Guidance on therapeutic product registration in Singapore

Authority: **Health Sciences Authority**

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CHAPTER A

GENERAL OVERVIEW

1 FOREWORD

This guidance document outlines the regulatory processes and requirements for therapeutic product registration and should be read in conjunction with the relevant legislation in Singapore, including:

- Health Products Act 2007; and
- Health Product (Therapeutic Products) Regulations 2016.

The Health Products Act (HPA) provides for the legislative basis for regulating the manufacture, import, supply, presentation and advertisement of therapeutic products, one of the health products categories regulated under the *Act*.

1.1 Scope of This Guidance Document

This guidance document describes the procedures and requirements for submitting an application to register a therapeutic product, or to make a variation application to a registered therapeutic product.

Under the First Schedule of the HPA, a therapeutic product means any substance that:

(a) is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:

(i) for preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or any symptom thereof;

(ii) for investigating, modifying, or replacing any physiological process;

(iii) for influencing, controlling or preventing conception; or

(iv) for inducing anaesthesia.

(b) has as its constituent any of the following active ingredients:

(i) any chemical or botanical element, naturally occurring chemical or botanical material or chemical product obtained by chemical change or synthesis;

(ii) any metabolite from a micro-organism;

(iii) any macromolecule extracted from an organism; or

(iv) any substance derived from a biological system, including any of the following:

(A) a whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;

(B) a part of a micro-organism, such as a sub-unit vaccine;

(C) a plasma-derived product; or

(D) a biotechnology-derived substance, such as a protein or polypeptide;

(c) exerts an inherent effect either pharmacologically, chemically or by other physiological means, leading to its use for a therapeutic preventive, palliative or diagnostic purpose; and

(d) is not any of the following:

(i) a medical device;

(ii) a cell, tissue or gene therapy product;

(iii) whole blood or any blood component;

(iv) any Chinese proprietary medicine;

(v) any homoeopathic medicine;

(vi) any medicated oil or balm;

(vii) any quasi-medicinal product; or

(viii) any traditional medicine.

To avoid doubt, items d(vi), (v), (vi), (vii) and (viii) have the same meaning as defined in the Medicines Act 1975 in paragraph 2 of the Medicines (Traditional Medicines, Homoeopathic Medicines & Other Substances) (Exemption) Order.

In making an application for a therapeutic product, applicants should ensure that the submission requirements as specified in this guidance document are duly fulfilled. In a situation where an applicant proposes an alternative to any of the specified requirements, such a proposal should be accompanied by scientific justification and discussed with HSA prior to making the submission to avoid potential rejection of the application. Information on pre-submission consultation can be found in Chapter B; 5.4.

HSA may also request for additional information to supplement the specified submission requirements if this is deemed necessary for the assessment of the safety,

efficacy and quality of the product for which an application is made. Information on the submission requirements can be found in the following Chapters of this guidance.

Within this document, the term '*quality*' is used to describe chemical, pharmaceutical and biological data, while the term '*non-clinical*' is used to describe preclinical, pharmacological and toxicological data.

Applicants are advised to check the HSA website for the latest version of this guidance document and other related therapeutic product registration guidelines.

1.2 Therapeutic Product Registration

A therapeutic product registered under the HPA is specific to the product with respect to its:

- proprietary or brand name;
- pharmaceutical formulation;
- pharmaceutical dosage form (i.e. physical presentation) and strength; and
- indication(s) and dosing regimen.

Different formulations, dosage forms and strengths of the same chemical or biologic entity are considered as different products and will require separate registrations for the individual product.

1.2.1 Forensic Classification

In Singapore, a therapeutic product may be registered under one of the following forensic classifications, which determines its level of control for access:

- Prescription-Only Medicine (POM): A therapeutic product that can only be obtained from a doctor or a dentist, or from a pharmacist with a valid prescription.
- Pharmacy-Only Medicine (P): A therapeutic product that can only be obtained under the supervision of a pharmacist at a retail pharmacy without requiring a prescription.
- General Sale List Medicine (GSL): A therapeutic product that can be obtained from any retailer without medical supervision.

Prescription-Only Medicines (POM) control is generally required for a product containing a new chemical / biologic entity, and in one or more of the following situations:

(a) The product is indicated for the treatment of a condition or symptom that must be appropriately diagnosed and managed by a doctor, and may pose a direct [1] or indirect [2] danger to human health, even when used correctly, if used without medical supervision;

(b) The product is likely to present a direct or indirect danger to human health due to potential risks of inappropriate use, abuse, addiction or illegal use; or

(c) The product is normally prescribed for parenteral administration, or requires administration in an appropriate clinical setting under medical supervision.

Pharmacy-Only Medicines (P) control is required for products that do not warrant POM control and meet all of the following criteria:

(a) The product is indicated for short-term treatment of a minor condition or symptoms that can be readily identified and managed by self-medication;

(b) The selection of the product for treating the condition or symptoms requires consultation with a pharmacist;

(c) The correct and safe use of the product requires counselling by a pharmacist on the

duration of treatment, contraindications, drug interactions, precautions or warnings; and

(d) The product presents minimal risk of misuse, with low potential for abuse.

General Sale List Medicines (GSL) control may be considered for products that meet all of the following criteria:

(a) The product is indicated for self-limiting, common, and easily recognised ailments;

(b) The product is reasonably safe and can be sold or supplied without the need for consultation with or counselling by a healthcare professional;

(c) The product has no significant contraindications, drug interactions, or safety concerns that would necessitate medical supervision for its use;

(d) The product presents minimal risk of misuse, with no known potential for abuse;

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[1] Direct danger: Such risks may include significant adverse reactions and drug interactions.
[2] Indirect danger: Such risks may include masking of an underlying condition and potentially delay a diagnosis which may be exacerbated by the treatment.

(e) The likelihood of misdiagnosis by the individual resulting in severe health consequences is low; and

(f) The product is presented in an appropriate pack size(s) which reflects the intended duration of self-treatment without medical supervision.

2 APPLICANT AND REGISTRANT RESPONSIBILITIES

The applicant of a product registration refers to the local company that is submitting a therapeutic product application in Singapore. The product registration applicant company may authorise its employees or designated external parties, all of whom are referred to as the "applicant representative", to submit the application for product registration in Singapore.

According to Section 30(10) of the HPA, an applicant, in making an application for the registration of a therapeutic product, must ensure that all information contained in the application is truthful and is not misleading. An applicant must inform HSA of any

emerging information that may affect the benefit-versus-risk assessment of the therapeutic product to which the application relates, as soon as the applicant becomes aware of such information.

The applicant is responsible for submitting the application and all the accompanying supporting documents (including but not limited to the dossier, responses to HSA's queries and commitment letters).

HSA may require a statutory declaration by the applicant verifying any information contain in or relating to the application.

HSA may register the product subject to post-approval commitments. In such circumstances, the applicant will be required to furnish a letter of commitment stating the undertakings concerned. Upon the approval of an application to register a therapeutic product, the product is registered and is assigned a registration number and entered in the Register of Therapeutic Products. The applicant of the product registration becomes the product registrant.

The product registrant should refer to Part 8 of the HPA and Part 6 of the HP (TP Regulations) 2016 for duties imposed on registrants.

It should be emphasised that product registrants must comply with the registration conditions and the post-approval commitments specified in the registration. The registration conditions can be viewed at Enquire@PRISM.

For submission of documents to fulfil registration conditions, please use this form (Submission of Documents to Fulfil Therapeutic Product Registration Conditions - https://go.gov.sg/fulfil-tp-reg-conditions).

3 WHETHER A THERAPEUTIC PRODUCT IS SUBJECT TO PATENT

An applicant for registration of a therapeutic product is required to make a declaration on whether the therapeutic product for which registration is sought is subject to a subsisting restraining patent, pursuant to Regulation 23 of the Health Products

(Therapeutic Products) Regulations, hereafter referred to as the *Regulations*. A "restraining patent" refers to a patent mentioned in regulation 23(1)(a) of the *Regulations*.

The declaration must be made in the form specified in Appendix 1 – Form 1 of this guidance document and furnished at the time of making the application, as well as at any other such time as HSA may require. A second declaration is required prior to the grant of registration.

A registration application may be declared as one of the following categories:

- Category A1: where no restraining patent is in force in respect of the therapeutic product to which the application relates;
- Category A2: where a restraining patent is in force in respect of the therapeutic product to which the application relates and the applicant is either the proprietor of the restraining patent, or if the applicant is not the proprietor of the restraining patent, the proprietor has consented to or acquiesced in the grant of the registration;
- Category A3: where a restraining patent is in force in respect of the therapeutic product to which the application relates, the applicant is not the proprietor of the restraining patent and the proprietor has not consented to or acquiesced in the grant of the registration, and the applicant is requesting for the grant of registration after the restraining patent expires. A Category A3 declaration is applicable only to an application that is made within 18 months of the expiry of the restraining patent from the point of application submission. Such an application may not be made earlier than 18 months before the restraining patent expires. Applicants who deviate from this guideline may be required to withdraw their application and resubmit it at the appropriate juncture;
- Category B: where a restraining patent is in force in respect of the therapeutic product to which the application relates, the applicant is not the proprietor of the restraining patent and the proprietor has not consented to or acquiesced in the grant of the registration, and in the applicant's opinion and to the best of his belief the restraining patent is invalid or will not be infringed by the performing of the act for which the registration is sought.

Where an application is declared as a Category B application, HSA will require the

applicant to serve a notice on the proprietor of the restraining patent in the form specified in Appendix 1 – Form 2 of this guidance document. An applicant may also be required to serve a notice where HSA considers it appropriate.

Where the proprietor of the restraining patent has made an application to a court pursuant to regulation 23(8)(a) and furnishes a written notice to HSA under regulation 23(8)(b) of the *Regulations*, the written notice must be accompanied by the following:

- Evidence of the application made under regulation 23(8)(a) of the *Regulations*; and
- A declaration made in the form specified in Appendix 1 – Form 3 of this guidance document that the aforementioned application relates to a restraining patent.

The information contained in this section serves solely as guidance on the requirement for submission of declaration on patent-related information in respect of an application for product registration. HSA does not provide advice on the category under which an application should be declared or whether a therapeutic product is subject to a subsisting restraining patent. An applicant requiring such assistance should seek appropriate legal advice.

4 PROTECTION OF CONFIDENTIAL SUPPORTING INFORMATION AND REGISTRATION EXCLUSIVITY

Regulation 26 and 29 of the *Regulations* provide for protection of confidential supporting information relating to innovative therapeutic product applications and exclusivity of safety and efficacy data, respectively.

Confidential information received in support of the registration of an innovative therapeutic product is protected for a period of 5 years from the date of receipt, during which HSA will not use the information to determine whether to grant any other registration applications. In this regard, confidential supporting information refers to trade secrets and information that has commercial value that would be, or is likely to be, diminished by disclosure.

A 5-year period of exclusivity is granted for a therapeutic product for which safety and efficacy data has been generated in support of its registration. During the exclusivity period, a subsequent similar therapeutic product will not be able to rely on such data generated for the earlier therapeutic product to obtain registration.

CHAPTER B REGISTRATION PROCESS

A company seeking to market a therapeutic product in Singapore must obtain marketing approval from HSA through making an application for product registration. The registration process involves a series of steps, as shown in Figure 1.

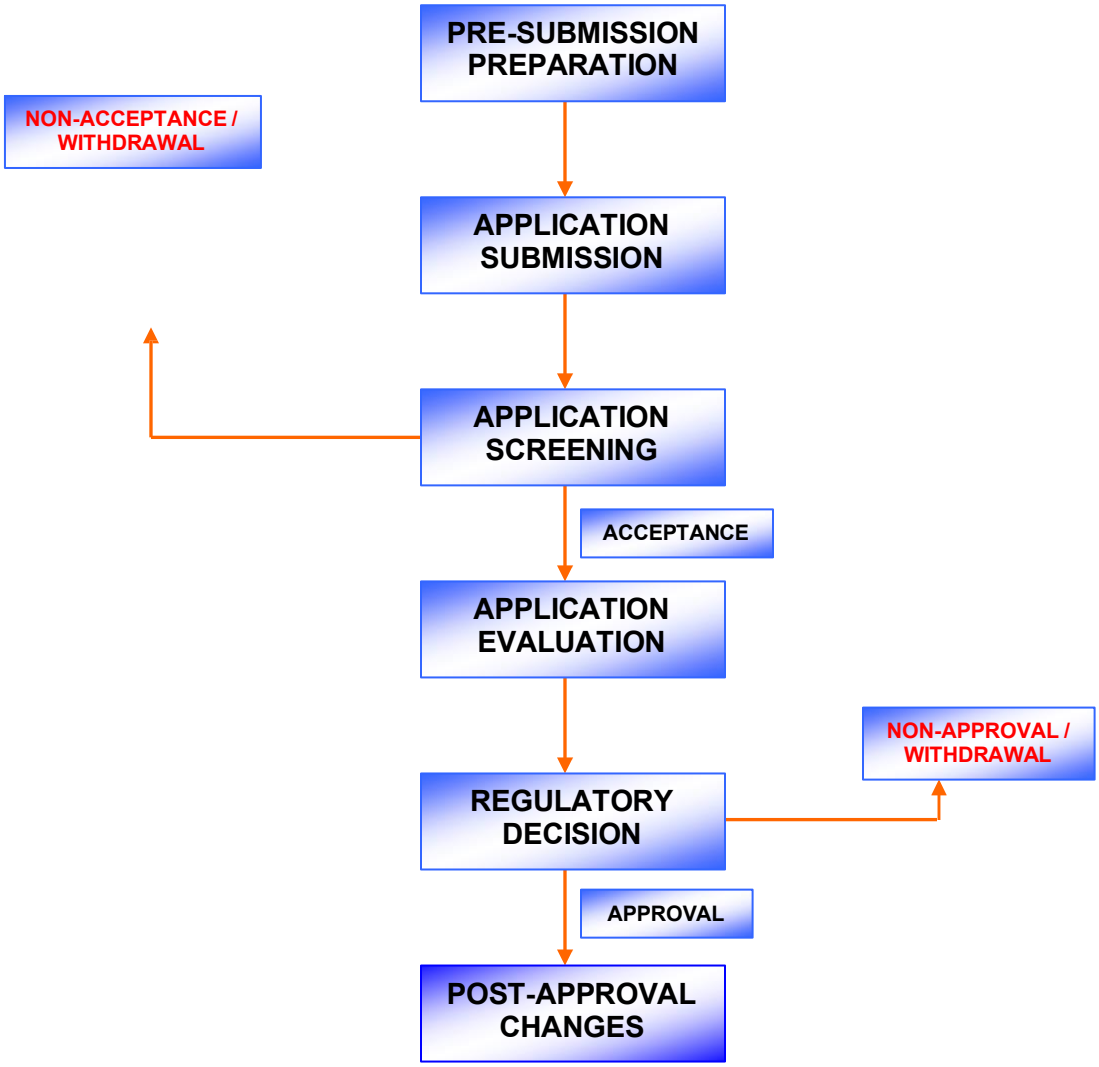

Figure 1 Registration Process for a Therapeutic Product

5 PRE-SUBMISSION PREPARATION

The following are important considerations for an applicant to register a therapeutic product:

(a) Knowing which type of application to apply for;

(b) Knowing which evaluation route to choose; and

(c) Understanding the requirements as specific in this guidance.

5.1 Product Types

A therapeutic product could contain either chemical or biological entity(ies) as the active ingredient(s).

A chemical entity refers to any chemical element, naturally occurring chemical material or chemical product obtained by chemical change or synthesis (including macromolecules produced by chemical synthesis, such as peptides/oligo- nucleotides), or any metabolites from a micro-organism (such as antibiotics).

A biological entity refers to any macromolecule extracted from an organism (such as proteins, nucleic acids, proteoglycans, cytokines and growth factors), or any substance derived from a biological system, including any of the following:

(a) A whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;

(b) A part of a micro-organism, such as a sub-unit vaccine;

(c) A plasma-derived product; or

(d) A biotechnology-derived substance, such as a protein or polypeptide.

5.2 Application Types

In applying for a new product registration for a therapeutic product in Singapore, there are two categories of applications – a new drug application (NDA) and a generic drug application (GDA):

NDA New Drug Application

NDA-1: For the first strength of a product containing a new[3] chemical or biological entity.

NDA-2: (a) For the first strength of a product

(i) containing a new combination of registered chemical or biological entities;

(ii) containing registered chemical or biological entity(ies) in a new dosage form (e.g. tablets, capsules, injectables), new presentation (e.g. single-dose vials, multi-dose vials, pre-filled syringe, starter packs), or new formulation (e.g. preservative-free);

(iii) containing registered chemical or biological entity(ies) for use by a new route of administration; or,

(iv) containing registered chemical or biological entity(ies) for new indication(s), dosage recommendation(s) and/or patient population(s).

(b) For products that do not fall under the descriptions for NDA-1, NDA-3 or GDA.

NDA-3: For subsequent strength(s) of a product that has been registered or has been submitted as an NDA-1 or NDA-2. The product name, active ingredient, dosage form, presentation, indication, dosing regimen and patient population should be the same as that for the NDA-1 or NDA-2.

[3] i.e. not a chemical or biological entity that is either registered or being concurrently submitted for registration in Singapore. Currently registered therapeutic products can be found in the Register of Therapeutic Products at www.hsa.gov.sg.

GDA Generic Drug Application

A generic drug application applies to a therapeutic product that contains one or more chemical entities, and that is essentially the same as a current registered product with respect to its qualitative and quantitative composition of active ingredients, pharmaceutical dosage form and clinical indication.

Follow-on biologic products (also known as biosimilar products) are not eligible for a GDA and are required to be submitted via a NDA.

GDA-1: For the first strength of a generic chemical product.

GDA-2: For subsequent strength(s) of the generic chemical product that has been registered or submitted as GDA-1. The product name and dosage form should be the same as that for the GDA-1.

In cases where multiple strengths of a generic product are submitted together, the strength of the product used in the BE study is considered as GDA-1. The remaining strength(s) should be submitted as GDA-2.

Figure 2 is a schematic diagram illustrating the various types of applications:

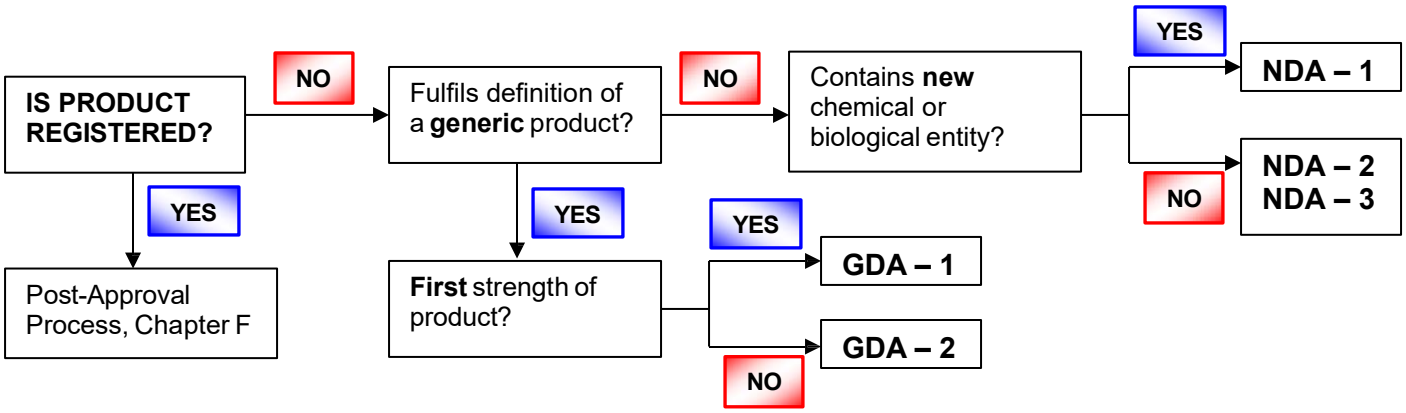

Figure 2 Schematic Diagram of Application Routes for Drug Registration

5.3 Evaluation Routes

There are four types of evaluation routes for registering a new therapeutic product:

Full route: Applies to any new product[4] that has not been approved by any drug regulatory agency at the time of application submission to HSA.

Abridged route: Applies to any new[6] or generic product that has been evaluated and approved by at least one drug regulatory agency.

Verification route: Applies to any new or generic product that has been evaluated and approved by HSA's reference drug regulatory agencies, which are EMA[5], FDA, Health Canada, MHRA[6], Swissmedic and TGA.

Verification-CECA route:

Applies to any generic product manufactured in India which has been evaluated and approved by HSA's reference drug regulatory agencies, which include EMA[4], FDA, Health Canada, MHRA[5], Swissmedic and TGA.

Applicants should refer to Chapters C, D and E for detailed information about the selection of appropriate evaluation routes for NDA, GDA and Biosimilar product applications, respectively.

5.4 Pre-Submission Consultation Mechanisms

There is a range of mechanism that enable companies to self-help, which includes the use of guidelines, flow charts, frequently asked questions (FAQ) and self-help tools as alternatives to pre-submission meeting.

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[4] For biosimilar products, refer to the Chapter E on biosimilars
[5] For products approved via the Centralised Procedure
[6] For products approved via the national procedure or where MHRA acted as the RMS for the MRP or DCP on or prior to 31 January 2020

For more information on TPB's pre-submission consultation mechanisms, refer to the website: Pre-submission Consultation Mechanisms

5.4.1 Pre-Submission Notification

A pre-submission meeting is not compulsory for making an application to HSA. Nonetheless, the applicant is required to notify HSA at least two months prior to the intended submission date for applications submitted via the full evaluation route. The notification should include information on the product name (if available), active ingredient(s), summaries of the quality, non-clinical and clinical data (e.g. Overviews), planned submissions in other countries, and planned date of submission to HSA.

5.4.2 Pre-Submission Meeting

An applicant may request for a pre-submission meeting to seek HSA's advice on specific issues relating to the data package for supporting an application submission, if the issue could not be addressed by the self-help mechanisms provided at Pre-submission Consultation Mechanisms.

A pre-submission meeting is reserved for scientific discussion and does not provide for screening or checking of the submission dossier for the applicant. To ensure the correctness of the application type and the completeness of the dossier, please refer to the documentary requirements sections in this guidance.

Before making a request for pre-submission meeting, the applicant must ensure that at least one of the criteria below is met:

i. The product is a novel therapeutic product developed using new or emerging technologies or methodologies; or
ii. The product is developed in the absence of, or deviates from local or international regulatory guidance.

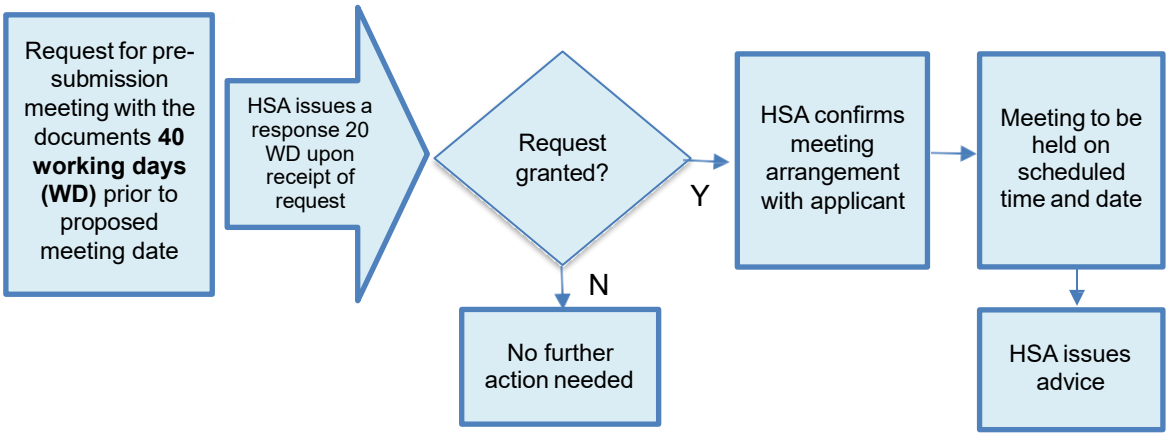
The following required documents must be submitted together with the request for pre-submission meeting:

1. Proposed agenda for the meeting;
2. Summary information which may include CMC/ non-clinical/ clinical information of the product and proposed application; and
3. Specific scientific issues that require advice.

HSA may reject the pre-submission meeting request if:

- The product does not fulfil the pre-submission meeting criteria above; or
- The request is not accompanied by the required documents; or
- The issues can be addressed via email instead of having a pre-submission meeting.

Overview of the Process



Advice given at pre-submission meetings will be based on information current at the time of the consultation and have no bearing on the eventual outcome of the application concerned.

6 APPLICATION SUBMISSION

The submission of an application comprises two key steps – (i) online submission of the application form via PRISM and (ii) submission of the technical dossier.

6.1 PRISM Application Form

All applications must be made online via PRISM. Please refer to Appendix 17 *Guideline on PRISM submission* for further details.

