summary of any other relevant data on the quality of the drug substance should be specified.

**Bibliography of Relevant Data**

List of articles, papers, reports and relevant supporting documents should be given.
GUIDE ON SUBMISSION OF QUALITY DATA FOR APPLICATION OF
REGISTRATION OF MEDICINAL PRODUCTS - QUALITY REQUIREMENTS
FOR DRUG PRODUCT

(Part II: Section 2)

INTRODUCTION

Quality requirements of drug products are required for all products including new chemical entities
(NCE), biotechnological products (Biotech) and generic products. This guide is divided into sections
A and B as detailed below.

A complete quality data on the drug product (finished product) should be provided according to the
format presented in DPS/DRS/02/B using the guidelines provided below.

Details and supporting documents required should be enclosed with the quality data submitted.
Information submitted must be sufficient to evaluate the quality of the drug product.

SECTION A: TABLE OF CONTENTS

A table of contents for the filed application should be provided.
SECTION B: QUALITY OVERALL SUMMARY

The tabulated information below can be used as a checklist to which information is required for the registration of the medicinal product concerned.

<table>
<thead>
<tr>
<th>No.</th>
<th>PARAMETERS</th>
<th>COMPONENTS</th>
<th>REQUIREMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P P1</td>
<td>DRUG PRODUCT</td>
<td><strong>Description and Composition</strong></td>
<td>NCE Biotech MaV MiV G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Description</td>
<td>✓ ✓ ✓' ✓' ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dosage form and characteristics</td>
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<td></td>
<td></td>
<td>- Accompanying reconstitution diluent(s) if any.</td>
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<td>- Type of container and closure used for the dosage form and reconstitution diluent(s), if applicable.</td>
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<tr>
<td></td>
<td></td>
<td>- Composition</td>
<td>✓ ✓ ✓' ✓' ✓</td>
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<tr>
<td></td>
<td></td>
<td>- Name, quantity stated in metric weight or measures, function and quality standard reference.</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>Pharmaceutical Development</td>
<td>2.1 Information on Development Studies</td>
<td>✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application.</td>
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<tr>
<td></td>
<td></td>
<td>2.2 Components of the Drug Product</td>
<td>✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Active Ingredient</td>
<td></td>
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<td></td>
<td></td>
<td>- Justification of the compatibility of the active ingredient with excipients listed in P1.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- In case of combination products, justification of the compatibility of active ingredients with each other.</td>
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<td></td>
<td></td>
<td>- Literature data.</td>
<td>✓' ✓' ✓</td>
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<tr>
<td></td>
<td></td>
<td>- Excipients</td>
<td>✓ ✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3 Finished Product</td>
<td>✓ ✓</td>
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<tr>
<td></td>
<td></td>
<td>- Formulation Development</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and</td>
<td></td>
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<tr>
<td>No.</td>
<td>PARAMETERS</td>
<td>COMPONENTS</td>
<td>REQUIREMENTS</td>
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<td></td>
<td>usage for NCE and Biotech).</td>
<td>NCE</td>
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<tr>
<td></td>
<td></td>
<td>- Overages</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Justification of any overage in the formulation(s) described in P1.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Physicochemical and Biological Properties</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parameters relevant to the performance of the finished product, e.g. pH, dissolution.</td>
<td>✓</td>
</tr>
<tr>
<td>2.4</td>
<td>Manufacturing Process Development</td>
<td>- Selection and optimisation of the manufacturing process.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P3.2, if applicable.</td>
<td>✓</td>
</tr>
<tr>
<td>2.5</td>
<td>Container Closure System</td>
<td>- Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.</td>
<td>✓</td>
</tr>
<tr>
<td>2.6</td>
<td>Microbiological Attributes</td>
<td>- Microbiological attributes of the dosage form, where appropriate.</td>
<td>✓</td>
</tr>
<tr>
<td>2.7</td>
<td>Compatibility</td>
<td>- Compatibility of the finished product with reconstitution diluent(s) or dosage devices.</td>
<td>✓</td>
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<tr>
<td></td>
<td></td>
<td>- Literature data.</td>
<td>✓</td>
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<td></td>
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<td></td>
<td>✓</td>
</tr>
<tr>
<td>P3</td>
<td>Manufacture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>Batch Formula</td>
<td>- Name and quantities of all ingredients.</td>
<td>✓</td>
</tr>
<tr>
<td>3.2</td>
<td>Manufacturing Process and Process Control</td>
<td>- Description of manufacturing process and process control.</td>
<td>✓</td>
</tr>
<tr>
<td>3.3</td>
<td>Control of Critical Steps and Intermediates</td>
<td>- Tests and acceptance criteria.</td>
<td>✓</td>
</tr>
<tr>
<td>3.4</td>
<td>Process Validation and/or Evaluation</td>
<td>- Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process.</td>
<td>✓</td>
</tr>
<tr>
<td>P4</td>
<td>Control of Excipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Specifications</td>
<td>- Specifications for excipients.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compendial requirements or equivalent information from the manufacturer.</td>
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</tr>
<tr>
<td>No.</td>
<td>PARAMETERS</td>
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<td>REQUIREMENTS</td>
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<td></td>
<td>NCE</td>
</tr>
<tr>
<td>4.2</td>
<td>Analytical Procedures</td>
<td>- Analytical procedures used for testing excipients where appropriate.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compendial requirements or equivalent information from the manufacturer.</td>
<td>✓</td>
</tr>
<tr>
<td>4.3</td>
<td>Excipient of Human or Animal Origin</td>
<td>- Information regarding sources and/or adventitious agents.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compendial requirements or equivalent information from the manufacturer.</td>
<td>✓</td>
</tr>
<tr>
<td>4.4</td>
<td>Novel Excipients</td>
<td>- For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterisation and controls, with cross reference to supporting safety data (non-clinical or clinical).</td>
<td>✓</td>
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<td>✓</td>
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</table>

P5 Control of Finished Products

<p>| 5.1 | Specification                   | - The specification(s) for the finished product.                          | ✓   | ✓      | ✓'  | ✓'  | ✓  |
|     |                                |                                                                           | ✓   | ✓      | ✓'  | ✓'  | ✓  |
| 5.2 | Analytical Procedures          | - Analytical procedures used for testing the finished product.           | ✓   | ✓      | ✓'  | ✓'  | ✓  |
|     |                                |                                                                           | ✓   | ✓      | ✓'  | ✓'  | ✓  |
| 5.3 | Validation of Analytical Procedures | - Information including experimental data, for the analytical procedure used for testing the finished product. | ✓   | ✓      | ✓'  | ✓'  | ✓  |
|     |                                | Non-compendial methods.                                                   | ✓   | ✓      | ✓'  | ✓'  | ✓  |
|     |                                | Verification of compendial method applicability – precision &amp; accuracy.   | ✓   | ✓      | ✓'  | ✓'  | ✓  |
| 5.4 | Batch Analyses                 | - Description and test results of all relevant batches.                   | ✓   | ✓      |     |     |    |
|     |                                | - Tabulated summary of batch analyses                                    | ✓   | ✓      |     |     |    |
| 5.5 | Characterisation of impurities | - Information on the characterisation of impurities.                      | ✓   | ✓      |     |     |    |
|     |                                | Compendial requirements or equivalent information from the manufacturer. | ✓   | ✓      | ✓'  | ✓'  | ✓  |
| 5.6 | Justification of Specifications | - Justification of the proposed finished product specification(s).       | ✓   | ✓      |     |     |    |
|     |                                | Compendial requirements or equivalent information from the manufacturer. | ✓   | ✓      | ✓'  | ✓'  | ✓  |
|     |                                |                                                                           | ✓   | ✓      | ✓'  | ✓'  | ✓  |
|     | Reference Standards or Materials | - Information on the reference standards or reference materials used for testing of the finished product. | ✓   | ✓      |     |     |    |
|     |                                |                                                                           | ✓   | ✓      |     |     |    |</p>
<table>
<thead>
<tr>
<th>No.</th>
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<td></td>
<td>✓</td>
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<tr>
<td>P7</td>
<td>Container Closure System</td>
<td>- Specification and control of primary and secondary packaging material, type of packaging and the package size, details of packaging inclusion (e.g. desiccant, etc.)</td>
<td>✓</td>
</tr>
<tr>
<td>P8</td>
<td>Stability</td>
<td>- Stability report: data demonstrating that product is stable through its proposed shelf-life. Commitment on post-approval stability monitoring.</td>
<td>✓</td>
</tr>
<tr>
<td>P9</td>
<td>Product Interchangeability Equivalence Evidence</td>
<td>- In Vitro Comparative dissolution study as required.</td>
<td>✓'</td>
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<tr>
<td></td>
<td></td>
<td>- In Vivo Bioequivalence study as required.</td>
<td>✓'</td>
</tr>
</tbody>
</table>

**Key**

* : if required  
NCE : New Chemical Entity  
Biotech : Biotechnological Products  
MaV : Major Variation  
MiV : Minor Variation  
G : Generics
SECTION C: BODY OF QUALITY DATA ON DRUG PRODUCT

The contents for the filed application should consist of information addressing the requirements provided below. The format of data provided should be according to that presented in DPS/DRS/02/B.

