HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

JANUARY 2024

CELL, TISSUE AND GENE THERAPY PRODUCTS GUIDANCE

GUIDANCE ON CELL, TISSUE AND GENE THERAPY PRODUCTS REGISTRATION IN SINGAPORE

HSA Health Sciences Authority

REVISION HISTORY

Guidance Version (Publish Date)
GN-ATPB-001 (Revision 2, January 2024)

TABLE OF CONTENTS

LIST OF APPENDICES

ABBREVIATIONS AND ACRONYMS

ACTD	ASEAN Common Technical Document
ACTR	ASEAN Common Technical Requirements
ASEAN	Association of Southeast Asian Nations
CHMP	Committee for Medicinal Products for Human Use (formerly Committee for Proprietary Medicinal Products)
CMC	Chemistry, Manufacturing and Controls
COA	Certificate of Analysis
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
CTGTP	Cell, Tissue and Gene Therapy Product
EIR	Establishment Inspection Report
EMA	European Medicines Agency European Union
FDA	Food and Drug Administration (United States of America)
GMP	Good Manufacturing Practice
HC	Health Canada
HPA	Health Products Act
HPRG	Health Products Regulation Group
HSA	Health Sciences Authority (Singapore)
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human use)
MAV	Major Variation
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MIV	Minor Variation
NDA	New Drug Application
PI	Package Insert (Singapore), Product Information
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMC	Pre-Market Consultation
RMP	Risk Management Plan
SPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration (Australia)
WHO	World Health Organisation

CHAPTER A GENERAL OVERVIEW

1 FOREWORD

This guidance document outlines the regulatory processes and requirements for cell, tissue and gene therapy products (CTGTP) registration and should be read in conjunction with the relevant legislation in Singapore, including:

- Health Products Act (Cap. 122D); and
- Health Product (Cell, Tissue and Gene Therapy Products) Regulations 2021.

The Health Products Act (HPA) provides for the legislative basis for regulating the manufacture, import, supply, presentation and advertisement of cell, tissue and gene 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 cell, tissue or gene product, or to make a variation application to a registered cell, tissue or gene therapy product.

Under the First Schedule of the HPA, cell, tissue or gene therapy products 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, treating, curing, or alleviating any disease, disorder, injury, ailment, handicap or abnormal physical or mental state, or any symptom thereof;
   (ii) for replacing, repairing, regenerating or reconstructing any anatomy, or for modifying or replacing any physiological process;
   (iii) for regulating, repairing, replacing, adding or deleting a genetic sequence or modifying genetic material;
   (iv) for supporting or sustaining life;

(b) has as a constituent any of the following substances or combination of substances:
   (i) viable or non-viable human cells or tissues;
   (ii) viable animal cells or tissues;
   (iii) recombinant nucleic acids, where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence that it contains or to the product of the genetic expression of its sequence;

(c) achieves its primary intended action by pharmacological, immunological, physiological, metabolic or physical means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose; and

(d) is not any of the following:
   (i) a recombinant vaccine for a preventive purpose;
   (ii) an *in-vitro* diagnostic product;
   (iii) bone marrow, peripheral blood or umbilical or placental cord blood from a human that is minimally manipulated and intended for homologous use;
   (iv) cells and tissues obtained from a patient that are minimally manipulated and re-implanted for homologous use into the same patient during the same surgical procedure;
   (v) organs and tissues that are minimally manipulated and intended for transplant;
   (vi) reproductive cells (sperm, eggs) and embryos intended for assisted reproduction;
   (vii) whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders;

For the purposes of above definition, “homologous use” means the use of a cell, tissue or gene therapy product to repair, reconstruct, replace or supplement the cells or tissue of an individual (called the recipient) if the cell, tissue or gene therapy product performs the same basic function or functions in the recipient as the original cells or tissue in the donor in the same anatomical or histological environment;

“Minimally manipulated”, in relation to a cell or tissue (but not a gene), means processing the cell or tissue by way of any process so that the biological

characteristics or functions of the cell or the structural properties of the tissue (as the case may be) are not altered, such as by —

(a) cutting or sizing;
(b) grinding;
(c) shaping;
(d) centrifugation;
(e) soaking in an antibiotic or antimicrobial solution;
(f) sterilization or irradiation;
(g) cell separation, concentration or purification;
(h) filtration;
(i) lyophilisation;
(j) freezing;
(k) cryopreservation; or
(l) vitrification.