6.2 Application Dossier

The technical dossier accompanying the application should be submitted within 2 working days of the PRISM application submission to prevent delays in the processing of the application. **The date of receipt of the actual technical dossier by HSA will be taken as the submission date where the processing time starts.**

Application dossiers should be organised in a CTD format. The CTD provides a common format for the preparation of a well-structured submission dossier. It uses a modular framework described in ICH Topic M4 and ASEAN guidelines on the *Common*

Technical Document for Registration of Pharmaceuticals for Human use: Organisation of the Dossier. This guidance document should be read in conjunction with the current version of the ICH CTD and the ACTD guidance documents.

Either the ICH CTD or the ACTD format is acceptable for making a submission to HSA. Table 1 summarises the organisation of the respective format:

Table 1 Format of the ICH CTD and ACTD

Documents	**Location in**	
	ICH CTD	**ACTD**
Administrative Documents and Product Information	Module 1	Part I
Common Technical Document Overview and Summaries	Module 2	*Incorporated in Parts II, III and IV*
Quality documents	Module 3	Part II
Non-clinical documents	Module 4	Part III
Clinical documents	Module 5	Part IV

Application checklists for both ICH CTD and ACTD dossiers are provided in Appendix 2A and 3A, respectively, to guide applicants on the submission requirements and to ensure completeness of the dossier. **Each application must be accompanied by the required application checklist duly completed by the applicant and attached in PRISM**.

Applicants should note that the CTD format cannot be changed once the application is submitted. Any subsequent variation applications for the product should follow the same format.

6.2.1 Submission Requirements

The complete application dossier – i.e. Modules 1 to 5 of the ICH CTD or Parts I to IV of the ACTD – must be submitted in an electronic format.

Applicants must organise the dossier (i.e. folders and subfolders) according to the CTD format and to include bookmarks in all documents to facilitate the retrieval of documents.

PDF files submitted must be in a format that is searchable, flattened (without layers) and without encryption. Files that are layered, password-protected, or have security restrictions will not be accepted.

Files containing the below scripts will not be accepted due to cybersecurity reasons:

S/N	Script Type	Extension
1	VB Script	*.vbs, *.vbe, *.vb
2	VBA	*.vba
3	JS Script	*.js, *.jse
4	Windows Script File	*.wsf, *.ws
5	Windows Script Component	*.wsc, *.wsh
6	Powershell	*.ps1, *.ps1xml, *.ps2, *.ps2xml, *.psc1, *.psc2
7	Monad (legacy Powershell)	*.msh, *.msh1, *.msh2, *.mshxml, *.msh1xml, *.msh2xml
8	Windows Shell	*.com
9	Batch	*.bat, *.cmd
10	Python	*.py, *.pyo, *.pyc, *.pyw, *.pys
11	Perl	*.pl, *.pls, *.p
12	Shortcut	*.lnk

As a general guide, folder or file names should not be named with "xxx**.P** (e.g. "3.2.P").

All documents required under Module 1/Part I must be submitted in softcopy in PRISM. Colour scanned copy of the original documents should be submitted and original hardcopy of documents are not required. However, HSA reserves the rights to request for the submission of the original or certified true copy of the submitted document if there is any doubt that the submitted scanned document is not an accurate reflection of the original document.

Please refer to section 6.2.3 for more information on certifying non-original documents if the original documents cannot be provided.

The dossier for **Modules 2 to 5/Parts II to IV**, may be submitted via the following

methods:

1. Upload into PRISM section 7 (Supporting Attachments)
2. Submit in a CD/DVD
3. Submit via a cloud-based file exchange software (EasiShare)

NOTE: Submission of dossier using other methods not listed above will not be accepted.

Submitting via a CD/DVD

The CD/DVD should be properly labelled or accompanied by a letter with the following information:

- PRISM application number;
- PRISM submission date;
- Product name;
- Application type;
- Contents of the CD/DVD (e.g. Module 2, 3 and 5); and
- Applicant's email address.

Upon receipt of the CD/DVD, HSA will issue an acknowledgement email to the applicant via the email address provided with the CD/DVD submission.

Applicants must ensure the access to the content of CD/DVD. For protected files, password(s) must be provided as appropriate.

Upon acceptance of the application for evaluation, applicants will be notified if additional copies of clinical documents (in CD/DVD) will be required.

Submitting via cloud-based file exchange software (EasiShare)

Refer to the guidance "Key Points to Note when Preparing Documents for Therapeutic Product Application Dossier Submission via EasiShare" and "EasiShare FAQ" available

at:

https://www.hsa.gov.sg/therapeutic-products/register/overview/application-dossier

6.2.2 Language and Translation

All documents submitted in support of an application to HSA must be in English.

For documents in their original language which is not English, a certified translation or a verified translation may be acceptable.

Translation type	Type of Documents	Requirements

Certified Translation	▪ **Official certificates** issued by the drug regulatory agency of a country ▪ **Proof of approval** issued by the drug regulatory agency of a country	**Notarisation & Authentication** (a) Notarisation ▪ These documents must be **notarised** by a notary public in country where document is issued. ▪ Details of particulars to be included by notary: (i) The name of the notary; (ii) A statement that the notary is duly admitted to practice in the place of issue of the certificate; (iii) The names of the signatories and the capacity in which they have executed the document, whether on their own behalf or in an official or representative capacity; (iv) A statement authenticating the signatures of the parties and, where appropriate, indicating that evidence has been produced to the notary proving the capacity in which they have executed the document; (v) The place and date of issue of the notarial certificate; and (vi) The signature and seal of the notary. (b) Authentication ▪ These documents must be **authenticated** (i.e. the origin of the document is attested to) by one of the following government bodies:

		(i) The Ministry of Foreign Affairs of the country in which the document was issued; or (ii) The Singapore Embassy/Consulate in the country where the document was issued. Applicants are advised to consult the Singapore Embassy/Consulate in the country where the document originated regarding the local requirements for document legalisation, as these may deviate from the process as outlined in the preceding paragraph.
Verified Translation	▪ **Technical documents** (e.g. package insert, submission dataset)	**Verification Document** ▪ A verification document must be provided by the **translator** of the document into the English language. ▪ The verification document must state that the **translation into English is accurate**. ▪ Details of particulars to be included in verification document: (i) the name of translator; (ii) a statement that he/she is well versed in English and the relevant foreign language; and (iii) a reference to the document being translated. Refer to the sample verification document for translator enclosed in Appendix 4.

With Singapore acceding to the Apostille Convention on 16 September 2021, for certified translated document issued by a country which acceded to the Apostille

Convention, an apostille certificate can be submitted *in lieu* of a notarised/authenticated certified translation.

6.2.3 Certifying Non-Original Documents

If the softcopy official document (e.g. CPP, GMP certificate) submitted to HSA in PRISM is not a scan of the original document, the document must be certified prior to submission. A certified true copy certifies that the photocopy presented is a true and accurate copy of the original document. Acceptable certification of documents to support therapeutic product applications to HSA can be done by the Company Director or Company Secretary as registered with ACRA or above, or by an independent authority such as a lawyer, notary public, Commissioner for Oaths/Declarations/Affidavits, Justice of Peace, the original issuer of the document or Embassy/Consulate. A notarised and authenticated copy is the same as a certified true copy.

A certified true copy of an approval letter requires certification by the drug regulatory agency that issued the approval letter, a notary public or the Singapore Embassy/Consulate in the country where the approval letter was issued. Certification of an approval letter is not required if the approval letter is available on the drug regulatory agency's website. In this instance, applicants can provide the internet address (URL) for validation by HSA.

7 APPLICATION SCREENING

Following a submission made via PRISM and the receipt of the application dossier by HSA, the application will be screened to ensure the correctness of the application type and the completeness of the dossier. **The date of receipt of the application dossier (i.e. the technical dossier [e.g. in a CD/DVD] including the application checklist) will be taken as the submission date and the start of the screening timeline.**

During screening, if an application is identified to be more appropriately submitted

under a different application type, the applicant will be informed of this change and the necessary actions to effect this change via an Input Request. More information on the change in application type is described in section 12.2.1.

For applications submitted without the following documents, the applicant will be requested to withdraw the application as screening cannot proceed:

- Module 3/Part 2 Drug Substance dossier*
- Module 3/Part 2 Drug Product dossier*
- Module 4/Part 3 Non-Clinical dossier (if applicable)*
- Module 5/Part 4 Clinical dossier*
- DMF and its accompanying Letter of Access (if applicable)#
- Assessment report from Reference Agencies (for verification route)
- Duly completed Application Checklist in MS EXCEL format
- Duly completed Patent Declaration Form

** Dossier must be in either ICH CTD or ACTD format*

 # Please refer to Appendix 11 for information on the procedures and documentary requirements in support of a DMF submission

Applicants should ensure that the PRISM application form is duly and accurately completed, and the dossier is compiled according to the required format before submitting the application to HSA.

If deficiencies are identified in an application dossier, a screening query stating the deficiencies will be issued via Input Request to the applicant. The stop-clock starts when an Input Request is sent and ends upon receipt of the applicant's response. **The total number of Input Requests sent during screening is capped at two**. Applicants will be given 20 working days to respond to each Input Request, starting from the date the Input Request is sent.

The application will only be accepted when all deficiencies have been adequately addressed, and HSA is satisfied that the dossier is complete for evaluation. An

acceptance notice will then be issued via PRISM and the date of acceptance of the application will be taken as the start of the evaluation timeline. For full and abridged applications, applicants may be required to submit additional copies of the dossier in CD/DVD format after acceptance.

If the applicant fails to address the deficiencies within two rounds of screening Input Requests, the application will not be accepted for evaluation. An Input Request will be issued to the applicant to withdraw the application. Any further responses to deficiencies will not be accepted. If the application is subsequently re-submitted, it will be processed as a new application.

NOTE: The screening process only checks for the completeness of the application dossier for evaluation. The acceptance of the dossier for evaluation does not denote the adequacy of the data for regulatory approval.

8 APPLICATION EVALUATION

Once the application is accepted, the evaluation stage begins. Evaluation queries may be issued via Input Request to the applicant if clarification or additional information is required.

The stop-clock starts when an Input Request is sent and ends upon receipt of the applicant's response.

Applicants are reminded that the submission of additional supporting data not requested by HSA following the acceptance of the application will not be considered, unless prior arrangement with HSA is made for the submission concerned. During the evaluation process, HSA may assess that the application is more suitably evaluated via an alternative route, in which case the application will be re-routed to the appropriate route. Any re-routing of the application will be discussed with the applicant.

HSA may engage external evaluators, experts and advisory committees in the evaluation process, when necessary. These experts include scientists and clinicians from both local and overseas institutions. All external evaluators and experts are bound

by agreement to protect the information made available to them. The identity of the external evaluators is kept confidential.

8.1 Evaluation Stages

The progress status of the evaluation is available for certain application types and evaluation routes. Table 2 describes the applicable product applications and the stages of the evaluation:

Table 2 Product Applications Applicable for Notification of Stages During Evaluation

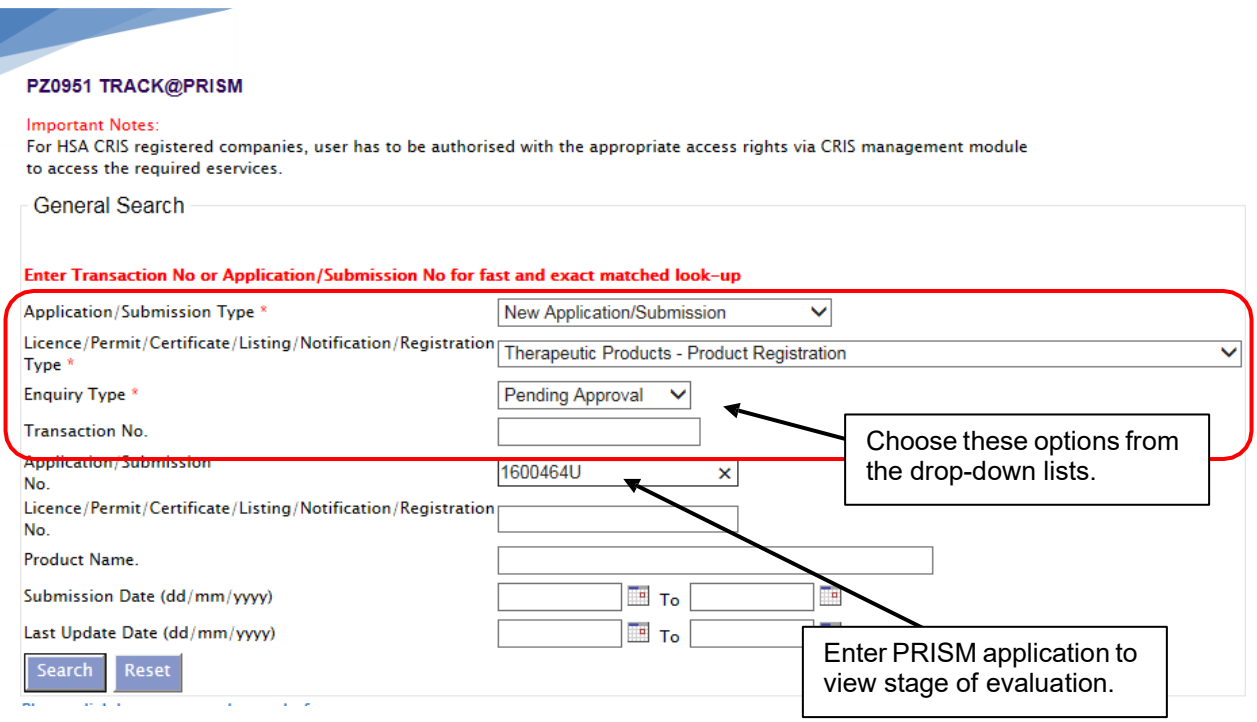
Stages of Notification to Applicant		**1st Stage**	**2nd Stage**	**3rd Stage**	**4th Stage**
		Evaluation Status			
Application Type	**Evaluation Route**	Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
NDA-1 NDA-2 NDA-3	Full or Abridged		Application		Evaluation is completed for the

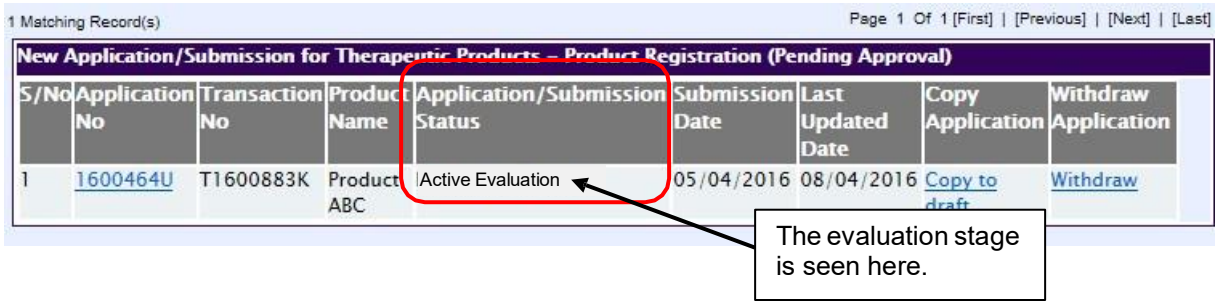
GDA-1 GDA-2	Abridged, Verification, or Verification-CECA	Application is accepted for evaluation and has entered the evaluation queue. This marks the start of the evaluation timeline.	is under active evaluation. Applicants can expect to receive the first set of evaluation queries (if any) from us towards the end of this stage.*	Application is approximately midway through the evaluation. Applicants are expected to submit the response to evaluation queries.	application. Application is now undergoing the regulatory decision phase, after which a regulatory decision# will be issued. Applicants can still expect further queries from HSA during this stage.

* For applications without any evaluation queries, recommended changes to product labels will be communicated to the applicant during the regulatory decision phase.

#The issuance of a regulatory decision marks the end of the evaluation timeline for a product application.

Applicants may view the evaluation stage via Track@PRISM. The following screenshots illustrate the change in stages of a pending application:





Applicants are also notified via system-generated emails whenever an evaluation stage change occurs.

After the application is accepted for evaluation, applicants can expect to receive the first evaluation Input Request by:

Type of Applications	Evaluation Route	No. of working days
NDA	Full	160
NDA	Abridged	120
GDA	Abridged	150

Note: excluding any stop-clock time between acceptance and issuance of first evaluation Input Request.

9 REGULATORY DECISION

A regulatory decision is made following the conclusion of the benefit-risk assessment by HSA based on the data submitted in support of the application. Applicants will be notified of one of the following outcomes:

- Approval – the application satisfies the registration requirements for quality, safety and efficacy;
- Approvable – when the application can be approved subject to adequate response to minor deficiencies;
- Non-approvable – when the application has major deficiencies; or
- Rejection – when the response provided by the applicant fails to address the major deficiencies specified in HSA's non-approvable decision.

'*Approval*' and '*rejection*' are final decisions issued by HSA.

For an '*approvable*' application, the applicant will be informed of the conditions for approval and is required to fulfil these conditions within a stipulated timeframe prior to the grant of a final approval.

For a '*non-approvable*' application, the applicant will be informed of the deficiencies leading to the non-approvable decision. If the applicant wishes to address the specified deficiencies, the response should be based on the original data set submitted to HSA and furnished within the stipulated timeframe. New data not previously reviewed by HSA during the evaluation of the application concerned will not be accepted.

An application will be considered withdrawn if the applicant fails to reply within the stipulated timeframe subsequent to an '*approvable*' or a '*non-approvable*' decision. Once the application is withdrawn, it is considered closed and the applicant will be required to make a new application if he wishes to pursue the regulatory approval for

the product concerned.

Upon an '*approval*' regulatory decision, the product will be added to the Register of Therapeutic Products.

HSA may register the product subject to post-approval commitments. In such circumstances, the applicant will be required to furnish a letter of commitment stating the undertakings concerned.

Applicants must take note of the registration conditions and the post-approval commitments specified in the registration. The registration conditions can be viewed at Enquire@PRISM.

For submission of documents to fulfil registration conditions, please use this form (Submission of Documents to Fulfil Therapeutic Product Registration Conditions - https://go.gov.sg/fulfil-tp-reg-conditions).

10 POST-APPROVAL CHANGES

Upon the registration of a product, product registrants are responsible for ensuring the product's quality, efficacy and safety through its life cycle.

HSA must be notified of any changes to the product's quality, efficacy and safety as per Chapter F of this guidance.

11 TARGET PROCESSING TIMELINES

Please refer to Appendix 5 for information on target processing timelines for the different application types and evaluation routes.

12 FEES

As the fees may be subject to revision from time to time, applicants are advised to visit the HSA website for updated information on fees .

Payment can be made via GIRO or other electronic payment modes such as eNets or eCredit card.

NOTE: Applicants are strongly encouraged to apply for eGIRO for the convenience of payment (apply eGIRO).

Regardless of payment mode selection, the collection of both screening and evaluation fee for applications submitted via the full evaluation route occurs upon issuance of the screening outcome.

12.1 Screening Fee

A screening fee is payable at the time of online submission via PRISM and is non-refundable once the application is submitted via PRISM.

For payment via GIRO, the screening fee will be debited upon the successful submission of an online application.

For payment via other electronic payment modes (i.e. eNETs or eCredit card), the screening fee must be paid before the application is considered successfully submitted online.

12.2 Evaluation Fee

An evaluation fee is payable upon the acceptance of the dossier for evaluation and is non-refundable once the application is accepted.

For payments via GIRO, the evaluation fee will be debited upon the acceptance of the application.

For payments via other electronic payment modes (i.e. eNETs or eCredit card), the evaluation fee will be collected together with the screening fee. In the event that the application is not accepted for evaluation, the fee collected will be refunded to the

applicant's mode of payment.

Applicants may opt for the progressive payment scheme for payment of evaluation fee. This is an opt-in scheme eligible for applicants who make payment via GIRO and is only applicable to the application types listed in Table 3:

Table 3 Product Applications Applicable for Progressive Payment Scheme

Percentage of Evaluation Fee Payable at Each Stage					
Application Type	**Evaluation Route**	**Evaluation Status**			
		Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
NDA-1 NDA-2 NDA-3	Full or Abridged	30%	40%	20%	10%
GDA-1 GDA-2	Abridged, Verification or Verification -CECA				

Once the application is submitted, the selected payment scheme (full or progressive) cannot be amended. Applicants who wish to change their selected payment scheme will have to withdraw and re-submit the application(s); and any upfront payment made (e.g. screening fee) is non-refundable.

For applications under the progressive payment scheme, in the event that the application is withdrawn during the evaluation stage, any fees that had been charged, but not debited from the GIRO account would remain payable. Any paid fee is non-refundable.

12.2.1 Changes to Application Types and Re-routing of Evaluation During Screening

If an application type or evaluation route is incorrectly selected, applicants will be informed via an Input Request. Such changes may result in a different evaluation fee upon acceptance of the application.

In the situation where the applicant decides not to pursue the application due to the changes, the screening fee is not refundable.

For applications which require withdrawal and resubmission, the screening fee is not refundable.

12.2.1.1 Change of Sub-Type within the Same Application Type

This refers to a change in the sub-type of the selected application type (e.g. from NDA-1 to NDA-2, NDA-2 to NDA-3, or GDA-1 to GDA-2).

The applicant will be informed of the change via an Input Request. However, applicants should not amend the application type field in the PRISM application form. The change will be effected by HSA at the point of acceptance of the application.

In the situation where the applicant decides not to pursue the application due to the said change, the applicant must withdraw the application prior to acceptance to avoid the evaluation fee being charged.

12.2.1.2 Change of Application between Different Application Types

This refers to a change in the application type between GDA to NDA or *vice versa*.

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

12.2.1.3 Change of Evaluation Route

This refers to a change in evaluation route (e.g. Full to Abridged, Verification to Abridged, Abridged to Verification, etc.).

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

CHAPTER C NEW DRUG APPLICATION SUBMISSION

This chapter applies to new drug applications for products containing new chemical and biological entities. Applicants are advised to refer to Chapter E for new drug applications for biosimilar products.

13 APPLICATION TYPES

NDA New Drug Application

NDA-1: For the first strength of a product containing a new[7] chemical or biological entity.

NDA-2: (a) For the first strength of a product

(i) containing a new combination of registered chemical or biological entities;

(ii) containing registered chemical or biological entity(ies) in a new dosage form (e.g. tablets, capsules, injectables), new presentation (e.g. single-dose vials, multi-dose vials, pre-filled syringe, starter packs), or new formulation (e.g. preservative-free);

(iii) containing registered chemical or biological entity(ies) for use by a new route of administration; or

(iv) containing registered chemical or biological entity(ies) for new indication(s), dosage recommendation(s) and/or patient population(s).

(b) For products that do not fall under the descriptions for NDA-1, NDA-3 or GDA.

NDA-3: For subsequent strength(s) of a product that has been registered or has been submitted as an NDA-1 or NDA-2. The product name, active ingredient, dosage form, presentation, indication, dosing regimen and patient population should be the same as that for the NDA-1 or NDA-2.

[7] i.e. not a chemical or biological entity that is either registered or being concurrently submitted for registration in Singapore. Currently registered therapeutic products can be found in the Register of Therapeutic Products at www.hsa.gov.sg.

14 EVALUATION ROUTES

There are three evaluation routes for an NDA – full, abridged and verification evaluation routes. The eligibility criteria are different for each evaluation route. Applicants should be familiar with the criteria for each evaluation route because each route has different documentary requirements.

Figure 3 is a schematic diagram illustrating the evaluation routes for NDAs:

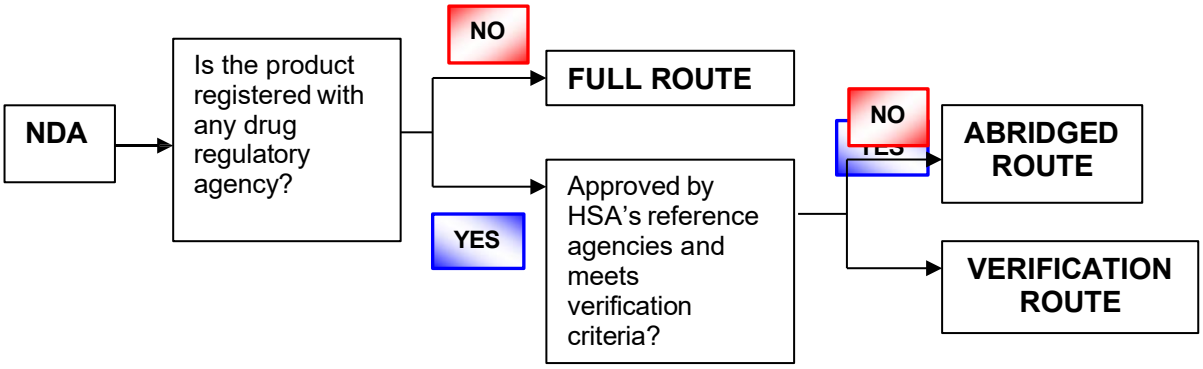


Figure 3 Schematic Diagram of Evaluation Routes for NDAs

14.1 Full Evaluation Route

Full evaluation applies to a product that has not been approved by any drug regulatory agency at the time of submission.

For a submission under the full evaluation route, the applicant is required to notify HSA at least two months prior to the intended submission date of the application dossier. The notification should include information on the product name (if available), active ingredient(s), summaries of the quality, non-clinical and clinical data (e.g. Module 2.4 Non-clinical Overview, Module 2.5 Clinical Overview), planned submissions in other

countries, and the planned date of submission to HSA.