P1. DRUG PRODUCT

P1.1 Description (Physical Characteristics)

Description of drug product encompasses the physical characteristics of the drug product that includes shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, and tablet coating, for example, sugar-coated, enteric-coated, etc.

Description of liquids should clearly state whether in the form of solution, suspension, emulsion, etc.

P1.2 Composition (Complete Formula)

The approved names and quantitative contents, in metric weights and measures, and the function of the contents of the finished product should be provided under the following headings:-

P1.2.1 Active Ingredient(s)

P1.2.2 Other Ingredients (adjuncts, excipients, preservatives, colour, flavour, etc. and their functions)

Content of each ingredient must be given as follows:

a) quantity per unit dose such as for tablet, capsule, etc.;

b) percentage composition as in %w/w, w/v, v/v, etc., such as for creams, ointment, lotion, injectables, etc.;

c) weight per ml such as for injectables, etc.;

d) quantity for measured dose such as for oral liquid preparations.

For injectable preparations, the total content either as weight or volume in each unit container should be given.

For ingredients used in tablet coating or capsule shells, constituents are required even though exact quantities are not.

Reference to quality standards used i.e. compendial monographs or manufacturer’s specifications for any of the ingredients should be stated.

P1.2.3 Overages

For overages, supporting data for its inclusion should be enclosed showing that the:-

a) overage would not result in the content of ingredient exceeding the upper limit stated in the in-process quality control (IPQC);

b) lower limit proposed for the decrease in strength applies only at the end of the proposed shelf-life of the drug product.
Reasons for its inclusion should be stated, i.e. whether overage is to cover losses during manufacture, to cover loss of potency on storage, to permit withdrawal and administration of labelled volumes, required doses, etc.

P1.3 Description of accompanying reconstitution diluent(s), if applicable.

P1.4 Type of container closure system / Pack size used for the dosage form and accompanying reconstitution diluent, if applicable.

The type of immediate container closure system or pack size used for the dosage form and accompanying reconstitution diluent, if applicable, should be briefly stated, for example, tablets in a bottle of 100’s, 500’s and/or blister pack of 50’s. If packed or repacked by a separate firm, details of the immediate container closure system, repacking process, quality control and stability data must be submitted by the repacker.

References

NCE Products
- ICH Guidelines Q6A

Biotech Products
- ICH Guidelines Q6B

P2. PHARMACEUTICAL DEVELOPMENT

P2.1 Information on Development Studies
(This section is applicable to NCE and Biotechnology Products only)

P2.1.1 This section is intended to provide a more comprehensive understanding of the drug product development and its manufacturing process. It is required for the original marketing application and can be updated to support new knowledge gained over the lifecycle of the drug product.

Information and data to be described in this section should establish that the type of dosage form selected, the formulation proposed, container closure system used, its microbiological attributes and instruction leaflet are appropriate for the purpose specified in the application. Additionally, this section presents information and data on the development studies conducted to establish that the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usages instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug product quality.

Aspects of drug substances, excipients, and manufacturing process that are critical and that present a significant risk to product quality, and therefore should be monitored or otherwise controlled, should be identified and discussed. These critical formulation attributes and process parameters are generally identified through and assessment of the extent to which their variation can have impact on the quality of the drug product.
P2.1.2 Bibliography of Development Studies

Supportive data and result from specific studies or published literature may be included within or attached to this section. Additional supportive data may be referenced to the relevant non-clinical sections of the application.

References

NCE Products
- ICH Guidelines Q6A

Biotech Products
- ICH Guidelines Q6B

P2.2 Component of Drug Product

P2.2.1 Active Ingredient

Justification on the compatibility of the drug substance with excipients should include:

- Physicochemical and biological characteristics of the drug substance that can influence the performance of the drug product and its manufacturability, for example, water content, solubility, particle size, polymorphic properties, biological activity, and permeability.
- Compatibility of the drug substance with excipients listed in Item P1.
- For drug products that contain more than one drug substance, the compatibility of the drug substances with each other should also be discussed.

For **major variation**, **minor variation** and **generic products**, literature data is sufficient.

P2.2.2 Excipients

Justification on the choice on excipients as listed in P1 should include information on the following:

- Concentration and characteristics of the chosen excipients as listed in Item P1.2.2 that can influence the drug product performance such as stability and bioavailability, or manufacturability relative to their respective function should be discussed.
- Compatibility of excipient with other excipients, for example combination of preservatives in dual preservative system, should be established.
- Ability of the excipients such as antioxidants to provide their intended functionality, and to perform throughout the intended drug product shelf-life, should be demonstrated.

Information on excipient performance can be used to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification as in item P5.6.

P2.3 Drug Product

P2.3.1 Formulation Development

This section requires a summary of manufacturer’s research and development in-vitro and in-vivo studies on drug release of the drug product; effects of special
formulation; physical characteristics of ingredients; for example, crystal form; particle size; solubilising agents; excipients, etc. on availability of drug substance.

It also requires information on manufacturer’s specifications (standards) for satisfactory availability that outlines routine tests to ensure availability and batch-to-batch uniformity of drug release.

Information provided should include the following:

i) Description on the development of the drug product that takes into consideration the proposed route of administration and usage;

ii) Highlights on the evolution of the formulation design from initial concept up to the final design taking into consideration the following:
- Choice of drug components such as properties of the drug substance, excipients, container closure system, any relevant dosing device;
- Manufacturing process;
- Experiences gained from the development of similar drug products.

iii) Summary of all formulations used in clinical safety and efficacy, bioavailability, or bioequivalence studies. Any changes between the proposed commercial formulation and those formulation used in pivotal clinical batches and primary stability batches should also be provided, as well as the rationale for the changes provided. Bioavailability studies for adults and children, as appropriate, should be available for dosage recommendations of controlled-release products.

iv) Results from comparative in vitro studies, for example, dissolution, or comparative in vivo studies, for example, bioequivalence that links clinical formulations to the proposed commercial formulation, when appropriate. This is important for drug products that carry a therapeutic dose that is close to its toxic dose, and those that carry solubility or physico-chemical properties that may alter the therapeutic efficacy or safety of the product when the formulation or the source of ingredients is changed.

v) Any special design features of the drug product such as tablet score line, overfill and anti-counterfeiting measure, should be identified and a rationale provided for their use.

vi) Rationale for their special formulations such as controlled-release tablets, depot injections, etc., should be provided.

P2.3.2 Overages

An overage is a fixed amount of the drug substance added to the formulation in excess of the label claim. Though the use of overages of drug substances in drug products is discouraged, any overages in the manufacture of the drug product as described under item P1 whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product.

Information should be provided on the following:

- Amount of overage;
- Reason for the overage, for example, to compensate for expected and documented manufacturing losses; and
Justification for the amount of overage.

P2.3.3 Physicochemical and Biological Properties

Properties addressed here are parameters relevant to the performance or manufacturability of the drug product that includes formulation attributes such as the following:

- pH;
- ionic strength;
- dissolution;
- redispersion;
- reconstitution;
- particle size distribution;
- aggregation;
- polymorphism;
- rheological properties;
- biological activity or potency; and
- immunological activity.

Studies to investigate the potential impacts of the physicochemical and biological properties of the drug product and the appropriateness of the drug product acceptance criteria should be reported.

P2.4 Manufacturing Process Development

Information provided here should include discussion on the following:

P2.4.1 Development of Manufacturing Process for Commercial Production batches

Selection, control and optimisation of the manufacturing process intended for commercial production batches as described in Item P3.2, in particular its critical formulation attributes together with the available manufacturing process options, and where relevant, choice on the method of sterilisation of the drug product and primary packaging material should be explained and justified.

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

Significant differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P3.2 that can influence the performance and manufacturability of the product should be explained and justified.

P2.5 Container Closure System

P2.5.1 Suitability of Container Closure System

Suitability of the container closure system used for the storage, transportation (shipping) and the intended use of the drug product should be discussed as per necessary.

Choice of materials for primary packaging and the possible interaction between drug product and the container or label includes the following:
P2.5.2 Performance of Dosing Device

Performance such as accuracy and reproducibility of the dose delivery from the dosing device used as part of the drug product, when used, should be mentioned.

P2.6 Microbiological Attributes

Microbiological attributes of the dosage form should discuss, where appropriate, the following:

P2.6.1 Non-sterile Products

Rationale for performing or not performing microbial limits testing for non-sterile products.

P2.6.2 Selection of Preservative Systems

Selection and effectiveness of preservative systems in product containing antimicrobial preservatives or the antimicrobial effectiveness of products that is inherently antimicrobial.