1.2 Classification of CTGTP

CTGTP will be risk-stratified into two classes:

Class 1 CTGTP (lower risk) would have to satisfy ALL of the following conditions:

(1) is the result of only minimal manipulation of human cell or tissue, i.e. biological characteristics or functions of the human cell or the structural properties of the tissue are not altered;

(2) is intended for homologous use (performing same function and administered at the same anatomical site or histological environment in the recipient as in the donor); and

(3) is not combined or used with -

(i) a health product categorised as a therapeutic product in the First Schedule to the Act; or

(ii) a health product categorised as a medical device in the First Schedule to the Act; and

(4) is assigned by the Authority as a Class 1 CTGT product due to a lower health risk to a user of the product

Class 2 CTGTP (higher risk) means a CTGT product that is other than a Class 1 CTGT product and it also includes CTGTP with viable animal cells and recombinant nucleic acids.

1.3 Class 1 CTGTP

Class 1 cell, tissue or gene therapy product includes human cells or tissue that has been subject to minimal manipulation, intended for a homologous use, and is NOT combined with a therapeutic product or a medical device.

Example of class 1 CTGTP: bone grafts, amniotic membrane, skin.

Class 1 CTGTP are exempted from product registration. Instead, the supplier would be required to notify HSA on the product and must receive HSA's written acceptance/ acknowledgement of notification before it can be supplied. Please use Singapore Health product Access and Regulatory E-system (SHARE) for Application for Notification of Class 1 CTGTP and refer to Appendix 1 to ensure the submission of a complete dataset for product notification. The supplier would also be required to ensure that the product was sourced from an accredited/licensed facility and that it is free from infectious agents.

1.4 Class 2 CTGTP

Class 2 cell, tissue or gene therapy product includes human cells or tissue that has been subject to more than minimal manipulation; or is intended for a non-homologous use; or is combined with a therapeutic product or a medical device. Class 2 CTGTP also includes xenogeneic cells or tissue or products with recombinant nucleic acids.

Example of class 2 CTGTP: Gene modified cells, cells grown on scaffold, culture expanded cells, vectors with therapeutic gene and xeno-based products.

All Class 2 CTGTP will require registration with HSA before they can be supplied in Singapore. In making an application, 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-market consultation can be found in Chapter B: 3.1.

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 chemistry, manufacturing and controls (CMC) data, while the term '*non-clinical*' is used to describe preclinical, pharmacological and toxicological data from animal studies.

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

2 APPLICANT RESPONSIBILITIES

The applicant of a product registration refers to the local company that is applying for the product registration. The company may authorise officers, permanent 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 CTGTP, 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 CTGTP 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 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.

CHAPTER B REGISTRATION PROCESS

A company seeking to register a Class 2 CTGTP in Singapore must obtain approval from HSA through making an application for product registration. The registration process involves a series of steps, as shown in Figure 1.