14.2 Abridged Evaluation Route

Abridged evaluation applies to a product that has been approved by at least one competent drug regulatory agency at the time of submission.

14.2.1 Priority Review

For NDAs submitted via the abridged evaluation route, the applicant may request for priority review for a life-saving drug if there are unmet medical needs. The following are the criteria that will be considered for granting a priority review:

(a) The drug is intended for the treatment of a serious life-threatening condition and demonstrates the potential to address local unmet medical needs, as defined by:
   (i) the absence of a treatment option; or
   (ii) the lack of safe and effective alternative treatments, such that the drug would be a significant improvement compared to available marketed products, as demonstrated by
      (A) evidence of increased effectiveness in treatment, prevention, or diagnosis;
      or
      (B) elimination or a substantial reduction of a treatment-limiting drug reaction.

(b) Disease conditions that are of local public health concern will be given primary consideration for priority review. Currently these include:
   (i) cancer; and
   (ii) infectious diseases: dengue, tuberculosis, hepatitis and malaria.

The request for priority review should be made at the point of the application submission and accompanied by justifications (attached in PRISM; see section 15.1 – Introduction (CTD/PRISM section 1.3)) for requesting for a priority review and how the product is expected to benefit patients, as substantiated by the following evidence:

- The seriousness of the disease condition, local and worldwide mortality rates, anticipated morbidity and debilitation as a consequence of the disease;
- Local epidemiology data and disease burden;
- The unmet needs, current available treatment options and standard therapies, and the inadequacy of current therapies;
- The extent to which the product is expected to have a major impact on medical practice, its major benefit, and how it addresses the unmet needs; and
- Clinical evidence supporting the claims of significant improvement compared to available treatments.

HSA reserves the right to deny a request for priority review if it is deemed appropriate. The decision for the granting of priority review would be conveyed to the applicant at the point of acceptance of the application for evaluation.

14.3 Verification Evaluation Route

Therapeutic products with similar indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use that have been approved by at least two of HSA's reference drug regulatory agencies may be eligible for submission via the verification evaluation route. HSA's reference drug regulatory agencies are:

- EMA via the Centralised Procedure
- FDA
- Health Canada
- MHRA via
  - the national procedure, or
  - as the RMS via the MRP or DCP on or prior to 31 January 2020
- Swissmedic
- TGA

However, approval by these reference drug regulatory agencies does not oblige HSA to approve the application. HSA may also re-categorise applications to other

evaluation routes if the applications did not meet the eligibility criteria and/or submission requirements.

The applicant must confirm one of the reference drug regulatory agencies as the primary reference agency. The chosen primary reference agency is defined as the reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted.

The pre-requisite requirements for the verification route include:

- The product has received full marketing approval by the reference agencies following a complete independent scientific assessment (i.e. the approval is not granted on the basis of less comprehensive data than normally would require or subject to post-approval conditions that require submission of additional data to confirm the product's benefit-risk profile);
- The application must be submitted to HSA within three years from the date of approval by the chosen primary reference agency;
- A declaration letter issued by the product owner/applicant must be provided stating that all quality aspects including the composition, manufacturing and quality standards of the drug product are identical to those approved by the chosen primary reference agency. However, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements;
- If a DMF is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen primary reference agency;
- The product does not need an independent assessment by HSA to contextualise the benefit-risk profile due to local disease epidemiology, medical practice and/or public health considerations. Examples of products that may require such contextualised assessment are anti-infectives, vaccines, etc.; and
- The product and its intended use – i.e. indication(s), dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, or approved via appeal process or are not pending deferral by a drug regulatory agency for safety and/or efficacy reasons.

The proposed indication(s), dosing regimen(s), patient group(s) and/or direction(s) for use should be the most stringent among those approved by the reference drug regulatory agencies. In the event that the chosen primary reference agency does not bear the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use, the clinical assessment report from the reference drug regulatory agency that does meet these requirements should be submitted. Reports from the public domain are acceptable. The proposed PI/PIL should be identical to that

bearing the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use (with the exception of country-specific information).

14.3.1 NDA-3 Applications

For the NDA-3 application type, the verification evaluation route may be applied to the registration of subsequent strengths of a currently-registered product in Singapore. To qualify for the verification evaluation route for an NDA-3 application:

- if the product has been evaluated and approved by at least one of HSA's reference drug regulatory agencies, then the NDA-3 must be submitted within two years from the date of approval by that reference drug regulatory agency; or
- if the product has been evaluated and approved by at least two of HSA's reference drug regulatory agencies, then the NDA-3 must be submitted within three years from the date of approval by the chosen primary reference agency.

All other eligibility criteria for the verification evaluation route as stated in section 14.3 above will apply to NDA-3 applications except for the following:

- The proposed indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use must be identical to the corresponding approved NDA-1 and/or NDA-2 product(s); and
- The proposed PI/PIL should also be consistent with that currently approved for the corresponding NDA-1 and/or NDA-2 product(s).

15 DOCUMENTARY REQUIREMENTS

Refer to Documentary Requirements in section 6.2 for submission requirements.

Table 4 outlines the CTD Modules/Parts required for NDAs submitted under each evaluation route:

Table 4 Dossier Submission Requirements for NDAs

Documents	Location in		Module/Part required for		
	ICH CTD	ACTD	Full NDA	Abridged NDA	Verification NDA
Administrative Documents	Module 1	Part I	Yes	Yes	Yes
Common Technical Document Overview and Summaries	Module 2	*Incorporated in Parts II, III and IV*	Yes	Yes	Yes
Quality documents	Module 3	Part II	Yes	Yes	Yes
Non-clinical documents	Module 4	Part III	Yes	ICH: No[#] ACTD: Overview only	ICH: No[#] ACTD: Overview only
Clinical documents	Module 5	Part IV	Yes	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group

[#]Non-clinical overview included in Module 2 of the ICH CTD.

15.1 Administrative Documents

The administrative documents relate to Module 1 of the ICH CTD or Part I of the ACTD and are applicable to all evaluation routes for NDAs. The following sections are to be submitted:

a) *Cover Letter (to attach under CTD/PRISM section 1.2 - Introduction)*

To include a cover letter stating the product name, and the number of CD/DVDs submitted in the application dossier.

Applicants should provide a concise and precise summary of the application in the Cover Letter.

Applicants should ensure that the application dossier is complete. The omission of any documents within the dossier or any deviation from the guidelines must be appropriately justified.

Requests for priority review should be stated in the Cover Letter, with the justification document appended in this section.

b) *Comprehensive Table of Contents (CTD/PRISM section 1.1)*

The comprehensive table of contents is a complete list of all documents provided in the application dossier listed by Module/Part. The location of each document should be identified by the Module/Part number.

NOTE: Each application must be accompanied by the required application checklist found in Appendix 2A or Appendix 3A, duly completed by the applicant and attached in PRISM.

c) *Labelling, Package Insert and Patient Information Leaflet (CTD/PRISM section 1.4)*

All proposed labels are to be submitted for registration in Singapore. Applicants are required to provide the artwork/drafts of the proposed Singapore product labels, PI and/or PIL for the product basedon the forensic classification of the product to be

registered, as described in Table 5:

Table 5 Requirement for PI or PIL According to Forensic Classification in Singapore

	Forensic Classification in Singapore		
	POM	**P**	**GSL**
Package Insert (PI), also known as prescribing information, SPC, or product monograph	**Required**	*Optional*	*Optional*
Patient Information Leaflet (PIL), also known as consumer medicine information (CMI)	*Optional, unless warranted*	**Required**	**Required**

Each product application must be accompanied by a proposed PI and/or PIL. When a product has multiple manufacturing sites involved in its manufacture for Singapore supply, all site information must be included in a single PI and/or PIL.

For products with different strengths or dosage forms:

- Applicants are encouraged to submit one common PI/PIL that covers all strengths or dosage forms
- If separate PI/PILs are to be registered for different strengths or dosage forms:
  - The content must remain consistent across all PI/PILs
  - Variations are permitted only for strength/dosage form-specific information

All artwork and drafts must be clearly legible in typed / printed format. The draft artwork of the outer carton and inner/blister labels should be consistent with the format, design and colour that are to be printed. Separate labels must be submitted for each different pack size of the drug product.

The product labels, PI and/or PIL must be in English. If non-English text is included in the labelling, applicants must provide an official statement to declare that the non-

English text is complete, accurate and unbiased information and is consistent with the English text.

Appendix 7 contains specific details on the product labelling requirements for Singapore.

d) Approved SPC/PI/PIL (CTD/PRISM section 1.5)

In this section, the applicant should submit the following:

i. The approved SPC, PI and/or PIL from the drug regulatory agency that issued the proof of approval; and
ii. the approved SPC, PI and/or PIL from all of HSA's reference drug regulatory agencies, where applicable.

The country from which the submitted SPC, PI and/or PIL originates should be appropriately indicated (e.g. in the document file name).

e) Assessment Report from Reference Agencies (CTD/PRISM section 1.6) This section refers only to applications submitted under the verification evaluation route. Assessment reports and supporting documents issued by the primary reference agency and inserted into this section must be unredacted and unedited. Applicants should refer to section 15.6.3 for specific details on the required documents.

f) Description of Batch Numbering System (CTD/PRISM section 1.7)

Detailed information on the system of assigning unique codes to different production batches of the product should be provided to allow for batch identification. Where applicable, examples of the batch numbering system should be included to illustrate how the batch number enables identification.

g) Proof of Approval (CTD/PRISM sections 1.8, 1.9)

Proof of approval is not required for NDAs undergoing a full evaluation.

For an abridged evaluation of an NDA, proof of approval from a competent drug regulatory agency is required.

A competent drug regulatory agency refers to a national regulatory authority participating in the World Health Organization's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and listed as such on the World Health Organization's website.

Proof of approval must come in the form of:

- a CPP that is valid at the time of submission; or
- an official approval letter that certifies that the product is currently registered in the country at the point of submission to HSA

NOTE: A search result from a competent drug regulatory agency official website stating that the product is currently approved by that drug regulatory agency is acceptable. This website information must be published in English by the drug regulatory agency, and verifiable by HSA.

Applicants must submit the approved SPC, PI and/or PIL along with the proof of approval from the drug regulatory agency.
For a verification evaluation of an NDA, proof of approval from at least two (or at least one or two for NDA-3, depending on the eligibility criteria stated in section 14.3.1) of HSA's reference drug regulatory agencies, including the chosen primary reference agency, is required.

If the SPC is in a non-English language, applicants should refer to section 6.2.2 for more information on acceptable translations.

Note that all aspects of the product's quality and intended direction(s) for use in Singapore should be the same as those approved by the drug regulatory agency that issued the proof of approval.

If information such as the product formula, manufacturing sites, etc. are present in the CPP, the information should be consistent with that proposed for the Singapore market.

Electronic CPPs issued by the regulatory authority are acceptable.

NOTE: CPPs that indicate that the product is not licensed in the exporting country (including scenario where the product is licensed for "solely for export only") are not acceptable proof of approval.

Approval letters should either be an original copy or a certified true copy and in English. Applicants should refer to sections 6.2.2 *Language and Translation* and 6.2.3 *Certifying Non-Original Documents* for more details.

HSA reserves the right to request for an original hardcopy of the CPP, if deemed appropriate.

If the brand name (trade name) of the product registered in the country which issued the proof of approval is different from that proposed in Singapore, the applicant is required to submit a declaration letter from the product owner to declare that both products marketed under the different brand names are identical in all aspects of quality, safety and efficacy except for the brand name.

h) Authorisation Letters (CTD/PRISM section 1.10)

All submitted authorisation letters should be on the authorising company's (i.e. product owner's) letterhead, dated and signed by the designated authorised person in the company.

If the product owner is not the local applicant, manufacturer and/or batch releaser; or the product owner's address is different from that of the local applicant, manufacturer and/or batch releaser, then the following authorisation letter(s) must be submitted:

i. *from Product Owner to the Applicant (Company)* (1.10.1) – this letter authorises the

local applicant to apply for and be the product registrant for a specific therapeutic product (product name to be stated as in PRISM) and be responsible for all matters pertaining to the registration of this product in Singapore.

ii. *from Product Owner to Manufacturer* (1.10.2) – this letter authorises the specified manufacturer to produce, pack and/or label the drug product intended for Singapore. If there are multiple drug product manufacturers, then the applicant may opt to submit one authorisation letter which clearly states all of the manufacturers (names and addresses) and their responsibilities relating to the drug product (such as the manufacturing operation of each manufacturer in relation to the product being submitted). For biologic drug products, an additional authorisation letter from the product owner to the drug substance manufacturer is required.

iii. *from Product Owner to Batch Releaser* (1.10.3) – this letter authorises the specified company to batch release the drug product. If there are multiple sites responsible for the batch release of the product, then the applicant may opt to submit one authorisation letter which clearly states all of the batch releasers (names and addresses) and their responsibilities.

The applicant may also issue an authorisation letter to authorise the specified secondary packager located in Singapore to pack and/or label the drug product intended for Singapore.

Applicants are to ensure that all names and addresses in the authorisation letters are consistent with the information provided in PRISM and the dossier. For manufacturers and batch releasers, the actual site address of the named company should be stated in the letter(s) – i.e. do not state the office address. Any discrepancy found will delay the registration process.

All authorisation letters should also state specific product details, including the product name, dosage form and strength as stated in the PRISM application form.

Applicants also have the option to combine the authorisation letters as stated above into one document, provided that all names, addresses and responsibilities are clearly

stated.

i) GMP Certification/Proof of GMP Compliance (CTD/PRISM section 1.11)

(A) Local Manufacturers

i. Drug substance manufacturer

A valid Active Ingredient Manufacturer's Licence (AIML) or a Therapeutic Product Manufacturer's Licence (TPML) if DS manufacturing is covered under the TPML is required at the point of application submission.

ii. Finished product manufacturer

A valid TPML is required at the point of product application submission and the TPML number must be stated in the product application. No additional documentary proof of GMP compliance needed.

(B) Overseas Manufacturers and Batch Releasers

Documentary evidence must be provided to certify that the manufacturer(s) complies with current applicable GMP standards.

The proof of GMP compliance must be submitted for all the following sites mentioned in the product submission:

i. Drug substance manufacturer

An applicant may submit any of the following types of GMP compliance evidence to support the application:

- Valid PIC/S GMP certificate with the drug substance (DS) of interest stated. If the DS of interest is not specified on the GMP certificate, a Written Confirmation[8] for the DS of interest from the PIC/S authority which issued the GMP certificate is to be supplemented;

8 Written Confirmation using the European Union (EU) template or any other official document from the PIC/S authority is acceptable.

- GMP inspection report, with the DS of interest included in the scope, together with the close-out letter (where applicable) for PIC/S authorities which do not issue GMP certificates;
- Valid Active Pharmaceutical Ingredient (API) Registration Certificate covering the DS of interest listed on EudraGMDP, the database of the European Community of manufacturing authorisations and of certificates of good manufacturing practice;
- CPP – API issued by FDA for the DS of interest;
- Other evidence such as a manufacturing licence issued by a PIC/S authority covering the DS of interest and demonstrating that the site complies with GMP requirements.

For applications supported by a valid CEP for the DS of interest, HSA leverages the GMP compliance assessment under the EDQM Inspection Program for the site(s) specified in the CEP, and submission of proof of GMP compliance for the drug substance manufacturer is optional.

Proof of GMP compliance is required for micronisation and sterilisation sites of the drug substance if these operations are performed by a different manufacturer. The GMP compliance evidence should indicate the specific manufacturing operation, i.e., micronisation or sterilisation.

ii. Finished product manufacturer performing bulk production (including solvent/diluent and drug product intermediate), primary and secondary packaging activities and batch releaser

The proof of GMP compliance must be submitted for all the sites sought in the application submission:

- Valid PIC/S GMP Certificate, or
- EIR and close out letter issued by FDA.

  Note: The close out letter (which may be in the form of an email correspondence) should indicate the inspection classification of the facility, conclusion that the inspection was closed out and that the manufacturer was in an acceptable state of compliance with regard to cGMP.

Applicants may reference to **GMP Certifications** on the Eudra GMDP website for GMP compliance status as an alternative to submitting physical GMP certificates . Applicants should provide a screen capture of the Eudra GMDP website for the specific finished product manufacturing site, as well as the URL to the website. The names and addresses of all manufacturers as well as the type of product and manufacturing operations should be consistently stated throughout the application – i.e. GMP certificate, Letter of Authorisation, CTD section S.2.1 and P.3.1 and PRISM application form.

In addition, supplementary GMP documentary evidence may be requested as **supporting documents,** where necessary:

- Certificate of a Pharmaceutical Product issued in WHO Format; or
- Manufacturer's License or Manufacturing Authorization incorporating the specific therapeutic product(s)/dosage form(s)
- Exit Notice
- Unredacted inspection report
- List of regulatory inspections
- Site Master File
- Contract/Quality agreements

NOTE: These supporting documents are not considered valid acceptable GMP documentary evidence on their own and should be accompanied acceptable GMP documentary evidence issued by a competent authority.

Accreditation documents/certificates issued by other drug regulatory agencies (for example, PMDA Accreditation Certificate of Foreign Drug Manufacturer, FDA Establishment Licence, Health Canada Establishment Licence, GMP Clearance outcome, Manufacturer Authorisations) are not acceptable proof of GMP compliance.

Proof of GMP compliance must be in English and valid at the time of submission to HSA with not less than 6 months before expiry. If the validity period/expiry date is not stated on the proof of GMP compliance, the document is deemed valid for a period of 3 years from date of last inspection or date of issuance of the document. Applicants should refer to section 6.2.2.

It should be noted that diluents used for reconstituting the drug product and are packaged together with the drug product will be considered as part of the final drug product. Thus, manufacturer(s) of the supplied diluent(s) must follow the same requirements applicable to the drug product, e.g. provide proof of GMP compliance.

(C) GMP Conformity Assessment for Overseas Finished Product Manufacturers by HSA

If the drug product is manufactured by a new overseas drug product manufacturing site not previously registered with HSA before 1st April 2004, a GMP Conformity Assessment will be conducted by HSA.

A GMP Conformity Assessment is specific to each manufacturing site, dosage form, manufacturing activities and local applicant company. For contract manufacturers, such manufacturing activities include terminal sterilisation of the drug product, mixing of excipient with drug substance (drug product intermediate), etc.

When applicable, applicants must also submit the application form to request for GMP Evidence Evaluation or for an Overseas GMP Audit with the required documents to the Therapeutic Products Branch (as part of the product registration application) as stipulated in the *Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer*. The relevant GMP Conformity Assessment application form should be completed and submitted as a supporting document in the product registration application. Hardcopy submission is not required.

HSA may request for a GMP Conformity Assessment if deemed necessary, or request for additional or updated documents as evidence of GMP compliance during the registration process. HSA reserves the right to conduct an audit of any overseas manufacturer irrespective of the documentary GMP evidence that is approved by HSA or any other PIC/S member authorities, if deemed appropriate.

If you are unsure whether HSA requires assessment of the manufacturing site(s), you should submit the GMP Conformity Assessment application together with the product registration application. HSA will inform you if the assessment is needed. Please note that any GMP Conformity Assessment application submitted without a concurrent product registration application will not be accepted.

(D) Drug product manufacturing sites that use parametric release

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a GMP Conformity Assessment is **product specific.** Eligibility criteria for such applications for overseas manufacturing sites are:

a) Country of origin must be a PIC/S country; and
b) Parametric release is approved by the local authority.

If the above criteria are met, then an approval letter and recent documentary evidence of approval status (e.g. GMP Certificate) for parametric release issued by the local authority should be provided. The manufacturing site and the product proposed for parametric release should be clearly stated on these documents.

For a local manufacturing site that would like to apply for parametric release, applicants are advised to contact HSA prior to submission as pre-approval inspection is required.

j) Patent Declaration (CTD/PRISM section 1.12)

A signed and dated patent declaration form is required for each NDA. Applicants should refer to section 3 for information on patent linkage and Appendix 1 – Form 1 for the Patent Declaration Form.

Guiding notes on filling the Patent Declaration form are provided below:

i. Section 1 '*Applicant Particulars*' - state the name and address of the local company.
ii. Section 2 '*Product Particulars*' - state the product name, name and strength of active ingredient and dosage form. All product particulars should be consistent with that stated in the product labels and other relevant documents as submitted in PRISM.
iii. Section 3 '*Application Category*' - declare the patent category (A1, A2, A3, or B) that the application falls under.
iv. Section 4 '*Information for Category A1 Applications*' - applicable if category A1 is selected in Section 3.
v. Section 5 '*Information for Category A2 Applications*' - applicable if category A2 is selected in Section 3. Check the box which is relevant and provide details of the restraining patent in force.
vi. Section 6 '*Information for Category A3 Applications*' - applicable if category A3 is selected in Section 3. Provide details of the restraining patent in force.
vii. Section 7 '*Information for Category B Applications*' - applicable if category B is selected in Section 3. Check the box which is relevant and provide details of the restraining patent in force.
viii. Section 8 '*Declaration*' - the patent declaration must be signed by the person authorised to make the declaration on behalf of the company named in Section 1. The authorised person is ordinarily an officer of the company such as Company Director or Company Secretary as registered with ACRA, or equivalent. Evidence

of such authorisation is to be submitted together with the declaration.

Evidence of authorisation for Section 8 of the form can be in the form of:

- An ACRA printout[9] (BizFile) listing the Company Directors/Secretary;

[9] The required information on the company's business profile should be obtained directly from ACRA's website (BizFile).

- A resolution of board of directors;
- A resolution of a general meeting of the company; or
- An extract of the relevant portion of the company's articles of association.

Declaration forms must bear the signatures of the authorised person in the company.

NOTE: The applicant should ensure that the information provided in the patent declaration form and the evidence of authorisation are current at the point of application submission.

The patent declaration form needs to be submitted twice – at the time of submitting the application for registration and prior to the issuance of the regulatory decision for registration (upon request by HSA), if the dossier was deemed satisfactory with respect to the product's safety, efficacy and quality aspects.

k) Declaration on Rejection, Withdrawal and Deferral (CTD/PRISM section 1.13)

The document required for this section is a declaration letter issued by the product owner or applicant that states that the application submitted to HSA and the directions of use including indication(s), dosing regimen(s) and patient population(s)

- have not been rejected or withdrawn;
- have not been approved via an appeal process; and
- are not pending deferral

by any drug regulatory agency. If any of the above conditions apply to the application,

details and reasons must be provided to HSA.

l) Declaration for NDA Verification (CTD/PRISM section 1.14)

This section applies only to the verification evaluation route.

A declaration letter issued by the product owner/applicant stating that all quality aspects including composition, manufacturing and quality standards of the drug product are identical to those approved by the chosen primary reference agency

must be provided.. In accordance with ASEAN stability requirements, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed.

If a DMF is submitted, a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen primary reference agency.

m) Registration Status in Other Countries (CTD/PRISM section 1.15)

The registration status of the product in other countries should be entered into PRISM section 4.9 – refer to Appendix 17 for further details.

Additional details of the product's registration status in other countries may be submitted in PRISM section 7 (Supporting Attachments). The document should be in the format shown in Table 6:

Table 6 Example of a Table of Information on Registration Status in Other Countries for CTD Section 1.15

Country	Application status	Status Date	Approved application indication/dosing regimen details#	Approved forensic classification+

Country 1	*Approved*	*12 Jan 2005*	*Adjuvant treatment of colorectal cancer stage III (Dukes C) following complete resection of primary tumour.*	*POM*
Country 2	*Approved*	*2 Feb 2006*	*Adjuvant treatment of colorectal cancer following surgery*	*POM*

Country	**Application status**	**Status Date**	**Approved application indication/dosing regimen details#**	**Approved forensic classification+**
Country 3	*Withdrawn by applicant*	*14 Apr 2002*	*Indication submitted 'Adjuvant treatment of colorectal cancer'. Withdrawn due to insufficient long term efficacy data (only phase II data submitted). Re-submitted on 16 June 2005 with completed phase III data for 'Adjuvant treatment of colorectal cancer following surgery'.*	*POM*

Country 4	*Approved*	*21 Nov 2004*	*Adjuvant treatment of colorectal cancer stage III (Dukes C) following complete removal of primary tumour.* *Notice of Compliance with Conditions issued on 16 April 2003 based on promising efficacy results with condition to furnish confirmatory efficacy data.*	*POM*
Country 5	*Pending*	*Submitted: 15 Jun 2005*	*Adjuvant treatment of colorectal cancer stage III (Dukes C) following surgery.*	*POM*

Applicable to information on reference agencies, Country of Origin, and all rejections/withdrawals/deferrals

Country	**Application status**	**Status Date**	**Approved application indication/dosing regimen details#**	**Approved forensic classification+**

+ Applicable to information on reference agencies and Country of Origin.

n) *Confirmation of Reference Agency's Approval of CMC Aspects (CTD/ PRISM section under Other Supporting Documents)*

For applications submitted under the abridged evaluation route and for which approval was obtained from at least one of HSA's reference agencies not more than 5 years before the date of submission to HSA, a copy of the completed Dossier Clarification Supplement should be submitted in PRISM (refer to Appendix 18 *Confirmation of Quality Dossiers with Reference Agency's Approval* for more information).

15.2 CTD Overview and Summaries

The ICH or ASEAN CTD overview and summary documents are to be inserted into Module 2 of the ICH CTD or into the relevant sections in Part II, III and IV of the ACTD. The ICH or ASEAN Quality Overall Summary can be submitted either in Word or PDF format.