P2.6.3 Container Closure System of Sterile Preparation

Integrity of the container closure system to prevent microbial contamination in sterile preparation.

P2.7 Compatibility

Compatibility of the drug product with reconstitution diluent(s) or dosage devices, for example, precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for labelling purposes. Where the label recommends dilution or mixing of solid dosage forms with, for example, drinks prior to administration, appropriate compatibility studies should be described.

For major variation, minor variation and generic products, literature data are acceptable.

P3. MANUFACTURE OF PRODUCT

P3.1 Batch Manufacturing Master Formula

The batch size and actual batch manufacturing master formula should be provided with name and quantities of all ingredients (active and excipients) including substance(s) which are removed in the course of manufacture. Information provided should include actual quantities (gm, kg, litres) of ingredient; supporting data and the reason for including overages; total number of dosage unit per batch; and description of all stages involved in the manufacture of the dosage form.
P3.2 Manufacturing Process and Process Control

P3.2.1 Brief Description and Principles

A brief description of the manufacturing process should be provided covering the following:

- A flow diagram could be presented showing the following:
  - Steps of the manufacturing process;
  - Points where materials enter the process.
- Critical steps and points at which process controls, intermediate tests or final product controls were conducted should be identified.
- Full description of manufacturing process must be sufficiently detailed to cover all essential points in each stage of manufacture.
- Assembling of the drug product into final containers should be described.
- For sterile product, description of manufacturing process should include preparation and sterilisation of components such as containers, closures, etc.

P3.2.2 In-process Quality Control (IPQC)

For IPQC, a summary of the tests performed, at which stage they were performed, frequency of sampling, and number of samples taken each time should be provided. It should cover raw materials, intermediate products and any other operations concerning the finished products.

Details of IPQC and specifications for quality assurance of the product should be supplied. Information should cover the following:

- Analytical controls and checks made on intermediate products, or criteria of acceptance and rejection. Analytical methods and test protocols must be described in detail.
- Stages at which controls and tests are performed should be indicated. Details of sampling plan and method should be given.
- Precautions and actions taken to detect and reduce or eliminate breakdown and defective products.
- Controls to ensure accurate and uniformity of fill or packing.

P3.3 Controls of Critical Steps and Intermediates

P3.3.1 Critical Steps

Tests and acceptance criteria performed at the critical steps of the manufacturing process should be provided (with justification, including experimental data). This is to ensure that the process is controlled.

P3.3.2 Intermediates

Information on the quality and control of intermediates isolated during the process should be provided.
P3.4 Process Validation and/or Evaluation

Description, documentation, and result of validation studies performed on critical steps or critical assays used in the manufacturing process should be provided. For example, validation of the sterilisation process or aseptic processing or filling in the manufacturing process.

For major variation, minor variation and generic products, information provided may be based on the ASEAN Guideline on Process Validation.

References

NCE Products
- ICH Guidelines Q6B

Biotech Products
- ICH Guidelines Q6B

P4. QUALITY CONTROL OF EXCIPIENTS

The quality control of excipients involves a complete account of routine tests performed on each batch of finished product and its ingredients, and specifications with which any sampling during the course of inspection would be expected to comply.

P4.1 Specification for Excipients

Quality control specifications are required for the inactive ingredients used in the manufacture of the drug product that include listing of the following:

- Tests for identity, assay of inactive ingredient(s) and other important ingredients such as impurities, degradation products and other limit tests, and general requirements such as disintegration, dissolution, sterility, etc;
- References to analytical procedures or test protocol used;
- Appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

The listed acceptance criteria established for excipients should conform to be considered acceptable for its intended use. Excipients of the drug product should be listed out with compendial reference (BP, USP, EP, JP, etc) used for specifications. The source of ingredients that include manufacturer and country of origin should also be included in the listing. For biological drug product, source of excipient should be stated such as species of animals, type of microorganisms, etc.

The name of compendial reference used, its edition and page should be clearly stated. Otherwise, source of monographs and test protocols that include full details of specifications and acceptance limits used would need to be indicated.

For major variation, minor variation and generic products, provision of compendial specifications or equivalent information from the manufacturer is sufficient.
P4.2 Analytical Procedures

P4.2.1 Description of Analytical Procedures

Analytical procedures describe in detail the steps necessary to perform each analytical test in the quality control of excipients. It should be in sufficient detail so as to be reproducible in tests carried out by another laboratory. Please refer to Annex 4.2.1 for a more detailed listing of requirements of analytical procedures performed on a drug product for excipients, whichever is applicable.

P4.2.2 Source of Compliance

It should be clearly indicated when the inactive ingredients are bought to a purchase specification with a certificate of analysis, or tested by the manufacturer (or on his behalf) for compliance of specifications.

For major variation, minor variation and generic products, provision of compendial specifications or equivalent information from the manufacturer is sufficient.

References

NCE Products
- ICH Guidelines Q2A
- ICH Guidelines Q5A and Q5D
- ICH Guidelines Q6B

Biotech Products
- ICH Guidelines Q6B

Note

Critical excipients are substances that affect stability and bioavailability of finished product, for example, preservatives, buffer components, dissolution enhancer and stabiliser.

P4.3 Excipients of Human and Animal Origin

Information provided should include the following:

P4.3.1 Description of excipients;

P4.3.2 Specification of excipients;

P4.3.3 Source of excipients, for example, gelatin, enzyme, etc; and

P4.3.4 Viral safety data on adventitious agents such as TSE, infectious viruses that can cause immunodeficiency diseases and hepatitis, and mycoplasma.

For major variation and generic products, provision of compendial specifications, if available, is sufficient. Otherwise, the same requirement for NCE and Biotech products apply.

References

NCE Products
- ICH Guidelines Q5A and Q5D
P4.4 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, the following information is required.

P4.4.1 Manufacture of Excipients

Details of manufacture of excipients should be provided.

P4.4.2 Safety Characteristics

Characterisation and controls with cross reference to supporting safety data either non-clinical or clinical.

P5. QUALITY CONTROL OF FINISHED PRODUCT

The quality control of the finished product involves a complete account of routine tests performed on each batch of finished product and its ingredients, and specifications with which any sampling during the course of inspection would be expected to comply.

P5.1 Specification for Finished Product

Quality control specifications are required for each batch of the finished product that includes listing of the following:

- Tests for identity, assay of inactive ingredient(s) and other important ingredients such as preservatives, impurities, degradation products and other limit tests, and general requirements such as disintegration, dissolution, sterility, etc;
- References to analytical procedures or test protocol used;
- Appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

The listed acceptance criteria established for the finished product should conform to be considered acceptable for its intended use. The list of tests for checks and release specifications together with the limits for acceptance for each batch of finished product should be enclosed with the details. Please refer to Annex 4.2.2 for the list of specifications required for the various dosage forms.

Ingredients of the drug product should be listed out with compendial reference (BP, USP, EP, JP, etc) used for specifications. The source of ingredients that include manufacturer and country of origin should also be included in the listing. For biological drug product, source of material should be stated such as species of animals, type of microorganisms, etc. The name of compendial reference used, its edition and page should be clearly stated. Otherwise, source of monographs and test protocols that include full details of specifications and acceptance limits used would need to be indicated.

Certificate of analysis for two batches of finished product should be enclosed. For vaccines, biological products and cytotoxics, certificate of analysis from the manufacturer for three batches of finished product should be enclosed and must be endorsed by the drug regulatory authority in the country of manufacture. For vaccines, the batch release certificate endorsed by the drug regulatory authority should be submitted.
NB. a) **Release Specifications** – Requirements for each batch at time of manufacture.
b) **Check Specifications** – Requirements with which regulatory authority in the country any sample of the product should comply during its shelf-life.

References

*NCE Products*
- ICH Guidelines Q6A

*Biotech Products*
- ICH Guidelines Q6B

### P5.2 Analytical Procedures

Analytical procedures describe in detail the steps necessary to perform each analytical test in the quality control of the finished product. It should be in sufficient detail so as to be reproducible in tests carried out by another laboratory. Please refer to Annex 4.2.1 for a more detailed listing of requirements of analytical procedures performed on a drug product, whichever is applicable.

It should be clearly indicated when the active ingredients are bought to a purchase specification with a certificate of analysis, or tested by the manufacturer (or on his behalf) for compliance of specifications.

References

*NCE Products*
- ICH Guidelines Q2A

*Biotech Products*
- ICH Guidelines Q6B

### P5.3 Validation of Analytical Procedures

The objective of validation of an analytical procedure used for testing the finished product is to demonstrate that it is suitable for its intended use. For major variation, minor variation and generic products that use non-compendial methods, verification for the applicability of compendial method used is required. Please refer to Annex 4.2.3 for more detailed requirements for the submission of analytical method validation data and documents to the Department of Pharmaceutical Services.

For **major variation**, **minor variation** and **generic products**, validation of analytical procedures is required for non-compendial methods only. Information provided may be based on the ASEAN Guideline on Analytical Validation. However, if compendial methods are used, verification for the applicability of the methods used is required.