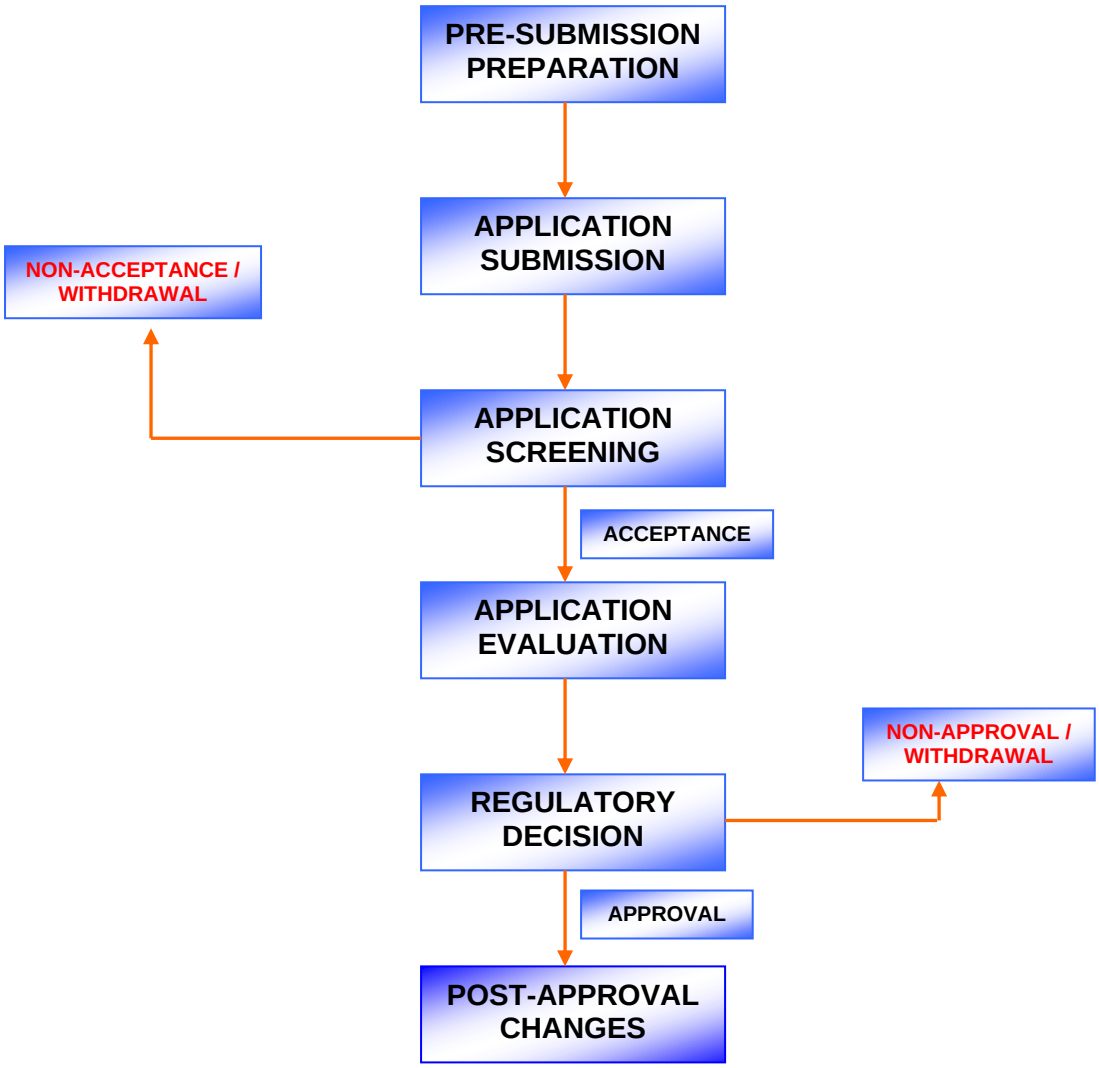

Figure 1 Registration Process for a Class 2 CTGTP

3 PRE-SUBMISSION PREPARATION

The following are important considerations for an applicant to register a class 2 CTGTP:

(a) Arranging for a pre-market consultation with HSA for advice.

(b) Knowing which type of application to apply for; and

(c) Knowing which evaluation route to choose.

3.1 Pre-Market Consultation (PMC)

Under the PMC, you can consult us on regulatory requirements, or seek feedback on your CTGTP dossier before submission to us. This may expedite CTGTP registration and facilitate early access of CTGTP. The pre-market consultation will also help you adhere to regulatory requirements in Singapore.

Table 1 summarises the scope of pre-market consultations at a glance:

Table 1 Pre-Market Consultations at a Glance

	Pre-Market Consultation
Scope	To seek feedback on Class 2 CTGTP product registration dossier requirements and application route
Target stakeholders	Stakeholders submitting an application for local product registration
Stage of CTGTP Lifecycle	Before registration application submission
Number of products to be discussed (per consultation)	Limited to a single product registration application
Duration (per consultation)	Up to 1 hour

Step 1: Book appointment online

When: Five months before the consultation.

How to book: Access online application form Application for Pre-Market Consultation for Class 2 CTGTP Registration and view scheduled pre-submission consultation appointments.

Step 2: Documents submission

When to submit: At least 30 days before the consultation. Please submit the documents early to allow us ample time to review them before the consultation.

What to submit:

- Completed consultation form (Appendix 2)
- Relevant information described in the form.

Information to be provided by replying to the confirmation e-mail, or a new e-mail with booking reference number in the subject.

Note:

- Incomplete information may result in the appointment being rescheduled or cancelled. Fees paid are not refundable.
- You may change or cancel the appointment by notifying via e-mail to HSA_CTGTP@hsa.gov.sg.
- Only one rescheduling is allowed per booking reference, which is subject to availability at the point of processing.

Step 3: Request for information

We will review the documents submitted and may ask for more information via e-mail before the appointment. If you fail to provide the information requested by the required time, your appointment may be rescheduled or cancelled.

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

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

(b) Knowing which evaluation route to choose; and

(c) Arranging for a pre-submission consultation with HSA for advice.

PMC channel is for stakeholders to seek feedback on their CTGTP dossier before registration application submission to us. This is to ensure supporting documents are complete and appropriate.

3.1.1 Type of Application

There are three types of applications for a new class 2 CTGTP:

NDA-1: For the first strength of a product containing a new CTGTP. This means the CTGTP is currently not a registered in Singapore.

NDA-2: For the first strength of a product containing:

- New combination of registered CTGTP
- Registered CTGTP in either of the following:
  - New dosage form, such as capsules and injectables.
  - New presentation, such as single-dose vials, multi-dose vials and pre-filled syringes.
  - New formulation, such as preservative-free.
- Registered CTGTP for use by a new route of administration.

For products that do not fall under the requirements for NDA-1 or NDA-3.