Overview and Summaries	**Location in CTD**	
	ICH CTD	**ACTD**
Quality Overall Summary	Module 2, section 2.3	Part II, section B
Non-clinical Overview & Summaries	Module 2, section 2.4 & 2.6	Part III, sections B & C, respectively
Clinical Overview & Summaries	Module 2, section 2.5 & 2.7	Part IV, sections B & C, respectively

15.3 Quality Documents

The quality documents relate to Module 3 of the ICH CTD or Part II of the ACTD. In addition to the ICH or ACTD technical content requirements, the following explanatory notes pertain to requirements specific to Singapore:

15.3.1 Body of Data – Drug Substance

The ICH M4Q Technical Guidelines and ACTR provide details on the information to be included in the drug substance sections of an application dossier.

NOTE: If a drug product contains more than one drug substance, the information within Module 3.2.S (ICH CTD) or Part II.S (ACTD) must be provided in its entirety for each drug substance.

All of the drug substance sections of the CTD – i.e. S.1 to S.7, are required in the application. Alternatively, applicants may submit either a DMF or CEP in lieu of the entire CTD drug substance sections.

Drug Master File (DMF)

A DMF is a dossier that contains detailed information about specific processes or components used in the manufacturing, processing, and packaging of a drug and is submitted solely at the discretion of the DMF holder.

The DMF is reviewed only in conjunction with the specific product registration application it supports. HSA does not issue standalone approval for DMF.

Appendix 11 describes the DMF process and documentary requirements for DMF submission.

Plasma Master File (PMF)

A Plasma Master File (PMF) contains information on the collection and control of source materials, and is required where a human plasma-derived product is used either as a starting material or as an excipient. The PMF may be submitted either

as a stand-alone document or as part of the application dossier. Appendix 8 describes the PMF data requirements for submission.

If the PMF is a stand-alone document, it should be filed separately from the application dossier for pre-marketing evaluation. The applicant may cross-reference a PMF of a human plasma-derived product that is used in currently registered products, where applicable.

Certificates of Suitability (CEP)

A CEP is a document issued by the EDQM that certifies the quality of a drug substance in compliance to the Ph. Eur. A CEP may be submitted *in lieu* of the CTD S Section or a DMF.

If reference is made to a CEP, the applicant must submit a copy of the valid CEP, including all annexes, and a copy of the Letter of Access from the CEP holder to authorise the applicant to refer to the CEP in support of their application.

The following additional requirements apply for CEP-based submissions:

i. If Ph. Eur. standard is claimed for the drug substance, the relevant CTDs should be submitted:
   (i) S.2.1;
   (ii) S.4.1 and S.4.4 from both the drug substance and drug product manufacturers; and
   (iii) S.6 and S.7 should be provided if the re-test period/shelf life is not stated on the CEP.

ii. If other standards are claimed for the drug substance, the relevant CTDs should be submitted:
   (i) S.2.1;
   (ii) S.4.1 to S.4.5 from both drug substance and drug product manufacturers; and
   (iii) S.6 and S.7 should be provided if re-test period/shelf life is not stated on the CEP.

NOTE: HSA reserves the right to request for any additional information about the CEP-certified drug substance if it is deemed appropriate.

If there is a CEP for animal-derived material used in the drug product, the applicant may submit the CEP together with the documents stipulated in Annex 1- section 1.1 of Appendix 9 *Guideline on the Registration of Human Medicinal Products Containing Materials of Animal Origin*.

It is the applicant's responsibility to submit the latest CEP updates, with annexes, as soon as they are available from EDQM.

Control of Drug Substance (CTD section 3.2.S.4)

As the drug product manufacturer is responsible for the quality control of the drug substance that is used in the drug product, information on the control of the drug substance, i.e., 3.2.S.4.1 to 3.2.S.4.5, must be provided from both the drug substance and drug product manufacturers.

Batch analysis data should be provided by the drug substance and drug product manufacturers, and, if available, from the same drug substance batches. Analytical results should be provided from a minimum of two batches from each proposed drug substance manufacturer and should be sufficient to support the specification(s) as well as to demonstrate consistency in manufacturing. The batches submitted should preferably be of production scale or at least pilot scale.

Stability Data of Drug Substance (CTD section 3.2.S.7)

At the time of submission, the minimum stability data required are as follows:

- At least 12 months of long term data and 6 months of accelerated data from at least three primary batches of the drug substance; and
- The batches should be at least of pilot scale and manufactured by a method that simulates the final commercial process.

Where multiple drug substance manufacturers are proposed for registration, if it can be demonstrated that the submitted data is representative of the proposed sites, it may be acceptable to extrapolate the stability data from one site to the other sites,

and stability data from each site may not be required at the point of submission. All the following criteria must be met for the stability data to be considered representative:

- The drug substance is manufactured using the same synthetic route and process. Scientific justification should be provided to demonstrate equivalence between the sites if differences exist;
- The drug substance is controlled by the same set of specifications;
- The drug substance is packaged in the same container closure system; and
- The drug substance is of comparable quality to the drug substance used in the stability batches.

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

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

Stability data from a site not proposed for registration may also be provided as supporting data.

15.3.2 Body of Data – Drug Product

The ICH M4Q technical guideline and ACTR also provide details on the information to be included in the drug product sections of an application dossier. For drug product intermediates and diluents, separate drug product sections should be submitted.

Pharmaceutical Development (CTD section 3.2.P.2)

Detailed descriptions and discussions, with relevant data, which relate to the development, and hence quality, of the drug product should be provided in the relevant dossier sections. Examples include, but are not limited to:

- polymorphism, solubility or particle size of the drug substance and its effect on the product's quality;
- a description and the results of the formulation development;
- the rationale for the choice of dissolution method and a discussion of its discriminatory nature, with data;
- compatibility of the container closure system with the product or preservative efficacy test results; and
- optimisation of the manufacturing process, with data.

Process Validation (CTD section 3.2.P.3.5)

The description, documentation *and* complete results of the validation studies on the manufacturing process should be provided in the dossier in this section. Particular care should be taken to ensure that the documents include critical processes for the

manufacturing process: for example, blend uniformity validation for oral dosage forms and terminal sterilisation or aseptic filling for sterile products.

Applicants should refer to the ASEAN Guidelines on Submission of Manufacturing Process Validation Data for Drug Registration and the ASEAN Guideline on Process Validation Q&A for the minimum data requirements for process validation. Other relevant international guidelines may also be referred to as appropriate.

Where ranges of batch sizes are proposed, it should be demonstrated that variations in batch size would not adversely alter the characteristics of the finished product.

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a more detailed discussion with supporting data on the process validation of the specific product in the proposed pack size or fill volume should be provided. In addition, risk assessment for parametric release should be based on prior knowledge, consistency of performance of the steriliser, historical batch analysis data, risk of loading pattern/container/ contamination from the environment to product sterility, re-processing plan, etc. A detailed discussion on the control strategy should also be provided. This includes but is not limited to, a tabulation of all validated critical process parameters and loading patterns, a description of the process and requirements for the release/rejection of a batch, bioburden monitoring and control program, the segregation of sterile products from

non-sterile products and the routine maintenance/re-validation program for the steriliser.

Control of Excipients (CTD section 3.2.P.4)

This section refers to all excipients used in the drug product formulation, including ingredients used in capsule shells and film coatings. The specifications and analytical method(s) for each excipient should be described, including the validation of any in-house test method(s), if applicable.

Information on proprietary ingredients, such as flavourings, colourants, coatings,

perfumes and/or printing inks, should be as detailed as possible. Applicants are advised not to use internal codes but instead to give commercial names for such ingredients. In cases where the formula of the proprietary ingredient is confidential, only the total quantity of the proprietary ingredient present in the final product needs to be captured in PRISM. The formula of the proprietary ingredient should then be provided by the proprietary ingredient manufacturer directly to HSA. A declaration letter from the proprietary ingredient manufacturer should also be provided, indicating that they will inform HSA (via email to HSA_TP_Enquiry@hsa.gov.sg) and the applicant should there be any change in the formulation of the proprietary ingredient.

A CoA for an excipient may be submitted *in lieu* of the excipient's specifications. If the standard claimed for an excipient is an officially recognised compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognised compendial monograph.

For excipients derived from human plasma, applicants should refer to the Appendix 8 on the data requirements.

For excipients derived from animal sources, applicants should refer to Appendix 9 for more information. The checklist found in Annex 1 of Appendix 9 serves as a guide to these documentary requirements for submission. Applicants should note that the completed checklist in Annex 1 is to be submitted in CTD section 3.2.P.4.5

with the supporting documents submitted in ICH CTD section 3.2.A.2 or ACTD section Q.A.2.

For milk and certain milk derivatives such as lactose, as these excipients are generally considered non-infectious, a declaration from the supplier of the excipient stating that the milk is from healthy cows fit for human consumption and that no other potentially infectious ruminant-derived materials were used in the manufacturing process would be sufficient. This declaration is to be submitted in CTD section 3.2.P.4.5.

Control of Drug Product (CTD section 3.2.P.5)

The drug product's release and shelf-life specifications should be declared in section 3.2.P.5.1.

For the parametric release of a terminally sterilised product, the release specification and certificate of analysis should indicate that parametric release is the method used for batch release. Additionally, sterility of the product is required to be demonstrated in the stability studies even if approval for parametric release has been granted.

Descriptions of all test methods with complete validation results of all in-house methods should be submitted in sections 3.2.P.5.2 and 3.2.P.5.3.

Descriptions (including size, origin and use) and test results of all relevant batches (e.g. pre-clinical, clinical, pilot and production batches) used to establish the specification and evaluate the consistency in manufacturing should be provided.

Batch analysis data and/or CoAs from three batches of the drug product should be provided in section 3.2.P.5.4.

The justification of the specifications (section 3.2.P.5.6) should be based on scientific knowledge and data collected during product development.

Container Closure System (CTD section 3.2.P.7)

Technical information about each component of the container closure system(s) used for the drug product should be included in the dossier. The technical information to be included in the dossier includes, but is not limited to, schematic diagrams, descriptions, specifications, analytical methods, CoAs and declarations of compliance to international standards.

Stability Data of Drug Product (CTD section 3.2.P.8)

Since 01 April 2014, HSA has implemented the ASEAN Guideline on Stability Study of Drug Product, a guideline on the conduct of stability studies for drug products for the ASEAN region. Applicants should familiarise themselves with this guideline prior to submission.

At the time of submission of the application, the minimum stability data required are as follows:

- At least 12 months of data under long term storage conditions and 6 months of data under accelerated storage conditions on at least three primary batches of the drug product; and
- The primary batches should be at least of pilot scale, manufactured by the same manufacturing process and packaged in the same container closure system as that proposed for Singapore.

Where multiple drug product manufacturers are proposed for registration, if it can be demonstrated that the submitted data is representative of the proposed sites, it may be acceptable to extrapolate the stability data from one site to the other sites, and stability data from each site may not be required at the point of submission. All the following criteria must be met for the stability data to be considered representative:

- The drug product is manufactured using the same formulation;
- The drug product is manufactured using the same manufacturing process, including equipment type, process parameters and in-process tests. Scientific justification should be provided to demonstrate equivalence between the sites if differences exist.
- The drug product is controlled by the same set of specifications;
- The drug product is packaged in the same container closure system; and
- The drug product is of comparable quality to the drug product used in the stability batches.

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

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

Stability data from a site not proposed for registration may also be provided as

supporting data.

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

If multiple primary packaging sites for the same container closure system are proposed for registration, transport validation of the bulk product to the other proposed primary packaging site(s) is required, unless otherwise justified.

15.4 Non-clinical Documents

The non-clinical documents relate to Module 4 of the ICH CTD or Part III of the ACTD.

Applicants should refer to the ICH CTD Guidelines M4S (Safety) technical guidelines or the ACTD Part III: Non-clinical guidelines for detailed information on the contents of non-clinical documents for the application dossier.

15.5 Clinical Documents

The clinical documents relate to Module 5 of the ICH CTD or Part IV of the ACTD.

Guidance on how to complete this Module/Part is provided in the ICH CTD Guidelines M4E (Efficacy) technical guidelines, in particular the ICH E3 guidance document on *Structure and Contents of Clinical Study Reports*, or the ACTD Part IV: clinical Guidelines.

Clinical studies should generally be conducted using the drug product formulation submitted in the application and in the appropriate patient population for the indication(s) and/or dosing regimen(s) as requested in the NDA.

Biopharmaceutic (e.g. bioavailability or bioequivalence) study reports are required if

the commercial formulation for the Singapore market differs from the clinical trial formulation used in the pivotal studies.

The submission of risk management plans (RMPs) in support of all NDA-1 applications is mandatory. For NDA-2 or NDA-3 applications, HSA may also request for RMPs to be submitted on a case-by-case basis when required, following the evaluation of the safety concerns described in the product application. Guidance on RMP submission requirements can be found here.

If the NDA is for a non-prescription medicine and is submitted via the abridged evaluation route, the applicant may submit a written request for a waiver of clinical data submission. Eligibility for a waiver is subject to the criteria defined in Appendix 6 *Guideline on Submission for Non-Prescription Therapeutic Products*. However, HSA reserves the right to request for the complete clinical data set if it is deemed necessary.

15.6 Documentary Requirements for Each Evaluation Route

15.6.1 Full Evaluation Route

Full information on the chemical/biological development, pharmaceutical/genetic development, toxicological, pharmacological and clinical data needs to be submitted in support of the application.

The technical documents required include:

- complete quality documents for both drug substance and drug product;
- complete pharmaco-toxicological or non-clinical documents; and
- complete clinical documents, i.e. all study reports from phase I to phase III, including tables and appendices.

15.6.2 Abridged Evaluation Route

All aspects of the product's quality and direction(s) for use [including dosing regimen(s), indication(s) and patient group(s)] should be the same as that approved by the drug regulatory agency that issued the proof of approval.

The technical documents required include:

- complete quality documents for both the drug substance and drug product;
- a non-clinical overview; and
- a clinical overview, summaries of clinical efficacy and clinical safety, synopses of relevant studies, a tabular listing of the clinical development programme and study reports of the pivotal studies (the tables and appendices to the pivotal study reports may be submitted upon request by HSA).

15.6.3 Verification Evaluation Route

The complete assessment report and other relevant supporting documents from the chosen primary reference agency must be submitted, as tabulated below. The assessment reports from the primary reference agency must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, quality and clinical reviews, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable.

Applications submitted to HSA without the unredacted/ unedited reports from the primary reference agency will not be accepted for evaluation via the verification route and rejected at screening.

Primary reference agency	**Documentary requirements**
EMA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

FDA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
Health Canada	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Primary reference agency	**Documentary requirements**
MHRA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
Swissmedic	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

TGA	• Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

[#] If the drug substance section is submitted to the primary reference agency as a DMF, the complete assessment report for the DMF, including the assessment on the Question & Answer (Q&A) documents between the DMF Holder & Agency and all annexes should be provided. Assessment reports, approval letters and/or documents pertaining to post-approval DMF updates should also be submitted, if applicable.

Administrative documents specific to the verification evaluation route that are required at the time of submission include:

(a) Section 1.9 – Official approval letters, or equivalent documents, from the relevant reference drug regulatory agencies that certify the registration status of the drug product;

(b) Section 1.13 – Official letter declaring that the application submitted to HSA or similar direction(s) of use, indication(s), dosing regimen(s) and/or patient group(s) have not been rejected, withdrawn, approved via appeal process[10], or pending deferral[11] by any drug regulatory agency, with reasons in each case if applicable;

(c) Section 1.14 – Official letter declaring that the DMF provided is the same as that submitted to the primary reference agency, if applicable; and

(d) Section 1.14 – Official letter from the applicant or product owner declaring that all quality aspects including the composition, manufacturing and quality standards of the drug product in Singapore are identical to that approved by the primary reference drug regulatory agency.

The technical documents required include:

- Quality documents:
  - From Sponsor:

- Complete documents for both drug substance and drug product (ICH Module 3/ACTD Part II) as initially submitted to the primary reference agency;
- Complete assessment reports including assessment on the Question & Answer documents between the Sponsor and primary reference agency, and other relevant supporting documents from the primary reference agency;
- Questions and answers between the primary reference agency and Sponsor – the answers should include the supporting documents used in response to the questions;
- All post-approval variations (if applicable) approved by the primary reference agency up to the time of submission to HSA, including the application letter for the variation, supporting documents for the variation, assessment report for the variation, questions and answers between the primary reference agency and Sponsor and the approval letter for the variation from the primary reference agency; and

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[10] Approval via appeal process includes, but is not limited to, the following: approval following negative opinion, approval following rejection, approval following non-approvable etc.

[11] Deferral includes, but is not limited to, the following: non-approvable, approvable, conditional approval, conditional marketing authorisation, notice of compliance with conditions etc.

- Relevant documents required by HSA which have not been submitted to the primary reference agency, e.g. stability studies in accordance to ASEAN Stability Guidelines.

– From DMF Holder, if applicable:

- The initial open and closed parts of the DMF submitted to the primary reference agency should be provided to HSA, together with a copy of the Letter of Access;
- Complete DMF assessment report including assessment on the Question & Answer documents between the DMF holder and the primary reference agency, and other relevant supporting documents from the primary

reference agency;

- Questions and answers between the primary reference agency and DMF Holder – the answers should include supporting documents used in response to the questions; and
- All post-approval DMF updates (if applicable) approved by the primary reference agency up to the time of submission to HSA, including the application letter for the DMF update, supporting documents for the DMF update, assessment report for the DMF updates, questions and answers between the primary reference agency and Sponsor, and the approval letter for the DMF update from the primary reference agency.

- Non-clinical overview; and
- Clinical documents, assessment report from the primary reference agency, including assessment on the Question and Answer documents between the Sponsor and Agency, and other relevant supporting documents from the primary reference agency

Data submitted to HSA must be the same as the data package submitted to the reference drug regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application, but may also lead to re-routing of the dossier to the abridged evaluation route if significant undisclosed differences are discovered.

In the event that the chosen primary reference agency does not bear the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use among those approved by the reference drug regulatory agencies, a supplemental complete clinical assessment report[12] from the reference drug regulatory agency that approved the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use is required. The proposed PI/PIL should be identical to that bearing the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use (with the exception of country-specific information).

[12] A complete assessment from public domain is acceptable.

CHAPTER D GENERIC DRUG APPLICATION SUBMISSION

This chapter applies to applications to register generic products.

A generic drug application applies to a therapeutic product that contains one or more chemical entities, and that is essentially the same with a current registered product with respect to its qualitative and quantitative composition of active ingredients, pharmaceutical dosage form and clinical indication.

Follow-on biologic products (also known as biosimilar products) are not eligible for a GDA and are required to be submitted via an NDA.

16 APPLICATION TYPES

There are two application types for a generic drug application:

GDA Generic Drug Application

GDA-1: For the first strength of a generic chemical product.

GDA-2: For subsequent strength(s) of the generic chemical product that has been registered or submitted as GDA-1. The product name and dosage form should be the same as that for the GDA-1.

In cases where multiple strengths of a generic product are submitted together, the strength of the product used in the BE study is considered as a GDA-1. The remaining strength(s) should be submitted as GDA-2.

16.1 Generic Product

A generic product must have the same qualitative and quantitative composition in active ingredients and be of the same pharmaceutical form as a currently registered product in Singapore (known as the 'Singapore reference product'). A generic product must demonstrate bioequivalence to the Singapore reference product via appropriate bioequivalence studies.

The generic product must fulfil the following criteria:

(a) the generic product is the same pharmaceutical dosage form as the Singapore reference product. However, different conventional oral immediate-release dosage forms (i.e. tablets and capsules) are considered to be the same pharmaceutical form;

(b) the route of administration of the generic product is the same as the Singapore reference product;

(c) the conditions of use for the generic product fall within the directions for use (including indication(s), dosing regimen(s) and patient group(s)) for the Singapore reference product; and

(d) the generic product is bioequivalent with the Singapore reference product.

16.2 Singapore Reference Product

The Singapore reference product must be a currently registered product that has been granted market authorisation based on the evaluation of the product's quality, efficacy and safety – i.e. a dossier with chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. If such a reference product is not registered in Singapore, then an alternate registered comparator product may be used if adequately justified (e.g. a registered generic therapeutic product widely used by local hospitals) by the applicant and agreed upon by HSA.

The generic product should contain the same active ingredient(s) and strength(s) and be the same pharmaceutical dosage form as the Singapore reference product.

For generic products containing a different salt, ester, ether, isomer, mixture of isomer, complex or derivative of the active ingredient compared to the Singapore reference product, applicants are required to submit data to demonstrate that the different form does not differ from the active ingredient in the Singapore reference product in terms of safety and/or efficacy.

Applicants are advised to search Register of Therapeutic Products to identify the Singapore reference product.

Applicants submitting GDAs should also refer to Appendix 10 and Common questions related to generic drug applications for further details on product interchangeability and biowaiver requests.

17 EVALUATION ROUTES

There are three evaluation routes for a GDA: abridged, verification and verification-CECA evaluation routes. The eligibility criteria are different for each evaluation route. Applicants should be familiar with the criteria for each evaluation route because each route has different documentary requirements.

Figure 4 is a schematic diagram illustrating the evaluation routes for GDAs:

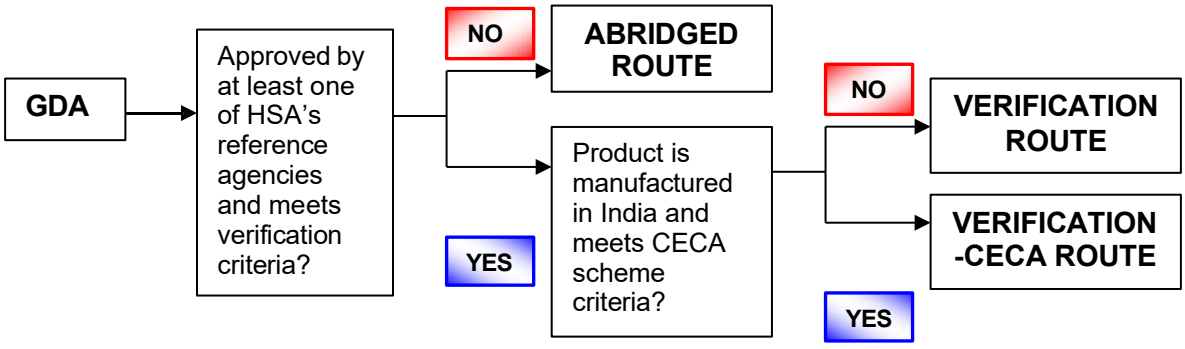

Figure 4 Schematic Diagram of Evaluation Routes for GDAs

17.1 Abridged Evaluation Route

Abridged evaluation applies to a product that has been approved by at least one drug regulatory agency at the time of submission.

17.2 Verification Evaluation Route

Therapeutic products that have been approved by at least one of HSA's reference drug regulatory agencies may be eligible for submission via the verification evaluation route. HSA's reference drug regulatory agencies are:

- EMA via the Centralised Procedure
- FDA
- Health Canada
- MHRA via
  - the national procedure, or
  - as the RMS via the MRP or DCP on or prior to 31 January 2020
- Swissmedic
- TGA

However, approval by these reference drug regulatory agencies does not oblige HSA to approve the application. HSA may also re-categorise an application to another evaluation route if the application fails to meet the eligibility criteria and/or submission requirements.

The pre-requisite requirements for the verification route include:

(a) The product has received full marketing approval by the reference agencies following a complete independent scientific assessment;

(b) The application must be submitted to HSA within two years from the date of approval by the chosen reference drug regulatory agency;

(c) A declaration letter issued by the product owner/applicant stating that all quality aspects including the composition, manufacturing and quality standards of the drug product are identical to those approved by the chosen reference drug regulatory agency must be provided. In accordance with ASEAN stability requirements, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed;

(d) If a DMF is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen reference drug regulatory agency;

(e) The product and its intended use – i.e. indication(s), dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, or approved via appeal process or are not pending deferral by a drug regulatory agency for efficacy and/or safety reasons.

The chosen reference drug regulatory agency is defined as the reference drug regulatory agency for which the qualifying supporting documents (as outlined in this guidance) will be submitted.

18 DOCUMENTARY REQUIREMENTS

Refer to Documentary Requirements in section 6.2 for submission requirements.

Table 7 outlines the CTD Modules/Parts required for GDAs submitted under each evaluation route:

Table 7 Dossier Submission Requirements for a GDA

Documents	Location in		Module/Part required for		
	ICH CTD	ACTD	Abridged GDA	Verification GDA	Verification -CECA GDA
Administrative Documents and Product Information	Module 1	Part I	Yes	Yes *(Refer to section 18.5.2)*	Yes *(Refer to section 18.5.2)*
Common Technical Document Overview and Summaries	Module 2	*Incorporated into Part II*	QOS	QOS	QOS

Quality documents	Module 3	Part II	Yes	Yes *(Refer to section 18.5.2)*	Yes *(Refer to section 18.5.2)*
Non-clinical documents	Module 4	Part III	No	No	No
Clinical documents	Module 5	Part IV	BE studies or biowaiver justification may be inserted in this section	Yes *(same dataset as that submitted to RA)*	Yes *(same dataset as that submitted to RA)*

18.1 Administrative Documents

The administrative documents relate to Module 1 of the ICH CTD or Part I of the ACTD and are applicable to the evaluation routes for GDAs. The following sections are to be submitted:

a) *Cover Letter (to attach under CTD/PRISM section 1.2 - Introduction)*

To include a cover letter stating the product name, and the number of CD/DVDs submitted in the application dossier.