References

*NCE Products*
- ICH Guidelines Q2A and Q2B

*Biotech Products*
- ICH Guidelines Q6B

*Major Variation, Minor Variation and Generic Products*
- ASEAN Guideline on Analytical Validation

### P5.4 Batch Analyses Report

The report should include the following:
P5.4.1  Description of the batches analysed that should include size, origin and use;

P5.4.2  Test results of all relevant batches, for example, pre-clinical, clinical pilot, scale-up, and if available production-scale batches, used to establish specification and evaluate consistency in manufacturing.

For **major variation, minor variation** and **generic products**, a tabulated summary of the batch analyses, with graphical representation where appropriate, should be provided.

References

*NCE Products*
- ICH Guidelines Q3A, Q3C and Q6A

*Biotech Products*
- ICH Guidelines Q6B

*Generic Products*
- Item 3.4

P5.5  Characterisation of Impurities

Impurities are termed by the following:
- By-products of synthesis arising from side reactions, in starting materials, isomerism, etc.;
- Residual solvents and reagents;
- Trace elements arising from catalysts or other sources; and
- Degradation products.

A summary of impurities monitored or tested for during and after manufacture of drug substance, as routine batch to batch impurities control should be given. The analytical methods used for detection and quantitation of the impurities, for example, HPLC and atomic absorption, and the specification limits (levels of acceptance) of these impurities should be briefly stated.

For **major variation, minor variation** and **generic products**, compendial requirement is sufficient or an equivalent such as information from the manufacturer.

References

*NCE Products*
- ICH Guidelines Q3B and Q6A

*Biotech Products*
- ICH Guidelines Q6B

P5.6  Justification of Specification

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. Justification should refer to the following consideration:

- Relevant development data;
- Pharmacopoeial standards;
- Test data for drug product used in toxicology and clinical studies;
- Results from accelerated and long term stability studies; and
- A reasonable range of expected analytical and manufacturing variability.
Justification of alternative approaches should be based on data derived from the new drug product manufacturing process using test results from stability and scale-up / validation batches, with emphasis on the primary stability studies. Presentation of test results in graphic format could be used to justify individual acceptance criteria, particularly for assay values and impurity levels. Justification for proposing exclusion of a test from the specification should be based on development data and on process validation data.

For major variation, minor variation and generic products, compendial requirement is sufficient or an equivalent such as information from the manufacturer.

References

NCE Products
• ICH Guidelines Q3B and Q6A

Biotech Products
• ICH Guidelines Q6B

P6. REFERENCE STANDARDS OR MATERIALS

Quality information and tabulated presentation of reference standards or materials used for testing of drug product should be included. It should have quality appropriate to its use as a substance prepared for use as the standard in tests performed on the drug product. Its purity should be measured by a quantitative procedure.

For major variation, minor variation and generic products, compendial requirement is sufficient or an equivalent such as information from the manufacturer.

References

NCE Products
• ICH Guidelines Q6A

Biotech Products
• ICH Guidelines Q6B

P7. CONTAINER CLOSURE SYSTEM

Aspects of the container closure system that are critical to the stability and quality of the drug product or those concerned with uniformity of dosage are covered in this section.

P7.1 Immediate Container Closure System / Primary Packaging

Description of container closure systems of primary packaging should briefly include the identity of materials of construction of each packaging component, capacity, closure and liner, name and address of manufacturer. Specifications of each packaging component that encompass composition and technical properties as well as critical dimensions with drawings where appropriate would be required.

P7.2 Outer Container / Secondary Packaging

Description of container closure systems of secondary packaging should briefly include the identity of materials of construction of each packaging component, its capacity, closure and liner, name and address of manufacturer. Specifications of each packaging component that
encompass composition and technical properties as well as critical dimensions with drawings where appropriate would be required.

For non-functional secondary packaging components, for example, those that do not provide additional protection nor serve to deliver the product, only a brief description should be provided.

For functional secondary packaging components, additional information should be provided.

P7.3 Packaging Inclusions

Details of any inclusions that are in contact with the drug product such as cushioning, desiccants, fillers, dose measuring devices, administration sets, and instruction to users should be provided. Apart from the packaging materials, similar information would be required for the inclusions as for the packaging materials. All inclusions must be clearly distinguishable by size, shape, weight, colour and texture from the drug product.

P7.4 Other Supporting Data

Other supporting data required would be quality control tests, test methods, and specification limits of the components in the container closure system. Non-compendial methods (with validations) should be included where appropriate.

Other reports that would be encouraged for submission are as the following:

- Compatibility of container closure system with the drug product especially for liquids and semi-solid dosage form;
- Moisture penetration or loss through the container closure system;
- Efficacy of container closure system especially in maintenance of sterility;
- Compatibility of inclusions with the drug product;
- Safety or toxicity of the packaging components.

P8. PRODUCT STABILITY

Evidence is required to demonstrate that:-

- Product is stable where it meets the finished product specifications throughout its proposed shelf-life;
- Toxic decomposition products are not produced in significant amount during this period;
- Potency and sterility of the finished product are maintained; and
- Efficacy of preservative is maintained

P8.1 Storage Conditions Included on Label

The recommended storage conditions of the finished product should be stated on the labels of inner and outer packaging.

Storage conditions of reconstituted product should be included where applicable.

P8.2 Proposed Shelf-life of Product

The proposed shelf-life or expiry date of the finished product must be stated on the labels of inner and outer packaging. It must be substantiated by stability studies and should not exceed the period supported by the stability data supplied.
Accelerated stability data for a minimum of 180 days is acceptable for NCE products. However, real-time stability data must be submitted subsequently. If the finished product is to be reconstituted before use, the shelf-life and/or expiry date of the original product as well as the reconstituted product should be stated.

P8.3 Stability Studies Summary and Conclusion

All criteria under ICH Guidelines for drug products are acceptable with the exception of real-time storage conditions which should be 30°C, 75% RH. Provision of moisture protection by the packaging should be taken into consideration.

A brief description of the completed stability studies performed on the drug product should be provided outlining the study protocols, conditions and parameters, monitoring of changes in characteristics of ingredients and degradation products, results, and conclusions of studies.

Details of the reports of the stability studies as outlined by item P8.5 together with relevant supporting documents should be enclosed.

References

NCE Products and Biotech Products
- ICH Guidelines Q1A (R2), Q1B, Q2A, Q2B and Q5C

Major Variation Products and Generic Products
- ASEAN Guideline on Stability Study

P8.4 Post-Approval Stability Protocol and Stability Commitment

When available real-time stability data on primary batches do not cover the shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf-life.

The types of stability commitment recommended are found in ICH Guidelines Q1A (R2) and the ASEAN Guideline on Stability Study of Drug Product. The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

A post-approval stability protocol and stability commitment report should be provided if the stability study submitted or the drug product has been conducted under different storage conditions and it cannot be demonstrated that the drug product will remain within its acceptance criteria stated under item P8.3.

An outline on the on-going or proposed post-approval stability studies performed on commitment batches should be provided that briefly describe the study protocols, conditions and parameters, monitoring of changes in characteristics of ingredients and degradation products, expected date of completion and/or proposed date of commencing the studies.

Details of the on-going stability studies including protocols and analytical methods used in the studies should be enclosed. Results and conclusions of the post-approval stability studies should be submitted to the Department of Pharmaceutical Services upon completion.

References

NCE Products
- ICH Guidelines Q1A (R2), and Q5C

Biotech Products
- ICH Guidelines Q5C

Generic Products
P8.5 Stability Data Reports

Detailed reports of stability studies should provide the following information:

- **Batches examined** that includes the number of batches, size of batches and batch numbers; a minimum of two batches required.

- **Conditions of storage** during the study such as temperature, humidity, light, oxygen, etc.

- **Containers and packaging** during the study where in the event the drug product was not in its final containers, evidence that results would not differ significantly, need to be shown.

- **Duration of study** and frequency (interval) of intermediate tests performed such as:
  - Tests to be carried out at the initial stages;
  - Frequency (interval) of intermediate tests should be 3 months for the first year and 6 months for the following year.

- **Monitoring of changes in characteristics of ingredients and degradation products includes** changes in the content and potency of active ingredients and degradation products as well as changes in the characteristics of the drug product such as appearance, colour, odour, flavour, disintegration time, dissolution, drug release rate, emulsion / suspension stability, particle size, viscosity, moisture content, etc. Other changes monitored include changes due to interaction between drug product and its container closure system such as leaching and sorption, loss of preservative efficacy, etc. Degradation products of ingredients should be identified and estimated, and their non-toxicity levels during the product shelf-life should be established.

- **Analytical methods** used during the tests and studies should be sufficiently specific and sensitive to changes monitored. If analytical methods are the same as those described under item 5, reference to the relevant sections could be made. Otherwise, other methods must be described in full.

- **Results** of stability studies should be presented in an appropriate format, for example, tabular, graphical and narrative. Information on analytical procedures used to generate the data and validation of these procedures should be included. Any changes in trends during the study should be noted.

- **Conclusions** should encompass discussion of results and when drawn from the studies including suitability of study protocol and analytical methods in determining stability of the drug product; stability of the drug product and deductions there from on the storage conditions and shelf-life; significance of amounts of degradation products detected since there is necessity for toxicity tests of stored materials; significance of loss of potency; or other changes observed.

All data generated and results provided should be duly signed by a responsible person i.e. QC officer.

References

All Products
- ASEAN Guideline on Stability Study
- ASEAN Guideline on Validation of Analytical Procedure

P9. PRODUCT INTERCHANGEABILITY

*(This requirement applies to major variation and generic products only)*

The ASEAN Guidelines for The Conduct of Bioavailability and Bioequivalence Studies provide guidance on the conduct of bioavailability and bioequivalence studies for the purpose of drug product registration.
P9.1 Type of Studies
The type of studies should refer to at least one of the following:
- Bioavailability Studies
- Bioequivalence Studies

Type of studies conducted should refer to the reference documents listed below.

P9.2 Protocols Used & Result of Studies Conducted
Report should include the protocols used and the result of the studies conducted on the finished product.

References
- ASEAN Guideline for Bioavailability and Bioequivalence Studies
- WHO Regulatory Support Series No. 5, “Bioequivalence Studies in Humans”

SECTION D: KEY LITERATURE REFERENCES

Summary of Other Data
A summary of other available quality data on the finished product should be provided and specified.

Bibliography of Relevant Data
A bibliography list, where applicable, should be included. Relevant supporting documents should also be enclosed.
GUIDELINES FOR SUBMISSION OF PROTOCOL OF ANALYSIS

I. General Requirements

1. The Protocol of Analysis must be in a standard format that contains information as stated below:-
   a) Product name
   b) Name and address of manufacturer
   c) Name, signature and designation of authorised person
   d) Effective date
   e) Review date

2. Protocol of analysis must consist of all test methods and specifications that are carried out by the manufacturer. Official pharmacopoeias, for example, BP/USP can be used as references. The tests and specifications in the pharmacopoeias are the minimum requirements.

3. Photocopies of methods / methods directly copied from pharmacopoeias are not acceptable. Manufacturers can use methods from those standard references but must have their own written and detailed procedure.

4. Manufacturers must confirm that all test methods in their protocol of analysis perform as expected. Copies of chromatograms (HPLC/GC/TLC), UV spectrum etc must be submitted together with the protocol of analysis.

5. Protocol of analysis must be properly ordered with proper numbering for all tests and specifications.

6. All references stated in the protocol of analysis must be submitted and clearly labelled.

7. Protocol of analysis submitted must be in either Malay or English language. Protocol of analysis in other languages will be rejected.

8. An authorised copy of latest certificate of analysis for the product concerned must be submitted with the protocol of analysis.

II. Specific Requirements

1. Identification test
   a) List of equipment and apparatus required
   b) List of chemical / reagents
   c) Preparation of sample and standard solutions
   d) Details of method and procedures
   e) Specification and acceptance criteria

2. Physical test (friability, uniformity of weight, pH, viscosity, etc)
   a) List of equipment required together with test parameters
   b) Sample preparation (if any)
   c) Specification and acceptance criteria
3. Disintegration test
   a) Equipment required
   b) Test parameters
   c) Test medium
   d) Specification

4. Dissolution test
   a) Equipment and apparatus required
   b) List of chemical / reagents required
   c) Test parameters i.e. type and volume of dissolution medium, rotation rate, temperature of solution and time
   d) Preparation of dissolution medium, preparation of sample and standard solution (if any) etc.
   e) Type and method of analysis (HPLC, UV etc) and test procedures. For example, if HPLC method is used, test method has to include the preparation of mobile phase, brand and type of column used, run time, detector used for example – UV, injection volume, system suitability test and other parameters.
   f) Typical chromatograms / UV spectrum for sample & standard solution, system suitability etc.
   g) Complete formula for calculation. For example, ‘slow release’ products calculation must include quantity of active substance in the medium volume which has been taken out for analysis.
   h) Test specification

5. Impurities / degradation / purity test
   a) Equipment and apparatus required
   b) List of chemical and reagents required
   c) Preparation of sample and standard solutions
   d) Detailed method and procedures
   e) Complete formula for calculation
   f) Typical chromatogram of system suitability test, sample & standard solutions if applicable
   g) Specification / acceptance criteria

6. Assay and uniformity of content
   a) List of equipment and apparatus required
   b) List of chemical and reagents required
   c) Preparation of sample and standard solutions
   d) Detailed method and procedures
   e) Complete formula for calculation
   f) Typical chromatogram / spectrum of system suitability test, sample & standard solutions if applicable
   g) Specification / acceptance criteria

7. Pyrogen / abnormal toxicity test
   a) List of equipment, apparatus, glassware and reagents required
   b) Preparation of sample solution and injection dose
   c) Test method & procedure
   d) Test interpretation
   e) Test specification

8. Bacterial Endotoxins Test (LAL)
   a) List of apparatus, glassware and reagents required
   b) Preparation of standard solution, LAL reagent / substrate and sample
   c) Determination of Maximum Valid Dilution (MVD) and endotoxin limit
d) Detailed test procedure

e) Calculation and interpretation of test result

f) Test specifications

9. Microbial Limit Test

9.1 Determination of microbial contamination test

a) List of apparatus and culture required

b) Preparation of test medium and growth promotion test

c) Sample preparation including method for neutralising of preservatives for samples that contain preservatives

d) Complete test procedure by 'surface speed' for bacteria and 'pour plate' for fungi

e) Colony counting

f) Specifications and acceptance criteria

9.2 Test for specified microorganisms and total viable aerobic count

a) List of apparatus and culture required

b) Preparation of test medium and growth promotion test

c) Sample preparation including method for neutralising of preservatives for samples that contain preservatives

d) Complete test procedure for each of specific microorganism involved

e) Observation on colonies presence

f) Specifications and acceptance criteria

10. Sterility Test

a) List of apparatus required

b) List of biological and chemical substance required:
   i. Culture medium
   ii. List of rinsing solution, buffer solution and diluent
   iii. Neutralising agent (if any)
   iv. List of specific type cultures required

c) Method Used
   Examples include membrane filtration method, direct inoculation, etc.

d) Method of preparation of the following solutions / materials:
   i. Culture medium, for example, Fluid Thioglycollate Medium and Soyabean Casein Digest Medium
   ii. Rinsing solution, buffer solution and diluents
   iii. Neutralising agent (if any)
   iv. Microorganism culture

e) Growth promotion test for medium used in sterility testing (specific aerobes, anaerobes and fungi)

f) Preparation of sample solution (including neutralising procedure of antimicrobial agent for antibiotic samples and samples which contain preservatives)

g) Complete test procedure for sterility test

h) Specifications and acceptance criteria

i) Validation procedure & validation data (if applicable)

11. Microbiological Assay

a) List of apparatus required

b) List of biological and chemical substances required

c) Procedure for the preparation of following solutions / substances:
   i. Culture Mediums
   ii. Rinsing Solutions
iii. Buffer Solutions
iv. Diluents
v. Microorganism culture used in assay
d) Test Method (e.g. agar diffusion, turbidimetric, randomised block, dose, etc)
e) Test Procedure
   i. Preparations of solutions containing antimicrobial agents which may be present in the sample to be tested (if applicable)
   ii. Preparation of standard solutions (including any steps to counteract the antimicrobial properties of any preservatives, etc present in the sample)
   iii. Preparation of test solutions (including any steps to neutralise the antimicrobial properties of any preservatives, etc present in the sample)
   iv. Dilution schemes for test and standard solutions
   v. Application of test & standard solutions (volume, Latin Squares, etc)
   vi. Incubation temperature & time
   vii. Procurement of test data
f) Complete calculation for the test including ANOVA tablet and other data showing validity of test results
g) Specifications and acceptance criteria
MINIMUM GENERAL QUALITY CONTROL SPECIFICATIONS FOR PHARMACEUTICAL DOSAGE FORMS

A. TABLETS, CAPSULES and LOZENGES

1. Visual Appearance, such as colour, surface appearance – smooth, mottling, etc.
2. Identification of active ingredient(s).
3. Assay for active ingredient(s).
4. Limit Tests for degradation products/related substances/contaminants, and other tests specified in monographs of official compendia.
5. Uniformity of diameter for uncoated tablets only.
6. Uniformity of content for products containing 50mg and below of active ingredients.
7. Disintegration Test for tablets and capsules only.
8. Dissolution Test.
9. Hardness Test for tablets and lozenges only.
10. Friability Test for tablets and lozenges only.
11. Moisture content.
12. Microbial Limit Test.