Applicants should ensure that the application dossier is complete. The omission of any documents within the dossier or any deviation from the guidelines must be appropriately justified.

Applicants should also give a concise summary of the application – for example, an overview of the bioequivalence study and the Singapore reference product used in support of the application.

b) *Comprehensive Table of Contents (CTD/PRISM section 1.1)*

The comprehensive table of contents is a complete list of all documents provided in the application dossier listed by Module/Part. The location of each document should be identified by the Module/Part number.

NOTE: Each application must be accompanied by the required application checklist found in Appendix 2A or Appendix 3A, duly completed by the applicant and attached in PRISM.

c) *Labelling, Package Insert and Patient Information Leaflet (CTD/PRISM section 1.4)*

All proposed labels are to be submitted for registration. Applicants are required to provide the artwork/drafts of the proposed Singapore product labels, PI and/or PIL for the product. The clinical information in the proposed PI/PIL should be consistent with that currently approved for the Singapore reference product.

The submission of the proposed PI or PIL is dependent on the forensic classification of the product to be registered, as described in Table 8:

Table 8 Submission of Proposed PI or PIL According to Forensic Classification in Singapore

	Forensic Classification in Singapore		
	POM	**P**	**GSL**
PI, also known as prescribing information, SPC, or product monograph	**Required**	*Optional*	*Optional*
PIL, also known as CMI	*Optional, unless warranted*	**Required**	**Required**

One PI and/or PIL must be registered for each product application. When a product has

multiple manufacturing sites involved in its manufacture for Singapore supply, all site information must be included in a single PI and/or PIL.

For products with different strengths or dosage forms:

- Applicants are encouraged to submit one common PI/PIL that covers all strengths or dosage forms
- If separate PI/PILs are to be registered for different strengths or dosage forms:
  - The content must remain consistent across all PI/PILs
  - Variations are permitted only for strength/dosage form-specific information

All artwork and drafts must be clearly legible in typed / printed format. The draft artwork of the outer carton and inner/blister labels should be consistent with the format, design and colour that are to be printed. Separate labels must be submitted for each different pack size of the drug product.

The product labels, PI and/or PIL must be in English. If non-English text is included in the labelling, applicants must provide an official statement to declare that the non-English text is complete, accurate and unbiased information and is consistent with the English text.

Appendix 7 of this guidance contains specific details on the product labelling requirements for Singapore.

d) Approved SPC/PI/PIL (CTD/PRISM section 1.5)

In this section, the applicant should submit the approved SPC, PI and/or PIL from the drug regulatory agency that issued the proof of approval.

For applications submitted under the verification and verification-CECA evaluation routes, the SPC/PI/PIL approved by the chosen reference drug regulatory agency should be submitted.

The country from which the submitted SPC, PI and/or PIL originates should be appropriately indicated (e.g. in the document file name).

e) Assessment Report from Reference Agencies (CTD/PRISM section 1.6) This section refers only to applications submitted under the verification or verification-CECA evaluation routes. Assessment reports and supporting documents issued by the chosen reference drug regulatory agency and inserted into this section must be unredacted and unedited. Applicants should refer to section 18.5.2 *Verification and Verification-CECA Evaluation Routes* for specific details on the required documents.

f) Description of Batch Numbering System (CTD/PRISM section 1.7)

Detailed information on the system of assigning unique codes to different production batches of the product should be provided to allow for batch identification. Where applicable, examples of the batch numbering system should be included to illustrate how the batch number enables identification.

g) Proof of Approval (CTD/PRISM sections 1.8, 1.9)

Proof of approval is not required for GDAs undergoing abridged evaluation for finished products manufactured (up to primary packaging) in Singapore.

For an abridged evaluation of an imported GDA, proof of approval from a competent drug regulatory agency is required. For a verification or verification-CECA evaluation of a GDA, proof of approval from the chosen reference drug regulatory agency is required.

A competent drug regulatory agency refers to a national regulatory authority participating in the World Health Organization's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and listed as such on the World Health Organization's website.

Proof of approval must come in the form of:

- a CPP that is valid at the time of submission; or

- an official approval letter that certifies that the product is currently registered in the country at the point of submission to HSA)

NOTE: A search result from a competent drug regulatory agency official website stating that the product is currently approved by that drug regulatory agency is acceptable. This website information must be published in English by the drug regulatory agency, and verifiable by HSA.

Applicants must submit the approved SPC, PI and/or PIL along with the proof of approval from the drug regulatory agency.

If the SPC is in a non-English language, applicants should refer to section 6.2.2 of this guidance document for more information on acceptable translations.

Note that all aspects of the product's quality should be the same as those approved by the drug regulatory agency that issued the proof of approval.

If information such as the product formula, manufacturing sites, etc. are present in the CPP, the information should be consistent with that proposed for the Singapore market.

Electronic CPPs issued by the regulatory authority are acceptable.

NOTE: CPPs that indicate that the product is not licensed for marketing in the exporting country (including scenario where the product is licensed for "solely for export only") are not acceptable proof of approval.

Approval letters should either be an original copy or a certified true copy and in English. Applicants should refer to sections 6.2.2 *Language and Translation* and 6.2.3 *Certifying Non-Original Documents* for more details.

HSA reserves the right to request for a CPP, if deemed appropriate.

If the brand name (trade name) of the product registered in the country which issued the proof of approval is different from that proposed in Singapore, the applicant is required to submit a declaration letter from the product owner to declare that both products marketed under the different brand names are identical in all aspects of quality, safety and efficacy except for the brand name.

h) Authorisation Letters (CTD/PRISM section 1.10)

All submitted authorisation letter(s) should be on the authorising company's (i.e. product owner's) letterhead, dated and signed by the designated authorised person in the company.

If the product owner is not the local applicant, manufacturer and/or batch releaser; or the product owner's address is different from that of the local applicant firm, manufacturer and/or batch releaser, then the following authorisation letter(s) must be submitted:

i. *from Product Owner to the Applicant (Company)* (1.10.1) – this letter authorises the local applicant to apply for and be the product registrant for a specific therapeutic product (product name to be stated as in PRISM) and be responsible for all matters pertaining to the registration of this product in Singapore.

ii. *from Product Owner to Manufacturer* (1.10.2) – this letter authorises the specified manufacturer to produce, pack and/or label the drug product intended for Singapore. If there are multiple drug product manufacturers, then the applicant may opt to submit one authorisation letter which clearly states all of the manufacturers (names and addresses) and their responsibilities relating to the drug product (such as the manufacturing operation of each manufacturer in relation to the product being submitted).

iii. *from Product Owner to Batch Releaser* (1.10.3) – this letter authorises the specified company to batch release the drug product. If there are multiple sites responsible for the batch release of the product, then the applicant may opt to submit one authorisation letter which clearly states all of the batch releasers (names and addresses) and their responsibilities.

The applicant may also issue an authorisation letter to authorise the specified secondary packager located in Singapore to pack and/or label the drug product intended for Singapore.

Applicants are to ensure that all names and addresses in the authorisation letter(s) are consistent with the information provided in PRISM and the dossier. For manufacturers and batch releasers, the actual site address of the named company should be stated in the letter(s) – i.e. do not state the office address. Any discrepancy found will delay the registration process.

All authorisation letters should also state specific product details, including the product name, dosage form and strength as stated in the PRISM application form.

Applicants also have the option to combine the authorisation letters as stated above into one document, provided that all names, addresses and responsibilities are clearly stated.

i) GMP Certification/Proof of GMP Compliance (CTD/PRISM section 1.11)

(A) Local Manufacturers

i. Drug substance manufacturer

A valid Active Ingredient Manufacturer's Licence (AIML) is required at the point of application submission. If the site is also involved in the manufacturing of the finished product, the Therapeutic Product Manufacturer's Licence (TPML) may be submitted.

ii. Finished product manufacturer

A valid TPML is required at the point of product application submission and the TPML number must be stated in the product application. No additional

documentary proof of GMP compliance needed.

(B) Overseas Manufacturers and Batch Releasers

Documentary evidence must be provided to certify that the manufacturer(s) complies with current applicable GMP standards.

The proof of GMP compliance has to be submitted for all the following sites mentioned in the product submission:

i. Drug substance manufacturer

An applicant may submit any of the following types of GMP compliance evidence to support the application:

- Valid PIC/S GMP certificate with the drug substance (DS) of interest stated. If the DS of interest is not specified on the GMP certificate, a Written Confirmation[13] for the DS of interest from the PIC/S authority which issued the GMP certificate is to be supplemented;
- GMP inspection report, with the DS of interest included in the scope, together with the close-out letter (where applicable) for PIC/S authorities which do not issue GMP certificates;
- Valid Active Pharmaceutical Ingredient (API) Registration Certificate covering the DS of interest listed on EudraGMDP, the database of the European Community of manufacturing authorisations and of certificates of good manufacturing practice;
- CPP – API issued by FDA for the DS of interest;
- Other evidence such as a manufacturing licence issued by a PIC/S authority covering the DS of interest and demonstrating that the site complies with GMP requirements.

For applications supported by a valid CEP for the DS of interest, HSA leverages the GMP compliance assessment under the EDQM Inspection Program for the site(s) specified

in the CEP, and submission of proof of GMP compliance for the drug substance manufacturer is optional.

Proof of GMP compliance is required for micronisation and sterilisation sites of the drug substance if these operations are performed by a different manufacturer. The GMP compliance evidence should indicate the specific manufacturing operation, i.e., micronisation or sterilisation.

ii. Finished product manufacturer performing bulk production (including solvent/diluent and drug product intermediate), primary and secondary packaging activities and batch releaser

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[13] Written Confirmation using the European Union (EU) template or any other official document from the PIC/S authority is acceptable.

The proof of GMP compliance must be submitted for all the sites mentioned in the product submission:

- Valid PIC/S GMP Certificate, or
- EIR and close out letter issued by FDA.

Note: The close out letter (which may be in the form of an email correspondence) should indicate the inspection classification of the facility, conclusion that the inspection was closed out and that the manufacturer was in an acceptable state of compliance with regard to cGMP.

Applicants may reference to **GMP Certifications** on the Eudra GMDP website for GMP compliance status as an alternative to submitting physical GMP certificates. Applicants should provide a screen capture of the Eudra GMDP website for the specific finished product manufacturing site, as well as the URL to the website. Applicants should note that the names and addresses of all manufacturers as well

as the type of product and manufacturing operations should be consistently stated throughout the application – i.e. GMP certificate, Letter of Authorisation, CTD section S.2.1 and P.3.1 and PRISM application form.

In addition, supplementary GMP documentary evidence may be requested for submission as **supporting documents,** where necessary:

- Certificate of a Pharmaceutical Product issued in WHO Format; or
- Manufacturer's License or Manufacturing Authorization incorporating the specific therapeutic product(s)/dosage form(s)
- Exit Notice
- Unredacted inspection report
- List of regulatory inspections
- Site Master File
- Contract/Quality agreements

NOTE: These supporting documents are not considered valid acceptable GMP documentary evidence on their own and should be accompanied acceptable GMP documentary evidence issued by a competent authority.

Accreditation documents/certificates issued by other drug regulatory agencies (for example, PMDA Accreditation Certificate of Foreign Drug Manufacturer, FDA Establishment Licence, Health Canada Establishment Licence, GMP Clearance outcome, Manufacturer Authorisations) are not acceptable proof of GMP compliance.

NOTE: For applications submitted via the verification-CECA evaluation route, a valid GMP certificate and the latest inspection report as issued by the chosen reference drug regulatory agency must be submitted.

Proof of GMP compliance must be in English, valid at the time of submission to HSA

and with not less than 6 months before expiry. If the validity period/expiry date is not stated on the proof of GMP compliance, HSA will consider the document valid for a period of 3 years from date of last inspection or date of issuance of the document. Applicants should refer to section 6.2.2.

It should be noted that diluents used for reconstituting the drug product and are packaged together with the drug product will be considered as part of the final drug product. Thus, manufacturer(s) of the supplied diluent(s) must follow the same requirements applicable to the drug product, e.g. provide proof of GMP compliance.

(C) GMP Conformity Assessment for Overseas Finished Product Manufacturers by HSA

If the drug product is manufactured by a new overseas drug product manufacturing site not previously registered with HSA before 1st April 2004, a GMP Conformity Assessment will be conducted by HSA.

A GMP Conformity Assessment is applicable to each specific manufacturing site, dosage form, manufacturing activities and local applicant company. This also includes contract manufacturers who perform certain manufacturing activities, such

as terminal sterilisation of the drug product, mixing of excipient with drug substance (drug product intermediate), etc.

When applicable, applicants must also submit the application form to request for GMP Evidence Evaluation or for an Overseas GMP Audit with the required documents to the Therapeutic Products Branch (as part of the product registration application) as stipulated in the *Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer*. The relevant GMP Conformity Assessment application form should be completed and submitted as a supporting document in the product registration application. Hardcopy submission is not required.

HSA may request for a GMP Conformity Assessment if deemed necessary, or to request for additional or updated documents as evidence of GMP compliance during the registration process. HSA reserves the right to conduct an audit of any overseas

manufacturer irrespective of the documentary GMP evidence that is approved by HSA or any other PIC/S member authorities, if deemed appropriate.

Submit your GMP Conformity Assessment applications together with your product registration application if you are unsure whether HSA requires assessment of your manufacturing sites. HSA will inform you if the assessment is needed.
Please note that GMP Conformity Assessment application forms submitted without a valid pending product registration application would not be considered.

iv. Drug product manufacturing sites that use parametric release

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a GMP Conformity Assessment is **product specific**. Eligibility criteria for such applications for overseas manufacturing sites are:

a) Country of origin must be a PIC/S country
b) Parametric release is approved by the local authority

If the above criteria are met, then approval letter and recent documentary evidence of approval status (e.g. GMP Certificate) for parametric release issued by the local authority should be provided. The manufacturing site and the product proposed for parametric release should be clearly stated on these documents.

For local manufacturing site that would like to apply for parametric release, applicants are advised to contact HSA prior to submission as pre-approval inspection is required.

j) Patent Declaration (CTD/PRISM 1.12)

A signed and dated patent declaration form is required for each GDA. Applicants should refer to section 3 for information on patent linkage and Appendix 1 – Form 1 for the Patent Declaration Form.

Guiding notes on filling the Patent Declaration form are provided below:

i. Section 1 '*Applicant Particulars*' - state the name and address of the local company.

ii. Section 2 '*Product Particulars*' - state the product name, name and strength of active ingredient and dosage form. All product particulars should be consistent with that stated in the product labels and other relevant documents as submitted in PRISM.

iii. Section 3 '*Application Category*' - declare the patent category (A1, A2, A3, or B) that the application falls under.

iv. Section 4 '*Information for Category A1 Applications*' - applicable if category A1 is selected in Section 3.

v. Section 5 '*Information for Category A2 Applications*' - applicable if category A2 is selected in Section 3. Check the box which is relevant and provide details of the restraining patent in force.

vi. Section 6 '*Information for Category A3 Applications*' - applicable if category A3 is selected in Section 3. Provide details of the restraining patent in force.

vii. Section 7 '*Information for Category B Applications*' - applicable if category B is selected in Section 3. Check the box which is relevant and provide details of the restraining patent in force.

viii. Section 8 '*Declaration*' - the patent declaration must be signed by the person authorised to make the declaration on behalf of the company named in Section 1. The authorised person is ordinarily an officer of the company such as Company Director or Company Secretary as registered with ACRA, or equivalent. Evidence of such authorisation is to be submitted together with the declaration.

Evidence of authorisation for Section 8 can be in the form of:

- An ACRA printout[14] (BizFile) listing the Company Directors/Secretary;
- A resolution of board of directors;
- A resolution of a general meeting of the company; or
- An extract of the relevant portion of the company's articles of association.

Declaration forms must bear the signatures of the authorised person in the company.

NOTE: The applicant should ensure that the information provided in the patent declaration form and the evidence of authorisation are current at the point of application submission.

The patent declaration form needs to be submitted twice – at the time of submitting the application for registration and prior to the issuance of the regulatory decision for registration (upon request by HSA), if the dossier was deemed satisfactory with respect to the product's safety, efficacy and quality aspects.

k) Declaration on Rejection, Withdrawal and Deferral (CTD/PRISM section 1.13)

The document required for this section is a declaration letter issued by the product owner or applicant that states that the application submitted to HSA and the directions of use including indication(s), dosing regimen(s) and patient population(s)

- have not been rejected or withdrawn;

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[14] The required information on the company's business profile should be obtained directly from ACRA's website (BizFile).

- have not been approved via an appeal process; and
- are not pending deferral

by any drug regulatory agency. If any of the above conditions apply to the application, details and reasons must be provided to HSA.

l) Declaration for GDA Verification and Verification-CECA (CTD/PRISM section 1.14)

This section applies only to the verification and verification-CECA evaluation routes.

A declaration letter issued by the product owner/applicant must be provided to state that all quality aspects including composition, manufacturing and quality standards of the drug product are identical to those approved by the chosen reference drug

regulatory agency. However, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements.

If a DMF is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen reference drug regulatory agency.

m) *Registration Status in Other Countries (CTD/PRISM section 1.15)*

The registration status of the product in other countries should be entered into PRISM section 4.9 – refer to Appendix 17 of this document for further details.

Additional details of the product's registration status in other countries may be submitted in PRISM section 7 (Supporting Attachments). The document should be in the format shown in Table 6 in section 15.1 of this guidance document.

n) *Confirmation of Reference Agency's Approval of CMC Aspects (CTD/ PRISM section under Other Supporting Documents)*

For applications submitted under the abridged evaluation route and for which approval was obtained from at least one of HSA's reference agencies not more than 5 years before the date of submission to HSA, a copy of the completed Dossier Clarification Supplement should be submitted in PRISM (refer to Appendix 18 *Confirmation of Quality Dossiers with Reference Agency's Approval* for more information).

18.2 CTD Overview and Summaries

The ICH or ASEAN Quality Overall Summary is to be inserted into Module 2 of the ICH CTD or into Part II, section B of the ACTD. This document can be submitted either in Word or PDF format.

18.3 Quality Documents

The quality documents relate to Module 3 of the ICH CTD or Part II of the ACTD. In addition to the ICH or ACTD technical content requirements, the following explanatory

notes pertain to requirements specific to Singapore:

18.3.1 Body of Data – Drug Substance

The ICH M4Q technical guideline and ACTR provide details on the information to be included in the drug substance sections of an application dossier.

NOTE: If a drug product contains more than one drug substance, the information within Module 3.2.S (ICH CTD) or Part 2.S (ACTD) must be provided in its entirety for each drug substance.

All of the drug substance sections of the CTD – i.e. S1 to S7, are required in the application. Alternatively, applicants may submit either a DMF or CEP in lieu of the entire CTD drug substance sections.

Drug Master File (DMF)

A DMF is a dossier that contains detailed information about specific processes or components used in the manufacturing, processing, and packaging of a drug. A DMF contains confidential information and is submitted solely at the discretion of the DMF holder.

The DMF is reviewed only in conjunction with the specific product registration application it supports. HSA does not issue standalone approval for DMF.

Appendix 11 describes the DMF process and documentary requirements for DMF submission.

Plasma Master File (PMF)

A Plasma Master File (PMF) contains information on the collection and control of source materials, and is required where a human plasma-derived product is used as an excipient. The PMF may be submitted either as a stand-alone document or as part of the application dossier. Appendix 8 describes the PMF data requirements for submission.

If the PMF is a stand-alone document, it should be filed separately from the application dossier for pre-marketing evaluation. The applicant may cross-reference a PMF of a human plasma-derived product that is used in currently registered products, where applicable.

Certificates of Suitability (CEP)

A CEP is a document issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) that certifies the quality of a drug substance in compliance to the Ph. Eur. A CEP may be submitted *in lieu* of the CTD S Section or a DMF.

If reference is made to a CEP, the applicant must submit a copy of the valid CEP, including all annexes, and a copy of the Letter of Access from the CEP holder to authorise the applicant to refer to the CEP in support of their application.

The following additional requirements apply for CEP-based submissions:

(a) If Ph. Eur. standard is claimed for the drug substance, the relevant CTDs should be submitted:
   (i) S.2.1;
   (ii) S.4.1 and S.4.4 from both the drug substance and drug product manufacturers; and
   (iii) S.6 and S.7 should be provided if the re-test period/shelf life is not stated on the CEP.

(b) If other standards are claimed for the drug substance, the relevant CTDs should be submitted:
   (i) S.2.1;
   (ii) S.4.1 to S.4.5 from both drug substance and drug product manufacturers; and
   (iii) S.6 and S.7 should be provided if re-test period/shelf life is not stated on the CEP.

NOTE: HSA reserves the right to request for any additional information about the CEP-certified drug substance if it is deemed appropriate.

If there is a CEP for animal-derived material used in the drug product, the applicant may submit the CEP together with the documents stipulated in Annex 1- section 1.1 of Appendix 9 *Guideline on the Registration of Human Medicinal Products Containing Materials of Animal Origin*.

It is the applicant's responsibility to submit the latest CEP updates, with annexes, as soon as they are available from EDQM.

Control of Drug Substance (CTD section 3.2.S.4)

As the drug product manufacturer is responsible for the quality control of the drug substance that is used in the drug product, information on the control of the drug substance, i.e., 3.2.S.4.1 to 3.2.S.4.5, must be provided from both the drug substance and drug product manufacturers.

Batch analysis data should be provided by the drug substance and drug product manufacturers, and if available, from the same drug substance batches. Analytical results should be provided from a minimum of two batches from each proposed drug substance manufacturer and should be sufficient to support the specification(s) as well as to demonstrate consistency in manufacturing. The batches submitted should preferably be of production scale or at least pilot scale and should include the batch(es) used in the bioequivalence or biowaiver studies (where applicable).

Stability Data of Drug Substance (CTD section 3.2.S.7)

At the time of submission, the minimum stability data required are as follows:

- At least 12 months of long term data and 6 months of accelerated data from at least three primary batches of the drug substance; and
- The batches should be at least of pilot scale and manufactured by a method that

simulates the final commercial process.

Where multiple drug substance manufacturers are proposed for registration, if it can be demonstrated that the submitted data is representative of the proposed sites, it may be acceptable to extrapolate the stability data from one site to the other sites, and stability data from each site may not be required at the point of submission. All the following criteria must be met for the stability data to be considered representative:

- The drug substance is manufactured using the same synthetic route and process. Scientific justification should be provided to demonstrate equivalence between the sites if differences exist;
- The drug substance is controlled by the same set of specifications;
- The drug substance is packaged in the same container closure system; and
- The drug substance is of comparable quality to the drug substance used in the stability batches.

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

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

Stability data from a site not proposed for registration may also be provided as supporting data.

18.3.2 Body of Data – Drug Product

The ICH M4Q technical guideline and ACTR also provide details on the information to be included in the drug product sections of an application dossier. For drug product intermediates and diluents, separate drug product sections should be submitted.

Pharmaceutical Development (CTD section 3.2.P.2)

Detailed descriptions and discussions, with relevant data, which relate to the development, and hence quality, of the drug product should be provided in the

relevant dossier sections. Examples include, but are not limited to:

- polymorphism, solubility or particle size of the drug substance and its effect on the product's quality;
- a description and the results of the formulation development;
- the rationale for the choice of dissolution method and a discussion of its discriminatory nature, with data;
- compatibility of the container closure system with the product or preservative efficacy test results; and
- optimisation of the manufacturing process, with data.

Process Validation (CTD section 3.2.P.3.5)

The description, documentation and complete results of the validation studies on the manufacturing process should be provided in the dossier in this section. Particular care should be taken to ensure that the documents include critical processes for the manufacturing process: for example, blend uniformity validation for oral dosage forms and terminal sterilisation or aseptic filling for sterile products. Applicants should refer to the ASEAN Guidelines on Submission of Manufacturing Process Validation Data for Drug Registration and the ASEAN Guideline on Process Validation Q&A for the minimum data requirements for process validation. Other relevant international guidelines may also be referred to as appropriate.

Where ranges of batch sizes are proposed, it should be demonstrated that variations in batch size would not adversely alter the characteristics of the finished product.

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a more detailed discussion with supporting data on the process validation of the specific product in the proposed pack size or fill volume should be provided. In addition, risk assessment for parametric release should be based on prior knowledge, consistency of performance of the steriliser, historical batch analysis data, risk of loading pattern/ container/ contamination from the environment to product sterility, re-processing plan and etc. A detailed discussion on the control strategy should also be provided. This includes but is not limited to, a tabulation of all validated critical process parameters and loading patterns, a description of the process

and requirements for the release/rejection of a batch, bioburden monitoring and control program, the segregation of sterile products from non-sterile products and the routine maintenance/re-validation program for the steriliser.

Control of Excipients (CTD section 3.2.P.4)

This section refers to all excipients used in the drug product formulation, including ingredients used in capsule shells and film coatings. The specifications and analytical method(s) for each excipient should be described, including the validation of any in-house test method(s) if applicable.