B. SUPPOSITORIES and PESSARIES

1. Visual Appearance, such as colour, surface appearance – smooth, mottling, etc.
2. Identification of active ingredient(s).
3. Assay for active ingredient(s).
4. Limit Tests for degradation products/related substances/contaminants, and other tests specified in monographs of official compendia.
5. Uniformity of weight.
6. Uniformity of content for products containing 50mg and below of active ingredients.
7. Disintegration Test.
8. Release rate of active ingredient(s) from dosage form.
10. Microbial Limit Test, where applicable.
C. INJECTABLE PREPARATIONS (LIQUID)

1. Visual Appearance, such as colour, surface appearance – smooth, mottling, etc.
2. Identification of active ingredient(s).
3. Assay for active ingredient(s).
4. Limit Tests for degradation products/related substances/contaminants, and other tests specified in monographs of official compendia.
5. Clarity and Colour.
6. pH.
7. Extractable volume for volumes below 100mL, where applicable.
8. Particle count for volumes of 100mL and above.
9. Pyrogen Test for volumes of 15mL and above, where applicable.
10. Sterility Test.
11. Effectiveness of antimicrobial preservative(s), where applicable.
12. Container and closure compatibility with active ingredient(s), preservative(s), if any, and product as a whole.

D. PREPARATIONS (POWDERS TO BE RECONSTITUTED BEFORE USE)

1. Visual Appearance (original and reconstituted).
2. Identification of active ingredient(s).
3. Assay for active ingredient(s) -
   (a) Potency of dry powder.
   (b) Strength of reconstituted solution.
4. Limit Tests for degradation products/related substances/contaminants, and any other tests specified in monographs of official compendia.
5. pH (where applicable).
6. Loss on drying (where applicable).
7. Moisture Determination.
8. Crystallinity (where applicable).
10. Uniformity of content (powders with added substances).
11. Sterility Test.
12. Pyrogen Test.
13. Safety Test.
14. Histamine Test (where applicable).
15. Stability Studies.
E. LIQUID PREPARATION (NON-INJECTABLE) SUCH AS SYRUPS, ELIXIRS, SOLUTION, SUSPENSION, EMULSION, EYE DROPS, EAR DROPS, ETC.

2. Identification of active ingredient(s).
3. Assay of active ingredient(s).
4. Average total contents per bottle with the range permitted.
5. Limit Tests for degradation products/related substances/contaminants, and any other tests specified in monographs of official compendia.
6. pH.
7. Particle size agglomeration and particle size distribution for suspensions, emulsions, powders/granules for reconstitution before use, only.
8. Density, refractive index, viscosity, where applicable.
9. Microbial Limit Test.
10. Effectiveness of antimicrobial preservative(s), where present.
11. Sterility Test for sterile products, for example, eye drops only.

F. OINTMENTS, CREAMS (TOPICAL AND OPHTHALMIC)

2. Identification of active ingredient(s).
3. Assay of active ingredient(s).
4. Limit Tests for degradation products/related substances/contaminants, and any other tests specified in monographs of official compendia.
5. Viscosity.
6. Softening range.
7. Homogeneity.
8. pH, where applicable.
9. Release rate of active ingredient(s) from dosage form.
10. Sterility Test for sterile products only.
11. Microbial Limit Test for non-sterile products only.
12. Effectiveness of antimicrobial preservative, where present.
G. POWDERS (DOSAGE FORM)

2. Identification of active ingredient(s).
3. Assay of active ingredient(s).
4. Limit Tests for degradation products/related substances/contaminants, and any other tests specified in monographs of official compendia.
5. Moisture Determination.
6. Uniformity of Content.
7. Sterility Test for sterile powders only.
8. Microbial Limit Test for non-sterile powders only.

H. AEROSOLS, INHALATIONS, SPRAYS, ETC.

1. Identification of active ingredient(s).
2. Content of active ingredient(s) per spray:-
   (a) Amount of active ingredient(s) delivered by metering valve.
   (b) Amount of active ingredient(s) retained by oral adaptor (where applicable).
3. Limit Tests for degradation products/related substances/contaminants, and any other tests specified in monographs of official compendia.
4. Nett contents – total number of metered doses/sprays.
5. Particle size and tests for foreign particles.
6. Delivery rate.
7. Leak testing.
8. Pressure testing.
9. Moisture determination for non-aqueous products only.
10. Stability Studies.
GUIDE creativity FOR SUBMISSION OF ANALYTICAL METHOD VALIDATION FORMS

1. Introduction

The requirements for the submission of the analytical method validation data and documents by the industry to the Drug Quality Control Section at the Department of Pharmaceutical Services are presented in this guide.

All the analytical validation done by the industry should be in accordance to the ASEAN and ICH Technical Requirements Guidance Documents specifically:

Q2A: Text on validation on analytical procedures, 1994
Q2B: Validation on analytical procedure: methodology, 1996

2. Requirements

The industry is required to submit the following documents for evaluation by the Drug Quality Control Section:

a) Analytical method protocol for the testing of the raw materials (only the active pharmaceutical ingredients (API) and preservatives, if any). This should include the specifications and certificate of analysis. All analytical test procedures where possible should be in accordance with the official monograph of that ingredient in the latest edition of the official pharmacopoeia such as British Pharmacopoeia, United States Pharmacopoeia and WHO.

b) Analytical method validation protocol for the finished product. The protocol of analysis should be in accordance with the Drug Quality Control Section’s guidelines for the submission of protocol of analysis.

c) Protocol for the analytical method validation procedure carried out on the finished product. This procedure should include all details about the validation process including preparation of all solutions used – standards, samples, placebo etc, detection methods, test conditions, equipment used, statistical analysis & evaluation, calculations etc.

Types of analytical procedures to be validated include:

i. Identification tests
ii. Quantitative tests for impurities’ contents
iii. Limit tests for control of impurities
iv. Quantitative tests of the active ingredient in the sample.
v. Pyrogen / Bacterial endotoxin test
vi. Sterility test

A brief description of the type of tests considered in this document is provided below:

Identification tests are intended to ensure the identity of an active ingredient in the sample. This is normally achieved by comparison of a property of the sample e.g. spectrum, chromatographic behaviour, chemical reactivity, etc) to that of a reference standard.
Testing for impurities can be either a quantitative test or a limit test for the impurity in the sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test. Assay procedures are intended to measure the content of active pharmaceutical ingredient present in a given sample. The analytical data submitted must be able to support the claim that the analytical method employed has been validated.

Pyrogen Test and Limulus Amebocyte Lysate Test – Relevant validation data for pyrogen test and Limulus Amebocyte Lysate Test include product independent data such as equipment validation, validation of temperature system, lysate sensitivity and product dependent validation data such as inhibition / enhancement studies and validation for routine LAL tests according to the type of LAL test method employed e.g. Gel Clot method, quantitative end point method or quantitative kinetic method.

Sterility testing applied to products that are required to be sterile. A satisfactory result indicates that no contaminating microorganism has been found in the sample examined in the condition of the test. For sterility testing it is imperative that the testing procedure adopted by the manufacturers include all aspects of validation of the testing method including the precautions against microbial contamination.

d) Complete set of data obtained from the validation process. These include all raw data such as weights used, chromatograms, tabulated sets of value as well as graphs, statistical analysis & evaluation, calculations & formulae etc. Summary of data will not be accepted. Acceptance criteria for each characteristic / parameter should also be submitted. For products tested using analytical methods described in official pharmacopoeias, users are not required to validate accuracy and reliability of these methods, but must submit data verifying their suitability under actual conditions of use.

Certificate of analysis of two (2) batches of the finished product

Certificate of analysis for one batch of API used in the product

Summary on the validation process together with conclusion reached
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
         2.2.1.1 Absorption
         2.2.1.2 Distribution
         2.2.1.3 Metabolism
         2.2.1.4 Excretion
         2.2.1.5 Pharmacokinetic Drug Interaction (Non-clinical)
         2.2.1.6 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)
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.
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.
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Location of Study Report</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects</th>
<th>Healthy Subjects or Diagnosis of Patients</th>
<th>Duration of Treatment</th>
<th>Study Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>001</td>
<td>Vol 3, Sec. 1.1, p. 183</td>
<td>Absolute BA IV vs Tablet</td>
<td>Cross-over</td>
<td>Tablet, 50mg single dose, oral, 10 mg IV</td>
<td>20</td>
<td>Healthy Subjects</td>
<td>Single dose</td>
<td>Complete; Abbreviated</td>
</tr>
<tr>
<td>BE</td>
<td>002</td>
<td>Vol 4, Sec. 1.2, p. 254</td>
<td>Compare clinical study and to-be-marketed formulation</td>
<td>Cross-over</td>
<td>Two tablet formulations, 50 mg, oral</td>
<td>32</td>
<td>Healthy Subjects</td>
<td>Single dose</td>
<td>Complete; Abbreviated</td>
</tr>
<tr>
<td>PK</td>
<td>1010</td>
<td>Vol 6, Sec. 3.3, p. 29</td>
<td>Define PK</td>
<td>Cross-over</td>
<td>Tablet, 50mg single dose, oral</td>
<td>50</td>
<td>Renal Insufficiency</td>
<td>Single dose</td>
<td>Complete; Full</td>
</tr>
<tr>
<td>PD</td>
<td>020</td>
<td>Vol 6, Sec. 4.2, p. 147</td>
<td>Bridging study between regions</td>
<td>Randomised placebo-controlled</td>
<td>Tablet, 50mg, multiple dose, oral, every 8 hrs</td>
<td>24 (12 drug, 12 placebo)</td>
<td>Patients with primary hypertension</td>
<td>2 weeks</td>
<td>Ongoing; Interim</td>
</tr>
<tr>
<td>Efficacy</td>
<td>035</td>
<td>Vol 10, Sec. 5.1, p. 1286</td>
<td>Long term; Efficacy &amp; Safety; Population PK analysis</td>
<td>Randomised active-controlled</td>
<td>Tablet, 50mg, oral, every 8 hrs</td>
<td>300 (152 test drug, 148 active control)</td>
<td>Patients with primary hypertension</td>
<td>48 weeks</td>
<td>Complete; Full</td>
</tr>
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APPEAL FOR PROVISIONAL REGISTRATION OF REJECTED MEDICINAL PRODUCTS
(Form No: DPS/DRU/Appeal/01)

To:
Chairperson of Drug Registration Committee
Department of Pharmaceutical Services
Ministry of Health
Commonwealth Drive BB 3910
Bandar Seri Begawan
Brunei Darussalam

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

<table>
<thead>
<tr>
<th>Date of Rejection</th>
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<tbody>
<tr>
<td>Application No</td>
<td>L O A - P / / S</td>
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<tr>
<td>Name of Product</td>
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<tr>
<td>Active Ingredient(s)</td>
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<td>Proposed Indication(s)</td>
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<tr>
<td>Proposed Dosage Regimen(s)</td>
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<tr>
<td>Countries where product is registered with the above indication(s) and dosage regimen(s)</td>
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<tr>
<td>Countries where product is rejected/withdrawn</td>
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<tr>
<td>Reasons for appeal</td>
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<tr>
<td>Documents submitted to support appeal</td>
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Note: Only appeals accompanied by relevant new information or supporting documents not 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.

<table>
<thead>
<tr>
<th>Name of applicant</th>
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<tr>
<td>Designation</td>
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<tr>
<td>Name and address of company</td>
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<tr>
<td>Contact number</td>
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<td>Signature, date &amp; company Stamp</td>
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APPLICATION FOR VARIATIONS TO A REGISTERED MEDICINAL PRODUCT

(Form No: DPS/DRU/Vartn/01)

For guidance, please refer to the “Guideline on application for variations to a registered medicinal product”.

Sections A, B, and C must be completed neatly by all provisional product registration holders who wish to inform the Department of Pharmaceutical Services or submit their application for variation to a registered medicinal product. Section D, E and F are further sections that need to be filled in by provisional product registration holders where applicable.

Section A – Details of Provisional Product Registration

<table>
<thead>
<tr>
<th>Application No(s): (For official use only)</th>
<th>Provisional Product Registration No(s):</th>
<th>Expiry Date(s):</th>
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Product Name(s) & Strength:

Generic Name:

Name & Address of Registration Holder (Company):

Tel No:

Fax No:

Full Name of Person Responsible (Applicant):

Designation:

Signature of Person Responsible:

Date:

Section B – Category of Variations (Please tick ✓ where appropriate)

<table>
<thead>
<tr>
<th>Minor Variations</th>
<th>Major Variations</th>
<th>Expected effective date</th>
<th>Expected effective date</th>
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Section C – Types of Variations (Please tick ✓ the appropriate boxes)

<table>
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<tr>
<th>No.</th>
<th>Change(s) involved:</th>
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<tbody>
<tr>
<td>1.</td>
<td>Particulars of * Provisional Product Registration Holder / Importer / Distributor / Person Making Application on Behalf of Provisional Product Registration Holder * Please delete if not relevant</td>
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<td>2.</td>
<td>Manufacturer / Repacker</td>
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<td>3.</td>
<td>Product Shelf-life</td>
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<td>4.</td>
<td>Product Pack Size</td>
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<td>5.</td>
<td>Product Storage Condition</td>
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<td>6.</td>
<td>Type of Product Containers</td>
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<td>7.</td>
<td>Batch Numbering System</td>
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<td>8.</td>
<td>Product Owner</td>
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<td>9.</td>
<td>Product Name</td>
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<td>10.</td>
<td>Product Formulation</td>
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<td>11.</td>
<td>Product Physical Characteristics</td>
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<td>12.</td>
<td>Product Labelling</td>
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<td>13.</td>
<td>Package insert or patient information leaflet</td>
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<td>14.</td>
<td>Specifications of Active Ingredient</td>
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<td>15.</td>
<td>Specifications of Finished Product</td>
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<td>16.</td>
<td>Method of Analysis of Finished Product</td>
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<td>17.</td>
<td>Method of Manufacture &amp; QC of Finished Product</td>
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<td>18.</td>
<td>Others: ________________________________________________________</td>
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<td>19.</td>
<td>Inclusion of new indication</td>
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<td>20.</td>
<td>Inclusion of new dosage regime</td>
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For changes involving no. 1, please proceed to Section D1 & D2. For changes involving no. 2 to 18, please proceed to Section E. For changes involving no. 19 and 20, please proceed to Section F.
Section D1 - Details of Current and New Provisional Product Registration Holder / Importer / Distributor / Person Making Application on Behalf of Provisional Product Registration Holder

<table>
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<th>Particulars</th>
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<td><strong>Company Holding Provisional Product Registration</strong></td>
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<td>Store Address</td>
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<td><strong>Importer (which is not the Provisional Product Registration Holder)</strong></td>
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<td>Company Name</td>
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<td><strong>Distributor (which is not the Provisional Product Registration Holder)</strong></td>
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<td><strong>Person Making Application on Behalf of Provisional Product Registration Holder</strong></td>
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<td>Full Name</td>
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<td>Company Stamp</td>
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Section D2 – Provisional Product Registration(s) Affected by Change
(Please submit a separate list if the product owner and/or manufacturer are different or if space is not sufficient)

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<thead>
<tr>
<th>Name &amp; Address of Product Owner:</th>
<th>Name &amp; Address of Manufacturing Plant:</th>
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**Details of Current Valid Product Registration(s)**

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<th>Application Number</th>
<th>Provisional Product Registration Number</th>
<th>Name of Product</th>
<th>Name of Active Ingredient(s)</th>
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## Section E – Details of Proposed Change(s)

<table>
<thead>
<tr>
<th>Type of Variation</th>
<th>Current Product Details</th>
<th>Proposed Change(s)</th>
<th>Reasons for Change</th>
<th>Approved in Country of Origin? (Yes / No)</th>
<th>Enclosures</th>
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</table>
Section F – Details of Current and New Indications or Dosage Regime

<table>
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<tr>
<th>Current Indications / Dosage Regime</th>
<th>New Indication / Dosage Regime</th>
<th>New indication / Dosage Regime is Approved in Country of Origin? (Yes / No)</th>
<th>Countries Where New Indication / Dosage Regime are Approved?</th>
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</thead>
</table>

Note: Please submit clinical data to support the new indication or new dosage regime.
## SECTION G – RECEIPT OF APPLICATION (For official use only)

<table>
<thead>
<tr>
<th>DRUG REGISTRATION UNIT</th>
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<tbody>
<tr>
<td>Date application received:</td>
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<tr>
<td>Provisional Product Registration No(s):</td>
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<tr>
<td>Product Name(s) &amp; Strength:</td>
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<tr>
<td>Generic Name:</td>
</tr>
<tr>
<td>Name and signature of Drug Registration Unit officer:</td>
</tr>
<tr>
<td>Notes:</td>
</tr>
</tbody>
</table>
SECTION H - OUTCOME OF APPLICATION *(For official use only)*

Ref: ( ) DRU / Date:

Provisional Product Registration No. B R U / L / / / / / P

Product Name(s) & Strength: .................................................................

Name and address of applicant:

.................................................................................................

.................................................................................................

.................................................................................................