Information on proprietary ingredients such as flavourings, colourants, coatings, perfumes and/or printing inks should be as detailed as possible. Applicants are advised not to use internal codes but instead to give commercial names for such ingredients. In cases where the formula of the proprietary ingredient is confidential, only the total quantity of the proprietary ingredient present in the final product needs to be captured in PRISM. The formula of the proprietary ingredient should then be provided by the proprietary ingredient manufacturer directly to HSA. A declaration letter from the proprietary ingredient manufacturer should also be provided,

indicating that they will inform HSA (via email to HSA_TP_Enquiry@hsa.gov.sg) should there be any change in the formulation of the proprietary ingredient.

A CoA for an excipient may be submitted *in lieu* of the excipient's specifications. If the standard claimed for an excipient is an officially recognised compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognised compendial monograph.

For excipients derived from human plasma, applicants should refer to the Appendix 8 on the data requirements.

For excipients derived from animal sources, applicants should refer to Appendix 9 for more information. The checklist found in Annex 1 of Appendix 9 serves as a guide to these documentary requirements for submission. Applicants should note that the

completed checklist in Annex 1 is to be submitted in CTD section 3.2.P.4.5 with the supporting documents submitted in ICH CTD section 3.2.A.2 or ACTD section Q.A.2.

For milk and certain milk derivatives such as lactose, as these excipients are generally considered non-infectious, a declaration from the supplier of the excipient stating that the milk is from healthy cows fit for human consumption and that no other potentially infectious ruminant-derived materials were used in the manufacturing process would be sufficient. This declaration is to be submitted in CTD section 3.2.P.4.5.

Control of Drug Product (CTD section 3.2.P.5)

The drug product's release and shelf-life specifications should be declared in section 3.2.P.5.1.

For the parametric release of a terminally sterilised product, the release specification and certificate of analysis should indicate that parametric release is the method used for batch release. Additionally, sterility of the product is required

to be demonstrated in the stability studies even if approval for parametric release has been granted.

Descriptions of all test methods with complete validation results of all in-house methods should be included in sections 3.2.P.5.2 and 3.2.P.5.3.

Descriptions (including size, origin and use) and test results of all relevant batches (e.g. pre-clinical, clinical, pilot and production batches) used to establish the specification and evaluate the consistency in manufacturing should be provided.

Batch analysis data and/or CoAs from three batches of the drug product should be provided in section 3.2.P.5.4.

The justification of the specifications (section 3.2.P.5.6) should be based on scientific knowledge and data collected during product development.

Container Closure System (CTD section 3.2.P.7)

Technical information about each component of the container closure system(s) used for the drug product should be included in the dossier. The technical information to be included in the dossier includes, but is not limited to, schematic diagrams, descriptions, specifications, analytical methods, CoAs and declarations of compliance to international standards.

Stability Data of Drug Product (CTD section 3.2.P.8)

Since 01 April 2014, HSA has implemented the ASEAN Guideline on Stability Study of Drug Product, a guideline on the conduct of stability studies for drug products for the ASEAN region. Applicants should familiarise themselves with this guideline prior to submission.

At the time of submission of the application, the minimum stability data required are as follows:

- For critical dosage forms or unstable drug substances, at least 12 months of data under long term storage conditions and 6 months of data under accelerated storage conditions on at least three primary batches of the drug product
- For conventional dosage forms and stable drug substances, at least 6 months of data under long term storage conditions and 6 months of data under accelerated storage conditions on at least two primary batches of the drug product
- The primary batches should be at least of pilot scale, manufactured by the same manufacturing process and packaged in the same container closure system as that proposed for Singapore.

Where multiple drug product manufacturers are proposed for registration, if it can be demonstrated that the submitted data is representative of the proposed sites, it may be acceptable to extrapolate the stability data from one site to the other sites, and stability data from each site may not be required at the point of submission. All the following criteria must be met for the stability data to be considered representative:

- The drug product is manufactured using the same formulation;
- The drug product is manufactured using the same manufacturing process, including equipment type, process parameters and in-process tests. Scientific justification should be provided to demonstrate equivalence between the sites if differences

exist.

- The drug product is controlled by the same set of specifications;
- The drug product is packaged in the same container closure system; and
- The drug product is of comparable quality to the drug product used in the stability batches.

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

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

Stability data from a site not proposed for registration may also be provided as supporting data.

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

If multiple primary packaging sites for the same container closure system are proposed for registration, transport validation of the bulk product to the other proposed primary packaging site(s) is required, unless otherwise justified.

Product Interchangeability – Bioequivalence (CTD section 3.2.P.9.1)

Since 01 April 2004, *in vivo* bioequivalence (BE) data are required for Prescription Only Medicines (POM) in oral solid dosage forms.

GDA-2 applications will also require BE data if the application is for a POM in an oral solid dosage form, even if the first strength (GDA-1) application was submitted to HSA before 01 April 2004.

Applicants should be familiar with Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications*.

Applicants should ensure that the submitted BE study is complete, including all appendices and data, according to the relevant guidelines. Examples of information to be included in the report are:

(a) Signature of the Principal Investigator to attest the authenticity of the report;

(b) Audit certificate(s);

(c) BE site inspection report from a national regulatory agency or WHO, if available;

(d) Approval letter(s) from the Institutional Review Board/Independent Ethics Committee and the appropriate drug regulatory agency;

(e) Information about the reference and test products, such as the product name, strength, dosage form, batch number, manufacturing site, batch size of the test product, etc.;

(f) Certificates of Analysis of the reference and test products used in the BE study, including the batch size of the test product and manufacturing/expiry date of both products (where applicable);

(g) Bioanalytical study report and description of the bioanalytical method validation; and

(h) A signed statement confirming that the test product used in the BE study is the same formulation and is manufactured by the same process as that submitted for registration.

Applicants should also provide a copy of the product labels (e.g. outer carton, product insert) of the reference product used in the BE study for verification purposes.

It is highly recommended that the generic or test product used in the BE study be the same as the drug product submitted for registration in Singapore. If this cannot be fulfilled, then applicants should refer to Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications* for more information regarding eligibility and documentary requirements.

In instances when the reference product used in the BE study is not the Singapore

reference product, if the criteria listed in section 2 of Appendix 10 are fulfilled, then the following additional documents must be submitted in support of the application:

(a) A comparative table that lists the qualitative composition of both the BE and Singapore reference products;

(b) Comparative dissolution profiles between the BE and Singapore reference products; and

(c) Comparative dissolution profiles between the BE test and Singapore reference products.

For BCS-based biowaiver applications, justifications and relevant supporting documents should also be included under section 3.2.P.9.

Product Interchangeability – Comparative Dissolution Profile (CTD section 3.2.P.9.2)

Comparative dissolution profile data between the generic product and the Singapore reference product should be submitted in support of the following GDAs:

- POMs (immediate and modified release oral solid dosage forms); and
- P or GSL medicines (modified release oral solid dosage forms only).

For POMs supported by BE study data, the following additional comparative dissolution profile data should be submitted (applicable only when the BE reference product is not the Singapore reference product):

(a) Between the reference and test products used in the BE study; and

(b) Between the BE and Singapore reference products.

Applicants should also provide a copy of the product labels (e.g. outer carton, product insert) of the BE and Singapore reference products used in the comparative dissolution profile testing for verification purposes.

When a generic product is to be marketed in several strengths, applicants should refer to Section 3 of Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications* for more information on comparative dissolution profile testing requirements.

For BCS-based biowaiver applications, justifications and relevant supporting documents should also be included under section 3.2.P.9.

HSA reserves the right to request for any additional information required to determine the product interchangeability of the generic product to the Singapore reference product.

18.4 Non-clinical and Clinical Documents

Generally, non-clinical (animal) and clinical (human) data are not required to be included in a GDA. Instead, the data demonstrating the generic product's interchangeability with the Singapore reference product, e.g. *in vivo* BE and comparative dissolution studies, are required for submission.

Documentary requirements for establishing product interchangeability (including BCS-based biowaiver applications) can be found in Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications*.

RMP materials for the generic product must be provided if they are currently required for the SRP (copies of SRP RMP materials can be found here). Otherwise, where required, HSA may request for RMPs to be submitted on a case-by-case basis for GDAs, following the evaluation of the safety profile of the product described in the product application. Guidance on RMP submission requirements can be found here.

18.5 Documentary Requirements for Each Evaluation Route

18.5.1 Abridged Evaluation Route

All aspects of the product's quality which include, but are not limited to, the formulation, site(s) of manufacture, release and shelf life specifications and primary packaging should be the same as that approved by the drug regulatory agency that issued the proof of approval.

The technical documents required include:

- complete quality documents for both the drug substance and drug product; and
- BE studies or justifications for applying a biowaiver, where applicable.

18.5.2 Verification and Verification-CECA Evaluation Routes

The complete assessment report and other relevant supporting documents from the chosen reference drug regulatory agency must be submitted, as tabulated below. The assessment reports must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, quality and clinical reviews, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable.

Applications submitted to HSA without the unredacted/ unedited reports from the chosen reference agency will not be accepted for evaluation via the verification route and rejected at screening.

Reference agency	Documentary requirements
EMA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
FDA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Health Canada	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
MHRA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
Swissmedic	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Reference agency	**Documentary requirements**
TGA	• Complete Clinical and Quality# assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

If the drug substance section is submitted to the chosen reference agency as a DMF, the complete assessment report of the DMF, including assessment on the Question & Answer documents between the DMF Holder & Agency and all annexes should be provided. Assessment reports, approval letters and/or documents pertaining to post-

approval DMF updates should also be submitted, if applicable.

Administrative documents specific to the verification and verification-CECA evaluation routes that are required at the time of submission include:

(a) Section 1.4.3/1.4.4 – the proposed PI or PIL should be aligned to the currently-registered Singapore reference product PI or PIL;

(b) Section 1.9 – Official approval letter from the chosen reference drug regulatory agency that certify the registration status of the drug product;

(c) Section 1.13 – Official letter issued by the applicant or product owner declaring that the application submitted to HSA or similar direction(s) of use, indication(s), dosing regimen(s) and/or patient group(s) have not been rejected, withdrawn, approved via appeal process[15], or pending deferral[16] by any drug regulatory agency, with reasons in each case if applicable;

(d) Section 1.14 – Official letter issued by the applicant or product owner declaring that the DMF provided is identical to that submitted to the chosen reference drug regulatory agency, if applicable; and

(e) Section 1.14 – Official letter from the applicant or product owner declaring that all quality aspects including the composition, manufacturing and quality standards of the drug product in Singapore are identical to that approved by the chosen reference drug regulatory agency.

[15] Approval via appeal process includes, but is not limited to, the following: approval following negative opinion, approval following rejection, approval following non-approvable etc.

[16] Deferral includes, but is not limited to, the following: non-approvable, approvable, conditional approval, conditional marketing authorisation, notice of compliance with conditions etc.

Specifically for the verification-CECA evaluation route, a valid GMP certificate and the latest GMP inspection report as issued by the reference drug regulatory agency must be submitted.

The technical documents required include:

- Quality documents:

– From Sponsor:

  - Complete documents for both drug substance and drug product (ICH Module 3/ACTD Part II) as initially submitted to the chosen reference drug regulatory agency;
  - Complete assessment reports including assessment on the Question & Answer documents between the Sponsor and chosen reference drug regulatory agency, and other relevant supporting documents from the chosen reference drug regulatory agency;
  - Questions and answers between the chosen reference drug regulatory agency and Sponsor – the answers should include supporting documents used in response to the questions;
  - All post-approval variations (if applicable) approved by the chosen reference drug regulatory agency up to the time of submission to HSA, including the application letter for the variation, supporting documents for the variation, assessment report for the variation, questions and answers between the chosen reference drug regulatory agency and Sponsor, and the approval letter for the variation from the chosen reference drug regulatory agency; and
  - Relevant documents required by HSA which have not been submitted to the chosen reference drug regulatory agency, e.g. stability studies in accordance to ASEAN Stability Guidelines, comparative dissolution studies, etc.

– From DMF Holder, if applicable:

  - The initial open and closed parts of the DMF submitted to the chosen reference drug regulatory agency should be provided to HSA, together with a copy of the Letter of Access;
  - Complete DMF assessment report including assessment on the Question & Answer documents between the DMF holder and the chosen reference drug regulatory agency, and other relevant supporting documents from the chosen reference drug regulatory agency;
  - Questions and answers between the chosen reference drug regulatory

agency and DMF Holder – the answers should include supporting documents used in response to the questions; and

- All post-approval DMF updates (if applicable) approved by the chosen reference drug regulatory agency up to the time of submission to HSA, including the application letter for the DMF update, supporting documents for the DMF update, assessment report for the DMF updates, questions and answers between the chosen reference drug regulatory agency and Sponsor, and the approval letter for the DMF update from the reference drug regulatory agency.

- Clinical documents, such as BE studies or justification for biowaiver, as initially submitted to the chosen reference drug regulatory agency with all questions and answers, including supporting documents, between the reference drug regulatory agency and Sponsor; and
- Any additional documents to demonstrate product interchangeability with the Singapore reference product as described in section 18.3.2 *Body of Data – Drug Product*, where applicable.

Applicants are reminded that generic products applied through the verification and verification-CECA evaluation routes must still demonstrate product interchangeability to the Singapore reference product.

Data submitted to HSA must be the same as the data package submitted to the reference drug regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application, but may also lead to re-routing of the dossier

to the abridged evaluation route if significant undisclosed differences are discovered.

In addition, the BE test product must be manufactured at the same drug substance and drug product manufacturing sites by the same manufacturing processes as submitted in the GDA application dossier.

18.6 Documentary Requirements for Second Brand Registration of Chemical

18.6.1 Definition

A second brand product refers to a chemical drug product which is identical to a registered (original) drug product in all aspects of quality, safety and efficacy at the time of its submission for market authorisation and is submitted by the same product registrant of the original drug product.

18.6.2 Documentary Requirements

18.6.2.1 Administrative

A complete set of administrative documents as per *section 18.1 Administrative documents* has to be submitted. In addition, a declaration that the second brand product is identical to the original drug product in terms of quality, safety and efficacy is required.

18.6.2.2 Quality

A complete set of quality documents as per sections 18.2 *CTD overview and summaries* and 18.3 *Quality documents* has to be submitted. In addition, a comparative table of each CTD section between the second brand and original drug products is required and all differences between these two dossiers should be stated. The impact of these differences (if any) should generally be justified by the approval or submission of minor variation application - MIV (to state application number) to the original product dossier (see Chapter H – Minor Variation (MIV) Application Submission).

During the evaluation stage, if MIV has not been submitted for these differences to the original drug product dossier, then a MIV-2 application will be requested to update the original product dossier. A stop-clock will be imposed on the second brand product application until the update is completed. The product registrant is advised to file a MIV for the update of these differences prior to submission to avoid any delay in the review process of the second brand product.

Submission of BE studies are generally not required for second brand product applications if the original product was granted marketing authorisation based on the

evaluation of the product's quality, safety and efficacy. However if the original product was registered as a generic drug product before 01 April 2004, prior to the implementation of BE requirements, the current BE requirements will apply to the second brand product.

CHAPTER E BIOSIMILAR PRODUCT APPLICATION SUBMISSION

This chapter applies to new drug applications for biosimilar products.

A biosimilar product is a biological therapeutic product demonstrated to be similar, in physicochemical characteristics, biological activity, safety and efficacy to an existing registered biological product.

This chapter serves to provide guidance on the regulatory considerations of a biosimilar product, as well as the procedures and requirements for registration of a biosimilar product. Applicants are encouraged to refer to the relevant international guidelines e.g. EMA CHMP and WHO on biosimilar products. Alternative proposals to the recommended approach and requirements should be discussed with HSA and agreed upon in advance. HSA may consider such alternative proposals if substantiated by adequate scientific evidence and justifications, and may request for information or specify conditions not described in this document if deemed necessary to adequately assess the safety, efficacy and quality of the product.

19 APPLICATION TYPES

Biosimilar products are eligible for the NDA-2 and NDA-3 application types. When selecting the Product Type in PRISM section 3.2, select '*Biological Drug*'.

NDA New Drug Application

NDA-1: **Not** applicable to biosimilar products.

NDA-2: For the first strength of a biosimilar product with the same dosage form, route of administration and presentation as the SRBP.

NDA-3: For subsequent strength(s) of a biosimilar product that has been registered or has been submitted as an NDA-2. The product name, dosage form, presentation, indication, dosing regimen and patient population should be the same as that for the NDA-2.

19.1 Biosimilar Product

A biosimilar product is intended to be similar in terms of quality, safety and efficacy to a registered biological product.

Due to the complexity of biological molecules which pose challenges in characterisation to demonstrate the similarity of the products, the registration of a biosimilar product should be based demonstration of similarity to the SRBP in quality, non-clinical and clinical parameters via comparability exercise.

Demonstration of similarity of a biosimilar product to the SRBP in terms of quality is a prerequisite for determining the non-clinical and clinical data set required for registration. Significant differences between the biosimilar product and the SRBP detected during the comparability exercise would be an indication that the products are not similar and more extensive non-clinical and clinical data may be required to support the application for registration. If relevant differences are found in the quality, non-clinical, or clinical data, the product is unlikely to qualify as a biosimilar product.

Comparability exercises to demonstrate similarity are more likely to be applied to highly purified products, which can be thoroughly characterised (such as some biotechnology-derived therapeutic products). Vaccines, blood or plasma-derived products are not eligible for registration via the biosimilar pathway.

19.2 Singapore Reference Biological Product

The SRBP must be a currently registered therapeutic biological product registered in Singapore. A biosimilar product cannot be used as a reference product. The conditions of use for the biosimilar product must fall within the directions for use including

indication(s), dosing regimen(s) and patient group(s) of the SRBP. A biological product with no suitable SRBP will not qualify for registration as a biosimilar product in Singapore.

The active ingredient of a biosimilar product must be similar, in molecular and biological terms, to the active ingredient of the SRBP. The pharmaceutical form, strength, and the route of administration of the biosimilar product should be the same as that of the SRBP. Any deviation from or differences between the biosimilar product and the SRBP will have to be justified by appropriate studies. Applicants are advised to search Register of Therapeutic Products to identify the SRBP.

The SRBP should be used throughout the comparability assessment for quality, safety and efficacy studies during the development of a biosimilar product in order to allow for scientifically relevant and meaningful comparisons between the biosimilar and the SRBP.

The comparability exercise for a biosimilar product is designed to show that the biosimilar product has highly similar quality attributes when compared to the SRBP. If the comparative studies are performed with a reference product from a non- Singapore registered manufacturing source, the manufacturer needs to demonstrate that the reference product used is comparable to the SRBP and hence suitable to support the application for marketing authorisation of a biosimilar product by providing an additional bridging study. The type of bridging data needed will typically include data from analytical studies (e.g. structural and functional data) that compare the proposed biosimilar product, the SRBP and the reference product used in the comparability studies, and may also include clinical PK and/or PD bridging studies data for all three products. All comparisons should meet the target acceptance criteria for analytical and PK/PD similarity. A final determination regarding the adequacy of the scientific justification and bridging data will be made during the evaluation of the application.

20 EVALUATION ROUTES

A biosimilar product may be submitted via the abridged or verification evaluation route.

20.1 Abridged Evaluation Route

Abridged evaluation applies to a product that has been approved by at least one of the following reference drug regulatory agencies: EMA[17], FDA, Health Canada, MHRA[18], Swissmedic and TGA at the time of submission.

20.2 Verification Evaluation Route

Therapeutic products with similar indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use that have been approved by at least two of HSA's reference drug regulatory agencies may be eligible for submission via the verification evaluation route. HSA's reference drug regulatory agencies are:

- EMA via the Centralised Procedure
- FDA
- Health Canada
- MHRA via
  - the national procedure, or
  - as the RMS via the MRP or DCP on or prior to 31 January 2020
- Swissmedic
- TGA

However, approval by these reference drug regulatory agencies does not oblige HSA to approve the application. HSA may also re-categorise applications to other evaluation routes if the applications did not meet the eligibility criteria and/or submission requirements.

The applicant must confirm one of the reference drug regulatory agencies as the primary reference agency. The chosen primary reference agency is defined as the

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[17] For products approved via the Centralised Procedure
[18] For products approved via the national procedure or where MHRA acted as the RMS for the MRP or DCP on or prior to 31 January 2020

reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted.

The pre-requisite requirements for the verification route include:

- The product has received full marketing approval by the reference agencies following a complete independent scientific assessment;
- The application must be submitted to HSA within three years from the date of approval by the chosen primary reference agency;
- A declaration letter issued by the product owner/applicant must be provided stating that all quality aspects including the composition, manufacturing and quality standards of the drug product are identical to those approved by the chosen primary reference agency. However, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements;
- The product does not need independent assessment by HSA to contextualise the benefit-risk profile due to local disease epidemiology, medical practice and/or public health considerations. Examples of products that may require such contextualised assessment are anti-infectives, vaccines etc; and
- The product and its intended use – i.e. indication(s), dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, or approved via appeal process or are not pending deferral by a drug regulatory agency for safety and/or efficacy reasons.

20.2.1 NDA-3 Applications

For the NDA-3 application type, the verification evaluation route may be applied to the registration of subsequent strengths of a currently-registered product in Singapore. To qualify for the verification evaluation route for an NDA-3 application:

- if the product has been evaluated and approved by at least one of HSA's reference drug regulatory agencies, then the NDA-3 must be submitted within two years from the date of approval by that reference drug regulatory agency; or

- if the product has been evaluated and approved by at least two of HSA's reference drug regulatory agencies, then the NDA-3 must be submitted within three years

from the date of approval by the chosen primary reference agency.

All other eligibility criteria for the verification evaluation route as stated in section 20.2 above will apply to NDA-3 applications except for the following:

- The proposed indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use must be identical to the corresponding approved product; and
- The proposed PI/PIL should also be consistent with that currently approved for the corresponding NDA-2 product.

21 DOCUMENTARY REQUIREMENTS

Refer to Documentary Requirements in section 6.2 for submission requirements.

Table 9 outlines the CTD Modules/Parts required for NDAs submitted for registration of a biosimilar product.

Table 9 Dossier Submission Requirements for Biosimilar Products

Documents	**Location in**		**Module/Part required for**
	ICH CTD	**ACTD**	**Biosimilar product (all evaluation routes)**
Administrative Documents	Module 1	Part I	Yes
Common Technical Document Overview and Summaries	Module 2	*Incorporated in Parts II, III and IV*	Yes
Quality documents	Module 3	Part II	Complete quality module including comparability studies

Non-clinical documents	Module 4	Part III	Complete non-clinical module* including comparability studies
Clinical documents	Module 5	Part IV	Complete clinical module* including comparability studies

*The non-clinical and clinical dataset may be reduced based on criteria under section 21.4

21.1 Administrative Documents

The administrative documents of the application dossier for biosimilar products is the same as that described in section 15.1 *Administrative Documents* in Chapter C *New Drug Application Submission*.

21.2 CTD Overviews and Summaries

The CTD overviews and summaries are the same as that described in section 15.2 in Chapter C *New Drug Application Submission*.

21.3 Quality Documents

The complete quality dossier as per Module 3 of the ICH CTD or Part 2 of the ACTD for a new biological product must be submitted.

The SRBP used in the biosimilar product comparability exercise at the quality level must be clearly identified (e.g. brand name, pharmaceutical form, cell substrate, formulation, strength, manufacturing site of the reference medicinal product, number of batches, lot number, age of batches used).

Comparability data between the biosimilar product and the SRBP (in terms of quality) must be included in the quality dossier. The extent of the comparability studies and the assessment criteria should take into consideration:

- the complexity of the molecular structure;

- the capability of the methods used to demonstrate comparability; and
- their impact on quality, safety and efficacy.

For the development of a biosimilar product, the quality target product profile (QTPP) should be established based on the data obtained from extensive characterisation of the SRBP in order to relate the biosimilar product to the SRBP in terms of molecular characteristics and quality attributes. This QTPP should be considered as a development tool through which some target ranges may evolve during development, as further information on the SRBP becomes available.

For robust comparability analysis, a representative quality profile of the SRBP should be generated from multiple different batches of the SRBP when establishing the QTPP for the biosimilar product. Quantitative ranges should be established for the biosimilar comparability exercise based primarily on the measured quality attribute ranges of the SRBP and should not be wider than the range of variability of the representative SRBP batches, unless otherwise justified.

An extensive comparability exercise is essential to demonstrate that the biosimilar product has a highly similar quality profile when compared to the SRBP. The manufacturer must carefully design the comparability exercise based upon full knowledge of the molecular structure and its relevance to the mode of action. The result is a series of physicochemical tests, along or in combination with such biological tests as *in vitro* and *in vivo* bioassays, and receptor binding studies. These analyses should include side-by-side comparative studies to demonstrate the similarities and differences between the biosimilar product and the SRBP. Where comparability testing cannot establish similarity or where differences arise, the differences detected in the quality attributes will have to be appropriately justified with respect to their potential impact on safety and efficacy.

Extensive characterisation studies should be applied to the biosimilar and SRBP in parallel, to demonstrate with a high level of assurance that the quality of the biosimilar product is comparable to the SRBP. Methods used in the characterisation studies form an integral part of the quality data package. The selected methods should be

appropriately qualified for the purpose of comparability and demonstrate that the methods are of acceptable sensitivity and capable to detect slight

differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity).