Please be informed that your application for variations involving the change(s) as indicated in your application form dated ............ for the above-mentioned product is:

| (i)  | Noted                          | □ |
| (ii) | Approved                      | □ |
| (iii)| Approved for the product registration (s) stated in Section D2 | □ |
| (iv) | Not Approved (Please refer to the letter attached) | □ |
| (v)  | Others: _______________________ | □ |
| (vi) | Please inform doctors, pharmacists and users of the product of the relevant approved changes | □ |
| (vii)| Please submit to this department the original copy of product labels / package insert / patient information leaflet once printed | □ |
| (viii)| Incomplete. Additional data required are as follow: | □ |
|      | ________________________________________________________________ | |
|      | ________________________________________________________________ | |
| (ix) | Remarks: _________________________ | □ |

Date: ________________________                                            ___________________________

Chairperson
Drug Registration Committee
Department of Pharmaceutical Services
Ministry of Health
Brunei Darussalam
1. **Introduction**

All provisional product registration holders in Brunei Darussalam are required to inform the Department of Pharmaceutical Services, Ministry of Health on a change to any aspect of the pharmaceutical product i.e. variation(s) to what have been submitted previously to the department in their provisional product registration application. The change may include but is not limited to a 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 Department of Pharmaceutical Services is required before the changes can be made, with the exception to some minor variations that require only notification to the Department of Pharmaceutical Services.

2. **Categories of Variations**

Variations are classified into two categories:

(a) **Major variations:**

- Variations to authorised pharmaceutical product affecting one or more of the following aspects:
  - route of administration
  - strength, posology
  - indications, and/or
  - active ingredients
  - or that does not fall within the definition of minor variation.

- Applications for major variations usually require the submission of data necessary to establish quality, safety and efficacy of the new formulation resulting from the variations.

- This type of variation requires approval from the Department of Pharmaceutical Services.

(b) **Minor variations:**

- Variations to authorised pharmaceutical product not affecting one or more of the following aspects:
  - route of administration
  - strength, posology
  - indications, and/or
  - active ingredient(s)

- Applications for minor variations usually require the submission of data necessary to establish quality of the new formulation resulting from the variations.
• This type of variation requires only notification to the Department of Pharmaceutical Services.

Note: Appendix 6 shows the types of variations that fall within each category.

3. Application Form

The form to be used for both major and minor variations is Form No: DPS/DRU/Vartn/01.

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

4. Supporting Documents

The documents, packaging materials and product samples that are required to be submitted for the various types of variations are stated in Appendix 6.

For variations that result in changes of information on the product label, carton, package insert or patient information leaflet, the affected packaging materials with the new information should be submitted together.

5. Submission

Application form must be duly completed and supported by all of the required documents, packaging materials or product samples. 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
## APPENDIX 6

### TYPES OF VARIATIONS

1) **Types of Variations pertaining to Product Details**

<table>
<thead>
<tr>
<th>No.</th>
<th>Types of Variations</th>
<th>Category of Variations</th>
<th>Documents / Packaging Materials / Product Samples required to be submitted</th>
</tr>
</thead>
</table>
| 1.1 | Change of product name * | Major | - Product label, carton and package insert or patient information leaflet indicating new name  
| | | | - Confirmation by manufacturer or product owner that there are no changes to the product formulation and manufacturing process. |
| 1.2 | Change of product formulation involving excipients | Major | - Product full formula (in sealed envelope)  
| | | | - Stability data to support new formulation  
| | | | - Finished product specifications  
| | | | - Certificate of analysis of finished product  
| | | | - Product samples for both new and old formulation  
| | | | - Reasons for change |
| 1.3 | Change of tablet coating or capsule shell e.g. from sugar-coated to film-coated or capsule shell from bovine origin to vegecap | Major | - Formulation of new coating  
| | | | - Stability data to support new formulation  
| | | | - Finished product specifications  
| | | | - Certificate of analysis of finished product  
| | | | - Product samples for both new and old coating  
| | | | - Reasons for change |
| 1.4 | Change of product physical characteristics (e.g. inclusion or deletion of superficial marking of tablet, shape) | Major | - Product sample |
| 1.5 | Change of type of container | Major | - Stability data to support the use of the new packaging material |
| 1.6 | Inclusion of new pack size | Major | - Label, carton and package insert or patient information leaflet for new pack size |
| 1.7 | Change of storage conditions | Major | - Stability data to support the new storage conditions |
| 1.8 | Change of product shelf-life | Major | - Stability data to support the new shelf-life |
| 1.9 | Change of product label, carton, package insert or patient information leaflet involving only:  
| | | | - Change in design and layout without change in text content  
| | | | - Change in font size or colours of text  
<p>| | | | - Inclusion or deletion of barcodes | Minor | - New product label, carton, package insert or patient information leaflet |</p>
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<thead>
<tr>
<th></th>
<th>Types of Variations</th>
<th>Category of Variations</th>
<th>Documents / Packaging Materials / Product Samples required to be submitted</th>
</tr>
</thead>
</table>
| 1.10 | Inclusion of new indication or new dosage regime in product label of unit carton, package insert or patient information leaflet | Major                  | • New product label, carton, package insert or patient information leaflet with the changes highlighted  
• Clinical data to support new indication or new dosage recommendation  
• Countries where product is registered with the new indication or new dosage regimen |
| 1.11 | Change of product label, carton, package insert or patient information leaflet which does not fall under 1.9 & 1.10 | Major                  | • New product label, carton, package insert or patient information leaflet with the changes highlighted |
| 1.12 | Change of specifications of active ingredient                                     | Major                  | • New method of analysis with the changes highlighted  
• Certificate of analysis for active ingredient |
| 1.13 | Change of method / process of manufacture & quality control of finished product    | Major                  | • New method / process of manufacture & quality control of finished product with the changes highlighted  
• Data to support the new method of manufacture & quality control of finished product  
• Reasons for change(s) in the method / process of manufacture |
| 1.14 | Change of method of analysis of finished product                                  | Major                  | • New method of analysis / analysis protocol with the changes highlighted  
• Data to support the new method of analysis  
• Certificate of analysis for finished product |
| 1.15 | Change of finished product specifications                                         | Major                  | • New specifications of finished product with the changes highlighted  
• Data to support the new specifications  
• Certificate of analysis for finished product |
| 1.16 | Deletion of pack size                                                             | Minor                  | Nil |
| 1.17 | Change in batch numbering system                                                  | Minor                  | Nil |

2) Types of Variations pertaining to Product Registration Holder
2.1 Change of product registration holder*

| Major |
|--------|--------------------------------------------------|
| Letter issued by the product owner authorising the new product registration holder to hold the product registration in Brunei Darussalam and withdrawing the authorisation previously given to the current product registration holder |
| Letter issued by the new product registration holder confirming that there are no changes to the product or other details submitted previously |
| Business registration certificate issued by the Registry of Companies & Businesses |

2.2 Change of company name*

| Major |
|--------|--------------------------------------------------|
| Letter issued by the product owner authorising the new company to hold the product registration in Brunei Darussalam |
| Certificate on the change of corporate name issued by the Registry of Companies & Business |

2.3 Change of office address

| Minor |
|--------|--------------------------------------------------|
| Nil |

2.4 Change of store address

| Major |
|--------|--------------------------------------------------|
| Nil |

2.5 Change of person making application on behalf of company

| Minor |
|--------|--------------------------------------------------|
| Nil |

2.6 Change of pharmacist employed by the product registration holder

| Minor |
|--------|--------------------------------------------------|
| Nil |

3) Types of Variations pertaining to Local Importer or Distributor (who is not the product registration holder)

<table>
<thead>
<tr>
<th>No.</th>
<th>Types of Variations</th>
<th>Category of Variations</th>
<th>Documents / Packaging Materials / Product Samples required to be submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Change of company name</td>
<td>Minor</td>
<td>Nil</td>
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<tr>
<td>3.2</td>
<td>Change of office address</td>
<td>Minor</td>
<td>Nil</td>
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<tr>
<td>3.3</td>
<td>Change of store address</td>
<td>Major</td>
<td>Nil</td>
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<tr>
<td>3.4</td>
<td>Change of pharmacist employed by importer or distributor</td>
<td>Minor</td>
<td>Nil</td>
</tr>
</tbody>
</table>

4) Types of Variations pertaining to Manufacturer and Repacker

<table>
<thead>
<tr>
<th>No.</th>
<th>Types of Variations</th>
<th>Category of Variations</th>
<th>Documents / Packaging Materials / Product Samples required to be submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Change of manufacturer’s / repacker’s name *</td>
<td>Major</td>
<td>Letter issued by product owner authorising manufacturer with new name to manufacture the product</td>
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<td>GMP certificate (if not submitted previously)</td>
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<tr>
<td>4.2</td>
<td>Change of existing manufacturer’s / repacker’s office address</td>
<td>Minor</td>
<td>• Nil</td>
</tr>
</tbody>
</table>
| 4.3 | Change of existing manufacturer’s plant address | Major | • Certificate of Pharmaceutical Product (CPP) / GMP certificate (if not submitted previously) & Certificate of Free Sale (CFS)  
• Plant layout of new manufacturer  
• Declaration in writing that the formulation, manufacturing process and specifications are the same as already approved (Minor change maybe accepted if it is for the betterment of the product and justified)  
• Copy of approved release and end-of-shelf-life specifications  
• Certificate of analysis for one batch of the product 

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5) Types of Variations pertaining to Product Owner (who is not the manufacturer)
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* Denotes changes that require re-issue of product registration certificate