For process changes that may occur during the development of the biosimilar product, comparability exercise(s) for such process changes should be clearly identified and addressed separately from the comparability exercise performed against the SRBP. It is strongly recommended to generate the required quality, safety and efficacy data using the test product manufactured with the final manufacturing process (representing the quality profile of the batches to be commercialised) for the demonstration of biosimilarity against the SRBP.

21.4 Non-clinical and Clinical Documents

Non-clinical and clinical data generated with the biosimilar product are required.

The amount of non-clinical and clinical data required will depend on:

- the product or class of products;
- the extent of characterisation which is possible to undertake when using state- of-the-art analytical methods;
- observed or potential differences between the biosimilar product and the SRBP; and
- the clinical experience with the product class.

A case-by-case approach is needed for each class of products.

Guidance on risk management plan submission can be found here.

A statement that the product is a biosimilar medicinal product should be included in the package insert.

21.4.1 Non-clinical Documentation

Before initiating clinical development, non-clinical studies should be performed. These studies should be comparative in nature and should be designed to detect differences in response between the biosimilar product and the SRBP. Available

product specific guidelines and relevant international guidelines should be referred to in the design of an appropriate non-clinical study programme.

The requirements for the non-clinical documentation include:

- *In vitro* studies: Assays such as receptor-binding studies or cell-based assays should normally be undertaken to establish comparability in reactivity and the likely causative factor(s) if comparability cannot be established; and
- Animal studies should be performed to investigate the pharmacodynamic effects/ activities relevant to the clinical application, non-clinical toxicity as determined in at least one repeat dose toxicity study, including toxicokinetic measurements, and specific safety concerns.

Generally, other toxicological studies to investigated safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity are not required for biosimilar products, unless the observed differences between the biosimilar product and SRBP warrants further study.

21.4.2 Clinical Documentation

The requirements for clinical data will depend on the existing knowledge of the SRBP and the claimed therapeutic indication(s). In addition to international guidelines on biosimilar products, relevant disease specific guidelines should be referred to in the design of an appropriate clinical study programme.

The clinical data for the comparability study should be generated with the test product produced with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised. Any deviation from this is to be justified and supported by adequate bridging data. The type of bridging data needed will typically include comparability data from analytical studies (e.g. structural and

functional data) and may also include clinical PK and/or PD comparability data.

The clinical comparability exercise should begin with PK and PD studies followed by clinical efficacy and safety studies. It is a prerequisite to perform comparative PK

studies designed to demonstrate clinical comparability between the biosimilar product and the SRBP with respect to the key PK parameters. PD parameters are to be studied whenever feasible and the PD markers should be selected based on their clinical relevance.

Generally, comparative clinical studies are required for the demonstration of clinical comparability. In certain cases, comparative PK/PD studies between the biosimilar product and the SRBP may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

- The PK profile of the SRBP is well characterised;
- There is sufficient knowledge of the PD properties of the SRBP, including the binding to its target receptor(s) and intrinsic activity. There may be instances where the mechanism of action of the biological product is disease-specific. A relevant PD endpoint can be used when it is an established surrogate of efficacy or when it can be linked to the mechanism of action of the product; and
- The relationship between dose/exposure and response/efficacy of the SRBP is sufficiently characterised.

For comparative clinical studies to demonstrate clinical comparability between the biosimilar product and the SRBP, clinical comparability margins should be pre-specified and adequately justified. The most sensitive clinical model should be used to detect potential differences between the biosimilar product and the SRBP.

In cases where the SRBP has more than one indication, the efficacy and safety of the biosimilar product has to be justified, or demonstrated separately for each of the claimed indications. In certain instances, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the SRBP. Justification of extrapolation to other indications will depend on various factors, which may include the sensitivity of the clinical study population, clinical experience, available literature

data, mechanisms of action, target receptors, pattern of molecular signalling upon binding to the receptor, PK in different patient populations, PD parameters, patient-related factors, etc. Possible safety issues in different subpopulations should also be addressed.

Immunogenicity

Immunogenic responses may develop in patients who are treated with biological products, including biosimilars. The development of antibodies in some instances is a benign effect causing few, if any, undesirable symptoms in patients receiving therapy. On the other hand, the induced antibodies may be associated with undesirable consequences, which manifest themselves as mild to severe anaphylactoid reactions. Efficacy may also be diminished by the presence of neutralising antibodies or binding antibodies, which may affect PK. Therefore, the immunogenicity of a biosimilar product must be investigated.

Animal studies may not be able to predict immunogenicity of a biological product, particularly the more complex proteins as immunogenic response is species-dependent. The assessment of immunogenicity requires an optimal antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and PK or PD, and the impact of antibodies on clinical safety and efficacy. It is also important to consider the risk of immunogenicity in different therapeutic indications separately.

The extent of independent testing needed depends on various factors such as the indication, whether the product is to be administered chronically, the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule.

21.5 Documentary Requirements for Each Evaluation Route

21.5.1 Abridged Evaluation Route

The technical documents required include:

- complete quality documents for both drug substance and drug product including

comparability studies;

- non-clinical documents including comparability studies; and
- clinical documents including comparability studies

21.5.2 Verification Evaluation Route

The complete assessment report and other relevant supporting documents from the chosen primary reference agency must be submitted, as tabulated below. The assessment reports from the primary reference agency must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, quality, non-clinical and clinical reviews, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable.

Applications submitted to HSA without the unredacted/ unedited reports from the primary reference agency will not be accepted for evaluation via the verification route and rejected at screening.

Primary reference agency	**Documentary requirements**
EMA	• Complete Clinical, Non-clinical and Quality assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
FDA	• Complete Clinical, Non-clinical and Quality assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Primary reference agency	Documentary requirements
Health Canada	• Complete Clinical, Non-clinical and Quality assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
MHRA	• Complete Clinical, Non-clinical and Quality assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
Swissmedic	• Complete Clinical, Non-clinical and Quality assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable
TGA	• Complete Clinical, Non-clinical and Quality assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Administrative documents specific to the verification evaluation route that are required at the time of submission include:

(e) Section 1.9 – Official approval letters, or equivalent documents, from the relevant reference drug regulatory agencies that certify the registration status of the drug product;

(f) Section 1.13 – Official letter declaring that the application submitted to HSA or similar direction(s) of use, indication(s), dosing regimen(s) and/or patient group(s) have not been rejected, withdrawn, approved via appeal process[19], or pending deferral[20] by any drug regulatory agency, with reasons in each case if applicable; and

(g) Section 1.14 – Official letter from the applicant or product owner declaring that all quality aspects including the composition, manufacturing and quality standards of the drug product in Singapore are identical to that approved by the primary reference drug regulatory agency.

The technical documents required include:

- Quality documents:
  - From Sponsor:
    - Complete documents for both drug substance and drug product (ICH Module 3/ACTD Part II) as initially submitted to the primary reference agency;
    - Complete assessment reports including assessment on the Question & Answer documents between the Sponsor and primary reference agency, and other relevant supporting documents from the primary reference agency;
    - Questions and answers between the primary reference agency and Sponsor – the answers should include the supporting documents used in response to the questions;
    - All post-approval variations (if applicable) approved by the primary reference agency up to the time of submission to HSA, including the application letter for the variation, supporting documents for the variation, assessment report for the variation, questions and answers

[19] Approval via appeal process includes, but is not limited to, the following: approval following negative opinion, approval following rejection, approval following non-approvable etc.

[20] Deferral includes, but is not limited to, the following: non-approvable, approvable, conditional approval, conditional marketing authorisation, notice of compliance with conditions etc.

between the primary reference agency and Sponsor and the approval letter for the variation from the primary reference agency; and

- Relevant documents required by HSA which have not been submitted to the primary reference agency, e.g. stability studies in accordance to ASEAN Stability Guidelines.

- Non-clinical documents, assessment report from the primary refence agency, including assessment on the Question and Answer documents between the Sponsor and Agency, and other relevant supporting documents from the primary reference agency; and
- Clinical documents, assessment report from the primary reference agency, including assessment on the Question and Answer documents between the Sponsor and Agency, and other relevant supporting documents from the primary reference agency.

All of the data submitted to HSA must be the same as the data package submitted to the reference drug regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application, but may also lead to re-routing of the dossier to the abridged evaluation route if significant undisclosed differences are discovered.

CHAPTER F POST-APPROVAL PROCESS

Changes to a product registration throughout its life cycle must be submitted to HSA via a variation application. These include administrative/editorial, quality and clinical/non-clinical changes. In general, once the application has been approved/processed, the changes should be implemented by the next importation, or when logistically feasible.

22 APPLICATION TYPES

There are two types of variation applications – major variation applications (MAV) and minor variation applications (MIV).

MAV	Major Variation application for an existing registered product
MAV-1:	Any variation to the approved indication(s), route(s) of administration, dosing regimen(s), patient group(s), and/or inclusion of clinical information extending the usage of the product (e.g. clinical trial information related to an unapproved indication, dosing regimen and/or patient population; additional bacterial strains with clinical (*in vivo)* data to expand the indication(s) for antimicrobial products; additional viral serotypes/genotypes to expand the indication(s) for antiviral products, etc.).
MAV-2:	A change in the current approved forensic classification, also known as reclassification.
MIV	Minor Variation application for an existing registered product
MIV-1	A minor variation that • Is specified under Part A: Checklist on Dossier Requirements for MIV-1 variations of Appendix 13 (Chemicals) or Appendix 14 (Biologics). • Requires prior approval before the change(s) can be

implemented.

MIV-2 (Notification)	A minor variation that • Is specified under Part B: Checklist on Dossier Requirements for MIV-2 (Notification) Variation of Appendix 13 (Chemicals) or Appendix 14 (Biologics); • May be implemented within 40 days upon application submission if there are no objections raised by HSA.
MIV-2 (Do-and-Tell)	A minor variation that • Is specified under Part C: Checklist on Dossier Requirements for MIV-2 (Do-and-Tell) Variation of Appendix 13 (Chemicals) or Appendix 14 (Biologics); • Does not require prior approval, but must be submitted to HSA within 6 months following implementation of the specified changes. [Refer to Chapter H, 27.2.2 for more information]

HSA may re-categorise the application type if appropriate (e.g. MIV to MAV-1, MIV- 2 to MIV-1, or *vice versa*). Applicants will be notified if they are required to withdraw and resubmit the application according to the correct category.

Please refer to Chapters G and H for more information on MAV and MIV respectively.

23 VARIATION APPLICATION PROCESS

Figure 5 is a schematic diagram illustrating the variation approval process:

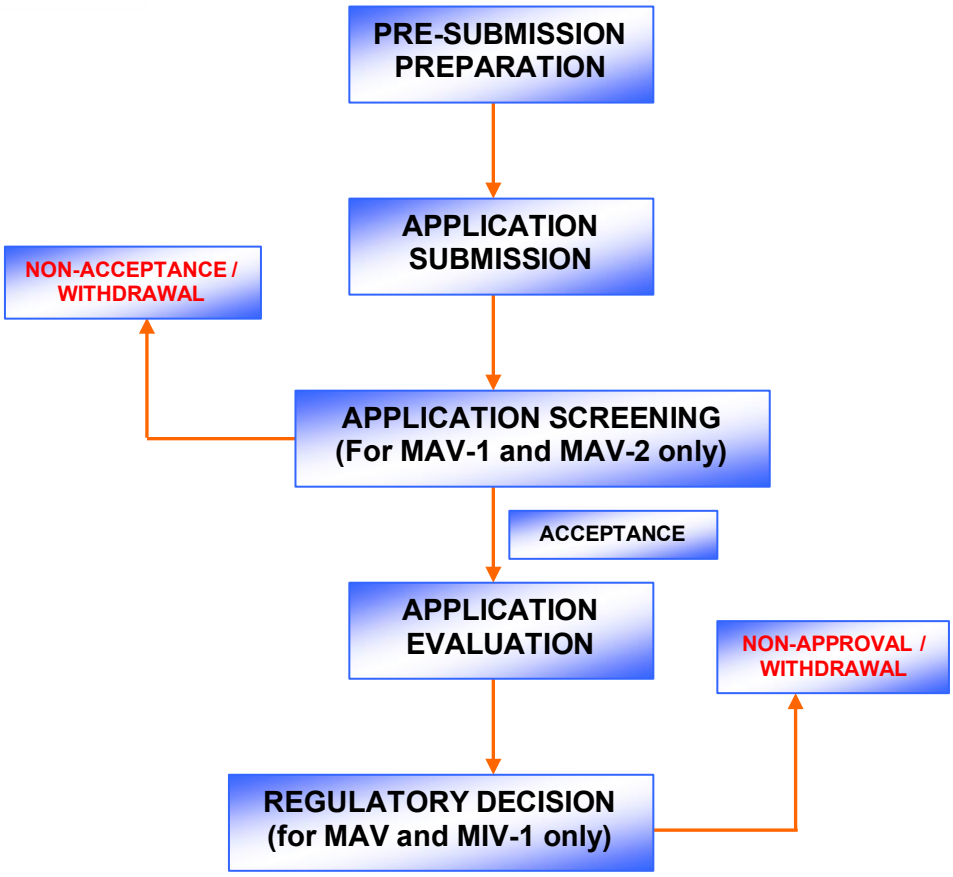


Figure 5 Schematic Diagram of the Variation Application Process.

For information on the variation application processing time, refer to Appendix 5 *Target Processing Timeline* of this guidance document.

23.1 Pre-Submission Consultation Mechanisms

There is a range of mechanisms that enable companies to self-help, which includes the use of guidelines, flow charts, frequently asked questions (FAQ) and self-help tools as alternatives to pre-submission meeting.

In the event that applicants are still unable to determine the type of variation, the MIV Enquiry Form may be submitted.

For more information on TPB's pre-submission consultation mechanisms, refer to the website: Pre-submission Consultation Mechanisms

23.1.1 Pre-Submission Notification

A pre-submission meeting is not compulsory for making an application to HSA. (see section 24.1 Evaluation Routes for more information on MAV-1 evaluation routes). Nonetheless, the applicant is required to notify HSA at least two months prior to the intended submission date for applications submitted via the full evaluation route. The notification should include information on the product name (if available), active ingredient(s), summaries of the clinical data (e.g. Overviews), planned submissions in other countries, and planned date of submission to HSA.

23.2 Application Submission

The submission of an application comprises two key steps – (i) online submission of the application form via PRISM and (ii) submission of the technical dossier.

23.2.1 PRISM Application Form

Applicants should refer to Appendix 17 *Guideline on PRISM Submission* for further details.

23.2.2 Variation Application Dossier

The technical dossier accompanying the application should be submitted within 2 working days of the PRISM application submission to prevent delays in the processing of the application. **The date of receipt of the actual technical dossier by HSA will be taken as the submission date where the processing time starts.**

The dossier submitted for variation applications should be in the same CTD format as that used for the original new product application.

Application checklists for both ICH CTD and ACTD dossiers are provided in Appendix 2B and 3B, respectively, to guide applicants on the submission requirements and to ensure completeness of the dossier. **Each MAV application**

must be accompanied by the required application checklist duly completed by the applicant and attached in PRISM.

23.2.2.1 Submission Requirements

The complete application dossier – i.e. Modules 1 to 5 of the ICH CTD or Parts I to IV of the ACTD – must be submitted in an electronic format.

Refer to section 6.2.1 on the Submission Requirements of the complete application dossier.

For submission requirements for MIV applications, please refer to Appendix 13 and Appendix 14 for registered chemical products and registered biological products, respectively.

23.2.2.2 Language and Translation

All documents submitted in support of an application to HSA must be in English. For documents in original language which is not English, a certified translation or a verified translation may be acceptable.

Translation type	Type of Documents	Requirements

Certified Translation	▪ **Official certificates** issued by the drug regulatory agency of a country ▪ **Proof of approval** issued by the drug regulatory	**Notarisation & Authentication** (10) <u>Notarisation</u> ▪ These documents must be **notarised** by a notary public in country where document is issued. ▪ Details of particulars to be included by notary: (i) The name of the notary; (ii) A statement that the notary is duly admitted to practice in the place of issue of the certificate;
	agency of a country	(iii) The names of the signatories and the capacity in which they have executed the document, whether on their own behalf or in an official or representative capacity; (iv) A statement authenticating the signatures of the parties and, where appropriate, indicating that evidence has been produced to the notary proving the capacity in which they have executed the document; (v) The place and date of issue of the notarial certificate; and (vi) The signature and seal of the notary.

		(10) <u>Authentication</u> ▪ These documents must be **authenticated** (i.e. the origin of the document is attested to) by one of the following government bodies: (i) The Ministry of Foreign Affairs of the country in which the document was issued; or (ii) The Singapore Embassy/Consulate in the country where the document was issued. Applicants are advised to consult the Singapore Embassy/Consulate in the country where the document originated regarding the local requirements for document legalisation, as these may deviate from the process as outlined in the preceding paragraph.
Verified Translation	▪ **Technical documents**	**Verification Document**

	(e.g. package insert, submission dataset)	▪ A verification document must be provided by the **translator** of the document into the English language. ▪ The verification document must state that the **translation into English is accurate**. ▪ Details of particulars to be included in verification document: (i) the name of translator; (ii) a statement that he/she is well versed in English and the relevant foreign language; and (iii) a reference to the document being translated. Refer to the sample verification document for translator enclosed in Appendix 4.

With Singapore acceding to the Apostille Convention on 16 September 2021, for certified translated document issued by a country which acceded to the Apostille Convention, an apostille certificate can be submitted *in lieu* of a notarised/authenticated certified translation.

23.2.2.3 Certifying non-original documents

If the softcopy official document (e.g. CPP, GMP certificate, etc.) submitted to HSA in PRISM is not a scan of the original document, the document must be certified prior to submission. A certified true copy certifies that the photocopy presented is a true and accurate copy of the original document. Acceptable certification of documents to support drug product applications to HSA can be done by the Company Director or Company Secretary as registered with ACRA or above, or by an independent authority such as a lawyer, notary public, Commissioner for Oaths/Declarations/Affidavits, Justice of Peace, the original issuer of the document or Embassy/Consulate. A notarised and authenticated copy is the same as a certified true copy.

A certified true copy of approval letters requires certification by the drug regulatory agency that issued the approval letter, notary public or Singapore Embassy/Consulate in the country where the approval letter was issued. Certification of approval letters is not required in the event the approval letter is available on the drug regulatory agency's website. In this instance, applicants should provide the internet address (URL) for validation by HSA.

23.3 Application Screening

MAV-1 and MAV-2 applications will be screened to ensure the correctness of the application type and the completeness of the dossier. **The date of receipt of the application dossier (i.e. the technical dossier [e.g. in a CD/DVD] including the application checklist) will be taken as the submission date and the start of the screening timeline.**

During screening, if an application is identified to be more appropriately submitted under a different application type, the applicant will be informed of this change and the necessary actions to effect this change via an Input Request. More information on the change in application type is described in section *23.6.2.1 Changes to Application Types and Re-routing of Evaluation During Screening*.

For applications submitted without the following documents, the applicant will be requested to withdraw the application as screening cannot proceed:

- Entire Module 5/Part 4 Clinical dossier
- Assessment report from Reference Agencies (for verification route)
- Duly completed Application Checklist in MS Excel format

Applicants should ensure that the PRISM application form is duly and accurately completed, and the dossier is compiled according to the required format before

submitting the application to HSA.

If deficiencies are identified in an application dossier, a screening query stating the deficiencies will be issued via Input Request to the applicant. The stop-clock starts when an Input Request is sent and ends upon receipt of the applicant's response. **The total number of Input Requests to allow for rectification of deficiencies during screening is capped at two**. Applicants will be given 20 working days to respond to each Input Request, starting from the date the Input Request is sent. Deficiencies which are not addressed within the 20 working days would be included in the second round of Input Request.

The application will only be accepted when all deficiencies have been adequately addressed, and HSA is satisfied that the dossier is complete for evaluation. An acceptance notice will then be issued via PRISM and the date of acceptance of the application will be taken as the start of the evaluation timeline.

If the applicant fails to address the deficiencies within two rounds of screening Input Requests, the application will not be accepted for evaluation. An Input Request will be issued to the applicant to withdraw the application. Any further responses to deficiencies will not be accepted. If the application is subsequently re-submitted, it will be processed as a new application.

NOTE: The screening process only checks for completeness of the application dossier for evaluation. The acceptance of the dossier for evaluation does not denote the adequacy of the data for regulatory approval.

For MIV-1 applications, applicants will receive an "Acceptance" notification sent within 3 working days after submission of an MIV-1 application via PRISM. For applications submitted under an incorrect application type and evaluation route (e.g. MAV-1 changes submitted as a MIV-1, or abridged application submitted as verification application), applicants will be requested to withdraw the application during evaluation.

23.4 Application Evaluation and Regulatory Decision

Once the application is accepted, the evaluation stage begins. Evaluation queries may be issued via Input Request to the applicant if clarification or additional information is required.

The stop-clock starts when an Input Request is sent and ends upon receipt of the applicant's response.

Applicants are reminded that the submission of additional supporting data not requested by HSA following the acceptance of the application will not be considered, unless prior arrangement with HSA is made for the submission concerned. During the evaluation process, HSA may assess that the application is more suitably evaluated via an alternative route, in which case the application will be re-routed to the appropriate route. Any re-routing of the application will be discussed with the applicant.

HSA may engage external evaluators, experts and advisory committees in the evaluation process, when necessary. These experts include scientists and clinicians from both local and overseas institutions. All external evaluators and experts are bound by agreement to protect the information made available to them. The identity of the external evaluators is kept confidential.

For MAV-1 applications (full and abridged evaluation routes), applicants can check on the progress of the evaluation and may view the evaluation stage via Track@PRISM. Table 10 describes the stages of the evaluation process for MAV- 1 applications.

Table 10 Variation Applications Applicable for Notification of Stages During Evaluation

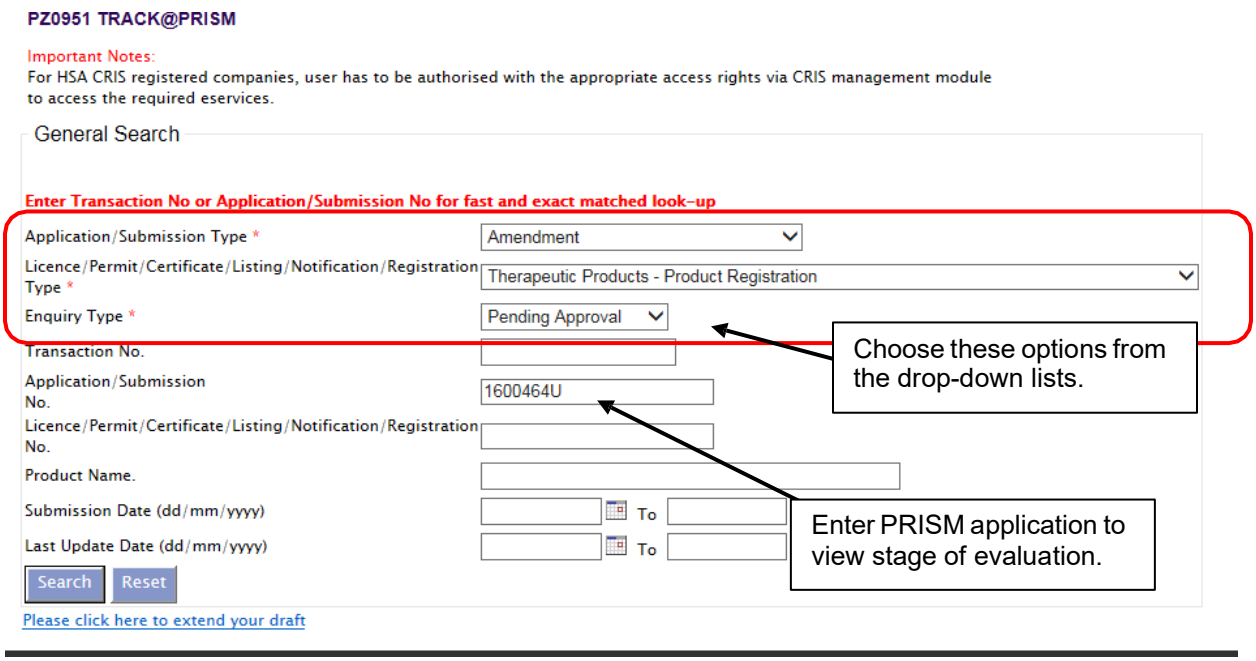
Stages of Notification to Applicant		1st Stage	2nd Stage	3rd Stage	4th Stage
		Evaluation Status			

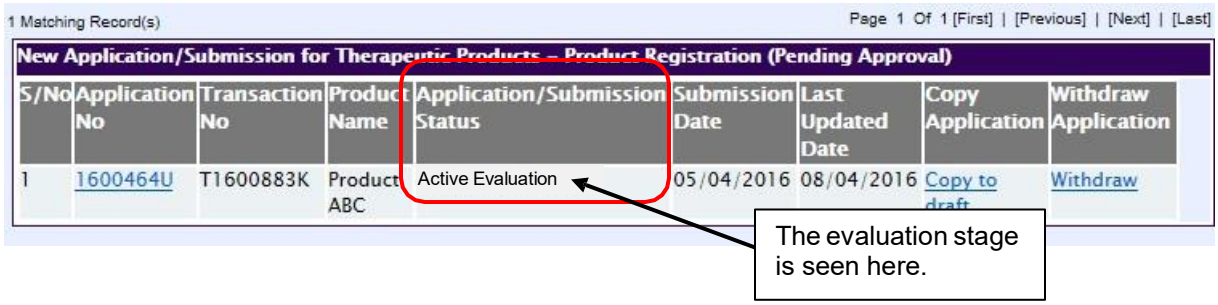
Application Type	Evaluation Route	Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
MAV-1	Full or Abridged	Application is accepted for evaluation and has entered the evaluation queue. This marks the start of the evaluation timeline.	Application is under active evaluation. Applicants can expect to receive the first set of evaluation queries (if any) from us towards the end of this stage.*	Application is approximately midway through the evaluation. Applicants are expected to submit the response to evaluation queries.	Evaluation is completed for the application. Application is now undergoing the regulatory decision phase, after which a regulatory decision# will be issued. Applicants can still expect further queries from HSA during this stage.

* For applications without any evaluation queries, recommended changes to product labels will be communicated to the applicant during the regulatory decision phase.

#The issuance of a regulatory decision would mark the end of the evaluation timeline for a product application.

The following screenshots illustrate the change in stages of a pending application:





Applicants are also notified via system-generated emails whenever an evaluation stage change occurs.

After the application is accepted for evaluation, applicants can expect to receive the first evaluation Input Request by:

Type of Applications	Evaluation Route	No. of working days

MAV-1	Full	160
MAV-1	Abridged	120

Note: excluding any stop-clock time between acceptance and issuance of first evaluation Input Request.

Upon approval/notification of a variation application, applicants will be informed via system-generated email and the product registration information in PRISM will be updated to reflect the changes (if applicable). Applicants may refer to Enquire@PRISM to view the latest product registration information (including registration conditions and post-approval commitments) of their products.

For submission of documents to fulfil registration conditions, please use this form (Submission of Documents to Fulfil Therapeutic Product Registration Conditions - https://go.gov.sg/fulfil-tp-reg-conditions).

23.5 Target Processing Timelines

Please refer to Appendix 5 for information on target processing timelines for the different application types and evaluation routes.

23.6 Fees

As the fees may be subject to revision from time to time, applicants are advised to visit the HSA website for updated information on fees.

Payment can be made via GIRO or other electronic payment modes such as eNets or eCredit card.

NOTE: Applicants are strongly encouraged to apply for eGIRO for the convenience of payment (apply eGIRO). subsequent payment for retention fee for the registered products.

Regardless of payment mode selection, the collection of both screening and evaluation fee for applications submitted via the full evaluation route occurs upon issuance of the screening outcome.

23.6.1 Screening Fee

The screening fee is only applicable for MAV-1 applications and is payable at the time of online submission via PRISM. The screening fee is non-refundable once the application is submitted via PRISM.

For payment via GIRO, the screening fee will be debited upon the successful submission of an online application.

For payment via other electronic payment modes (i.e. eNets or eCredit card), the screening fee must be paid before the application is considered successfully submitted online.

A screening fee is not applicable for other types of variation applications.

23.6.2 Evaluation Fee

There are two different evaluation fees for MAV-1 applications:

(a) Evaluation fees for a single-strength product or the first product in a series of products of different strengths; and

(b) Evaluation fees for each subsequent product in a series of products of different strengths.

An evaluation fee for a MAV-1 application is payable upon the acceptance of the dossier for evaluation and is non-refundable once the application is accepted. For payments via GIRO, the evaluation fee will be debited upon the acceptance of the application.

For payments via other electronic payment modes (i.e. eNets or eCredit card), the evaluation fee will be collected together with the screening fee. In the event that the application is not accepted for evaluation, the fee collected will be refunded to the applicant's mode of payment.

Applicants may opt for the progressive payment scheme for payment of evaluation fee. This is an opt-in scheme eligible for applicants who make payment via GIRO and is only applicable to the application types listed in Table 11:

Table 11 Variation Applications Applicable for Progressive Payment Scheme

Percentage of Evaluation Fee Payable at Each Stage					
		Evaluation Status			
Application Type	**Evaluation Route**	Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
MAV-1	Full or Abridged	30%	40%	20%	10%

Once the application is submitted, the selected payment scheme (full or progressive) cannot be amended. Applicants who wish to change their selected payment scheme will have to withdraw and re-submit the application(s); and any upfront payment made (e.g. screening fee) are non-refundable.

For applications under the progressive payment scheme, in the event that the application is withdrawn during the evaluation stage, any fees that had been charged, but not debited from the GIRO account would remain payable. Any paid fee is non-refundable.

23.6.2.1 Changes to Application Types and Re-routing of Evaluation During Screening

If an application type or evaluation route is incorrectly selected, applicants will be informed via an Input Request. Such changes may result in a different evaluation fee upon acceptance of the application.

In the situation where the applicant decides not to pursue the application due to the said changes, the screening fee is not refundable.

For applications which require withdrawal and resubmission, the screening fee is not refundable.

23.6.2.2 Change of Application between Different Application Types

This refers to a change in the application type between MAV-1, MAV-2, MIV-1 or MIV-2.

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

23.6.2.3 Change of Evaluation Route

This refers to a change in evaluation route (e.g. Full to Abridged, Verification to Abridged, Abridged to Verification, etc.).

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

23.6.3 Application Fee

An application fee for a MIV-1 application is payable upon the submission of the application in PRISM and is non-refundable.

CHAPTER GMAJOR VARIATION (MAV) APPLICATION SUBMISSION

This chapter applies to major variation applications for currently registered products.

24 MAV-1 APPLICATIONS

An MAV-1 application applies to variations to any of the following:

(a) approved indication(s);

(b) approved route(s) of administration;

(c) approved dosing regimen(s);

(d) approved patient group(s); and/or

(e) inclusion of clinical information extending the usage of the product – for example, clinical trial information related to an unapproved indication, dosing regimen and/or patient population; additional bacterial strains with clinical (*in vivo)* data to expand the indication(s) for antimicrobial products; additional viral serotypes/genotypes to expand the indication(s) for antiviral products, etc.

For each product registration, applicants may submit up to a maximum of three concurrent MAV-1 applications at any one time.

24.1 Evaluation Routes

There are three evaluation routes for an MAV-1 – full, abridged and verification. The eligibility criteria and documentary requirements are different for each evaluation route.

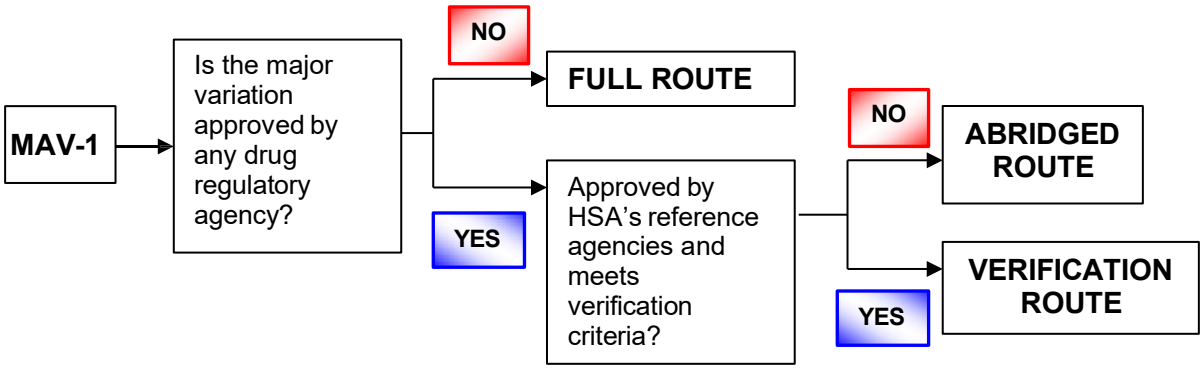


Figure 5 Schematic Diagram of Evaluation Routes for MAV-1s

24.1.1 Full Evaluation Route

Full evaluation will apply to a major variation that has not been approved by any drug regulatory agency at the time of submission.

For a submission under the full evaluation route, the applicant is required to notify HSA at least two months prior to the intended submission date of the application dossier. The notification should include information on the product name (if available), active ingredient(s), summaries of the quality, non-clinical and clinical data (e.g. Overviews), planned submissions in other countries, and the planned date of submission to HSA.

24.1.2 Abridged Evaluation Route

Abridged evaluation applies to a major variation that has been evaluated and approved by at least one competent drug regulatory agency. The proposed variation – i.e. the proposed indication(s), route(s) of administration, dosing regimen(s), patient group(s) and/or clinical information – should be the same as that approved by the regulatory agency that issued the proof of approval.

A competent drug regulatory agency refers to a national regulatory authority participating in the World Health Organization's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and listed as such on the

World Health Organization's website.

24.1.3 Verification Evaluation Route

A major variation that has been approved by at least two of HSA's reference drug regulatory agencies may be eligible for submission via the verification evaluation route. HSA's reference drug regulatory agencies are:

- EMA via the Centralised Procedure
- FDA
- Health Canada
- MHRA via
  - the national procedure, or
  - as the RMS via the MRP or DCP on or prior to 31 January 2020
- Swissmedic
- TGA

However, approval by these reference drug regulatory agencies does not oblige HSA to approve the application. HSA may also re-categorise applications to other evaluation routes if the applications did not meet the eligibility criteria and/or submission requirements.

The applicant must confirm one of the reference drug regulatory agencies as the primary reference agency. The chosen primary reference agency is defined as the reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted and which approved the strictest indication(s), route(s) of administration, dosing regimen(s), patient groups(s) and/or direction(s) for use among the reference drug regulatory agencies which approved the variation.

The pre-requisite requirements for the verification route include:

- The product has received full marketing approval by the reference agencies following a complete independent scientific assessment (i.e. the approval is not granted on the basis of less comprehensive data than normally would require or subject to post-approval conditions that require submission of additional data to confirm the product's benefit-risk profile);
- The application must be submitted within three years from the date of approval by the chosen primary reference agency;
- The product does not need independent assessment by HSA to contextualise the benefit-risk profile due to local disease epidemiology, medical practice and/or public health considerations. Examples of products that may require such contextualised assessment are anti-infectives, vaccines etc.; and
- The product and its intended use – i.e. indication(s), route(s) of administration, dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, approved via appeal process or pending deferral by a drug regulatory agency for safety and/or efficacy reasons.

24.2 Documentary Requirements

Refer to Documentary Requirements in section 23.2.2.1 for submission requirements.

Table 12 outlines the CTD Modules/Parts required for MAV-1s submitted under each evaluation route:

Table 2 Dossier Submission Requirements for MAV-1s

	Location in		Module/Part required for		
	ICH CTD	ACTD	Full MAV-1	Abridged MAV-1	Verification MAV-1

Administrative Documents and Product Information	Module 1	Part I	Yes	Yes	Yes
Common Technical Document Overview and Summaries	Module 2	*Incorporated into Parts II, III and IV*	Yes	Yes	Yes
Quality documents	Module 3	Part II	No	No	No
Non-clinical documents	Module 4	Part III	No§	No#	No#
Clinical documents	Module 5	Part IV	Yes	Study report(s) of pivotal studies and synopses of all studies (phase I-IV)	Study report(s) of pivotal studies and synopses of all studies (phase I-IV)
				relevant to requested indication, dosing and/or patient group	relevant to requested indication, dosing and/or patient group

§ If the proposed MAV-1 is related to non-clinical data, non-clinical summary and non-clinical overview as well as relevant study reports is required.

Non-clinical overview only, if applicable.

24.2.1 Administrative Documents

The three evaluation routes for an MAV-1 share the same documentary requirements for CTD Module 1/Part I. The documents required are:

(a) Section 1.1 – Comprehensive Table of Contents;

(b) Section 1.2 – Cover Letter – including the *Table of Amendment Details* of PRISM section 0.5;

(c) Section 1.4 – Labelling, Package Insert and Patient Information Leaflet –

(i) Both the proposed and currently approved Singapore product labels and PI/PIL are required.

(ii) For the proposed labelling/PI/PIL, a pristine and an annotated version (which highlights the changes made to the currently approved labelling) are required.

(iii) Annotations should be made on the current approved labelling materials based on the actual text to be added.

(iv) Current approved text proposed for deletion should be struck through, whereas newly added and proposed text should be underlined or highlighted.

(v) Current approved text that is not intended to be deleted should not be annotated.

(vi) Proposed changes to all labels must be clearly annotated, and **the final approved changes would be as annotated** in the final label submitted in PRISM.

(d) Section 1.5 – Approved SPC/PI/PIL from the drug regulatory agency that issued the proof of approval and from each of HSA's reference drug regulatory agencies (where applicable);

(e) Section 1.6 – Assessment Report from Reference Agencies – only for verification route (see section 24.2.5.3 *Verification Evaluation Route*);

(f) Sections 1.8, 1.9 – Proof of Approval – for an MAV-1, the official approval letter(s) must contain information on the requested Singapore variation. For the verification evaluation route, the approval letters issued by at least two reference drug regulatory agencies, including the chosen primary reference agency, should be submitted;

(g) Section 1.13 – Declaration on rejection, withdrawal and deferral; and

(h) Section 1.15 – Registration Status in Other Countries.

The requirements of the administrative documents stated above is the same as that described in section 15.1 *Administrative Documents* in Chapter C *New Drug Application Submission*.

> **NOTE**: Applicants must complete the relevant application checklists found in Appendix 2B or Appendix 3B and attach the completed application checklist under PRISM section 1.2.

24.2.2 CTD Overviews and Summaries

The following documents are to be submitted:

- a non-clinical overview, if applicable; and
- a clinical overview and summaries of clinical efficacy and clinical safety.

24.2.3 Quality Documents

Quality documents (Module 3/Part II) are not required for MAV-1 applications.

24.2.4 Non-clinical and Clinical Documents

Each evaluation route will have different non-clinical and clinical documentary requirements. Refer to section 24.2.5 *Specific Documentary Requirements for Each*

Evaluation Route below for more information.

For MAV applications, HSA may request for RMPs to be submitted on a case-by- case basis following the evaluation of the safety concerns described in the product application, where necessary. For such instances, please refer to the guidance on RMP submission requirements found here.

If the MAV-1 is for a non-prescription medicine and is submitted via the abridged evaluation route, the applicant may submit a written request for a waiver of clinical data submission. Eligibility for a waiver is subject to the criteria defined in Appendix 6 *Guideline on Submission for Non-Prescription Therapeutic Products*. However, HSA may request for the complete clinical data set if it is deemed appropriate.

24.2.5 Documentary Requirements for Each Evaluation Route

24.2.5.1 Full Evaluation Route

The technical documents required include:

- complete non-clinical documents, if applicable; and
- complete clinical documents; i.e. all study reports from phase I to phase III, including tables and appendices.

24.2.5.2 Abridged Evaluation Route

The technical documents required include:

- a non-clinical overview, if applicable; and
- a clinical overview, summaries of clinical efficacy and clinical safety, synopses of relevant studies, a tabular listing of the clinical development programme and study reports of the pivotal studies (the tables and appendices to the pivotal study reports may be submitted upon request by HSA).

24.2.5.3 Verification Evaluation Route

The complete assessment report[21] and other relevant supporting documents from the chosen primary reference agency must be submitted. The assessment report from the primary reference agency should include details of imposed licensing conditions, final product labelling, clinical reviews, and other information in relation to the product's approval.

Applications submitted to HSA without the assessment report from the primary reference agency will not be accepted for evaluation via the verification route and rejected at screening.

The technical documents required include:

- a non-clinical overview, if applicable; and
- Clinical documents and assessment report from the primary reference agency.

All the data submitted to HSA must be the same as the data package submitted to the reference drug regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application but may also lead to the re-routing of the dossier to the abridged evaluation route if significant undisclosed differences are discovered.

25 MAV-2 APPLICATIONS

An MAV-2 application applies to variations involving a change in forensic classification, or "reclassification", of a registered product. Examples of reclassification include from POM to P or from P to GSL.

Reclassification may also be undertaken when experience gained shows that there is a need to supervise the use of a product – i.e. from GSL to P or POM.

More information on reclassified medicines may be found on the HSA website.

[21] A complete assessment report from public domain is acceptable.

25.1 Evaluation Routes

Only the abridged evaluation route applies for MAV-2 applications.

25.2 Eligibility Criteria

A product currently classified as POM or P may be considered for reclassification to a lower tier of access control if it meets the following requirements:

(a) The product fulfils all criteria specified in section 1.2.1 for its proposed new forensic classification (either P or GSL, as applicable);

(b) The product demonstrates extensive documented safe and effective use, and there are no significant safety concerns or local public interest factors that would preclude its consideration for the proposed forensic classification; and

(c) The product is presented in an appropriate pack size with consumer-friendly labelling (PIL and/or outer carton).

25.2.1 Additional considerations

HSA will take into consideration the broader implications of the proposed reclassification in the local context, including impact on public health, public interest, and healthcare system readiness, where appropriate.

25.2.2 Justifications for the proposed reclassification

To apply for reclassification, the submission must include justifications comprising the following:

(a) The rationale for requesting a change in the forensic classification, supported by evidence and scientific data;

(b) The experience of patient exposure to the product, including:

- The period of product registration and duration of sale in each forensic classification (i.e. POM, P and/or GSL) in Australia, Canada, Switzerland, UK and US, where applicable
- The period of actual product sale in Singapore
- Overall patient exposure data, e.g. sales volume, patient-years of use

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(c) A summary of the product safety profile based on worldwide and local spontaneous adverse drug reaction reports, post-marketing surveillance studies, clinical trials and published literature;

(d) Potential problems and hazards arising from using the product without medical supervision; and

(e) Analysis of the hazard arising from misuse, inappropriate use or abuse, whether deliberate or accidental.

25.3 Documentary Requirements

Please refer to the application checklists in Appendix 2B or Appendix 3B for dossier format and requirements of MAV-2 application.

(a) Section 1.1 – Comprehensive Table of Contents;

(b) Section 1.2 – Cover Letter– including the *Table of Amendment Details* of PRISM section 0.5;

(c) Section 1.4 – Product Labels (if applicable);

(d) Section 1.5 – Approved SPC/PI/PIL in other countries;

(e) Section 1.8 – Proof of Approval – proof of the approved indication(s) and dosing regimen(s) for the reclassified product in at least one of HSA's reference agencies;

(f) Section 1.15 – Registration Status and Forensic Classification in other countries; and

(g) Module 2/Part IV – Summary of Clinical Safety – the summary must include the justifications for the proposed reclassification as detailed in Section 25.2.

The requirements of the administrative documents stated above is the same as that

described in section 15.1 *Administrative Documents* in Chapter C *New Drug Application Submission*.

NOTE: Applicants must complete the relevant application checklists found in Appendix 2B or Appendix 3B and attach the completed application checklist under PRISM section 1.2.

25.4 'Me-too' Reclassification

A me-too MAV-2 application may be submitted if it is riding on a previous forensic classification of an analogous product.

The documentary requirements include:

(a) Section 1.1 – Comprehensive Table of Contents;
(b) Section 1.2 – Cover Letter– including the justification for reclassification, and the *Table of Amendment Details* of PRISM section 0.5;
(c) Section 1.4 – Product Labels (if applicable); and
(d) Section 1.5 – Approved SPC/PI/PIL in other countries (if applicable).

The Summary of Clinical Safety in Module 2/Part IV is not required.

CHAPTER H MINOR VARIATION (MIV) APPLICATION SUBMISSION

This chapter applies to minor variation applications for currently registered products.

26 APPLICATION TYPES

There are two types of minor variation applications – MIV-1 and MIV-2:

MIV-1: A minor variation that

- Is specified under Part A: Checklist on Dossier Requirements for MIV-1 variations of Appendix 13

(Chemicals) or Appendix 14 (Biologics);

- Requires prior approval before the change(s) can be implemented.

MIV-2 (Notification) A minor variation that

- Is specified under Part B: Checklist on Dossier Requirements for MIV-2 (Notification) Variation of Appendix 13 (Chemicals) or Appendix 14 (Biologics);
- May be implemented within 40 days upon application submission if there are no objections raised by HSA.

MIV-2 (Do-and-Tell) A minor variation that

- Is specified under Part C: Checklist on Dossier Requirements for MIV-2 (Do-and-Tell) Variation of Appendix 13 (Chemicals) or Appendix 14 (Biologics);
- Does not require prior approval, but must be submitted to HSA within 6 months following implementation of the specified changes.

27 APPLICATION SUBMISSION

Applicants should be familiar with the guidelines and documentary requirements described in Appendix 13 (chemical) and Appendix 14 (biologics) before submitting minor variation applications. The appropriate variation may be selected with the aid of the MIV self-guided tool . Changes that do not require notification to HSA are listed in Section 4 of Appendices 13 and 14.

Any undisclosed variation(s) embedded in the submitted data, including any follow- on changes, will not be considered. Evaluation will be based on the data relevant to the proposed variation(s) unless HSA specifically requests for additional information.

For applications where there are proposed changes to the product labels:

(i) Both the proposed and currently approved Singapore product labels and PI/PIL are required.

(ii) For the proposed labelling/PI/PIL, a pristine and an annotated version (which highlights the changes made to the currently approved labelling) are required.

(iii) Annotations should be made on the current approved labelling materials based on the actual text to be added.

(iv) Current approved text proposed for deletion should be struck through, whereas newly added and proposed text should be underlined or highlighted.

(v) Current approved text that is not intended to be deleted should not be annotated.

(i) Proposed changes to all labels must be clearly annotated, and **the final approved changes would be as annotated** in the final label submitted in PRISM.

Applicants are strongly encouraged to submit variation applications for multiple strengths of the same therapeutic product at the same time. Applicants should also indicate in the PRISM application form and cover letter if the proposed change(s)

affect multiple products and if there are other pending variation (MAV/MIV) applications for the same therapeutic product.

Suggested guidance for further reading:

- Appendix 5 *Target Processing Timeline*
- Appendix 17 *Guideline on PRISM Submission*.

27.1 MIV-1 Applications

There are two submission routes – abridged or verification route.

An application may be submitted via the verification route if:

(i) The proposed variation(s) is identical to those approved by one of HSA's reference agencies; and
(ii) The application is accompanied by the proof of approval or approved product labels of that reference agency.

Applications that do not fulfil the above requirements should be submitted via the abridged route.

For each product registration, applicants may submit up to a maximum of five concurrent MIV-1 applications at any one time.

27.1.1 Submitting multiple/consequential changes

MIV-1 changes can be grouped into a single MIV-1 application if the changes are consequential. A consequential change refers to a change that is unavoidable and a direct result of another change, e.g., consequential change of manufacturing process due to a change of manufacturing site. Applicants should indicate the main change as the primary change and any consequential change(s) as the secondary change(s) in the PRISM application form.

Non-consequential MIV-1 changes should be submitted in separate MIV-1 applications, e.g., MIV-1 changes in product labelling for clinical information should not be grouped with any quality MIV-1 changes.

For MIV applications containing both MIV-1 and MIV-2 changes, the application should be categorised as MIV-1.

27.2 MIV-2 Applications

Please note that at any one time, there can only be one MIV-2 application per product registration. Multiple changes are allowed in a single MIV-2 application.

27.2.1 MIV-2 Notification

MIV-2 change(s) can be implemented if there is no objection from HSA within the notification timeline of 40 working days, excluding stop-clock.

27.2.2 MIV-2 Do-and-Tell

Please refer to Appendix 13C and 14C for the list of Do-and-Tell changes. Applicants have 2 submission options:

(i) 6-Monthly Notification

Consolidate all "Do-and-Tell" changes that have been implemented within a 6- month timeframe of the scheduled submission periods of January (changes made from July to December of the preceding year) and July (January to June of the present year).

(ii) Flexible Notification

Submit a Do-and-Tell change anytime as a MIV-2 submission, or together with other standard MIV-2 changes provided that the change was implemented within the preceding 6 months.

If the same Do-and-Tell change was amended and re-implemented during the 6- month timeframe, only the latest version of the change should be submitted. You may also combine Do-and-Tell changes in an MIV-1 application provided that these are consequential changes.

Please refer to the table below for examples:

	Scenario	**What you should do**

1	You have 3 Do-and-Tell changes implemented in March, May and June within the same year.	Combine the changes in one MIV-2 Do-and-Tell application and submit by the end of July of the same year.
2	You have implemented a Do-and-Tell change in March, but omitted this in your July submission package.	You may submit the omitted change as a standalone or combined MIV-2 application after the submission period, latest by September(6 months from implementation).
3	Your MIV-2 is still pending notification by HSA in January and you need to submit a Do-and- Tell variation.	You may submit the Do-and-Tell variation after the pending MIV-2 application has been processed (within 6 months of implementation), or make a written request to include the Do-and-Tell change in the pending MIV-2 application.
4	You have prepared one Do-and-Tell MIV-2 submission package scheduled for July. However you need to also submit an urgent MIV-2 variation at the same time.	You may combine both changes in the same MIV-2 application.

5	You have submitted a MIV-2 Do-and-Tell application which is pending processing. However, you need to submit an urgent MIV-2 change.	You may withdraw the pending MIV-2 Do-and-Tell application and resubmit a fresh MIV-2 application which incorporates both the additional MIV-2 change and the previously submitted Do-and-Tell change.