NDA-3: For subsequent strengths of a product that has been registered or has been submitted as a NDA-1 or NDA-2. The product name, dosage form, indication, dosing regimen and patient population should be the same as that for the NDA-1 or NDA-2 submission.

3.1.2 Type of Evaluation Route

There are two types of evaluation routes for registering a new class 2 CTGTP:

Full route: Applies to any new product that has not been approved by any comparable overseas regulator at the time of application submission to HSA.

Abridged route: Applies to any new product that has been approved by at least one of our comparable overseas regulators.

Our comparable overseas regulators consist of the following agencies:

- Therapeutic Goods Administration (TGA, Australia)
- Health Canada (HC, Canada)
- Food and Drug Administration (FDA, United States of America)
- European Medicines Agency (EMA) via the Centralised Procedure
- Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom)

For a submission under the full evaluation route, the applicant is required to notify HSA via email to HSA_CTGTP@hsa.gov.sg 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 substance(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.

3.2 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.

4 APPLICATION SUBMISSION

4.1 Application Dossier

Application dossiers should be organised in a Common Technical Document (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 or the 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 International Council for Harmonisation Common Technical Document (ICH CTD) and the Association of Southeast Asian Nations (ASEAN) CTD format CTD (ACTD) guidance documents.

Either the ICH CTD or the ACTD format is acceptable for making a submission to HSA. Table 2 summarises the organisation of the respective format:

Table 2 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 3 and Appendix 4, respectively, to guide applicants on the submission requirements and to ensure completeness of the dossier.

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 CTD format.

4.1.1 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.

Colour scanned copy of the original documents should be submitted and hardcopy of the original 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 4.1.3 for more information on certifying non-original documents if the original documents cannot be provided.

When submitting a CD/DVD, applicants are encouraged to 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.

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

The CD/DVD should be properly labelled with the following information:

- Product name;
- Application type; and
- Contents of the CD/DVD (Modules 1 to 5).

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

4.1.2 Language and Translation

All documents submitted in support of an application 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 5.

4.1.3 Certifying Non-Original Documents

If the softcopy official document (e.g. CPP, GMP certificate) 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 product registration application 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.

5 APPLICATION SCREENING

Following the receipt of the application dossier, 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.

For applications with the following major deficiencies, the applicant will be requested to withdraw the application, as screening cannot proceed without the relevant information.

- Dossier sections not submitted (drug substance, drug product, clinical); or
- Drug Master File (DMF) not submitted (where applicable)

Applicants should ensure that the dossier is compiled according to the required format. Failure to adhere to the required CTD format will lead to the non-acceptance of the dossier without screening.

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 a complete and satisfactory response to the query. 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 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 raised during screening, the application will not be accepted for evaluation. An Input Request will be issued to the applicant to withdraw the application. If the application is subsequently re-submitted, it will be processed as a new application.

NOTE: The screening process only checks for the correctness of the application type and 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.

6 APPLICATION EVALUATION

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

The stop-clock starts whenever HSA issues a query and ends upon the receipt of a complete and satisfactory response from the applicant.

In situations where the applicant is unable to provide a complete response within the specified timeframe, the applicant should notify HSA as soon as possible after receiving HSA's queries. The application will be considered withdrawn if the applicant fails to adhere to the specified response deadline.

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.

7 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 to pursue the regulatory approval for the product concerned.

Upon an '*approval*' regulatory decision, the product will be added to the Register of Cell, Tissue or Gene Therapy Products.

HSA may grant conditional registration with post-approval commitments to a Class 2 CTGTP that meet all the criteria:

- intended to treat an unmet medical need*;
- product safety established in early clinical trials; AND
- preliminary data shows meaningful evidence of therapeutic benefit (a clinically significant endpoint) versus other available therapies (standard of care)

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. Results of the confirmatory studies should be submitted within a prescribed timeline for evaluation before obtaining full marketing approval. If not, the product will have to be withdrawn from the local market.

NOTE: *Unmet medical need means absence of a treatment option or lack of safe and effective alternative treatment, the product would be a significant improvement compared to available marketed products, as demonstrated by evidence of increased effectiveness in treatment, prevention, or diagnosis; or elimination or substantial reduction of a treatment-limiting drug reaction.

8 POST-APPROVAL CHANGES

Upon the registration of CTGTP, 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 D of this guidance.

9 TARGET PROCESSING TIMELINES

Please refer to Appendix 6 for information on target processing timelines for the different application types and evaluation routes.

10 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 .

NOTE: Applicants are strongly encouraged to apply for a GIRO account (refer to GIRO application form) with HSA to facilitate payments for future submissions and subsequent payment for retention fee for the registered products.

10.1 Screening Fee

A screening fee is payable at the time of online submission and is non-refundable once the application is submitted. The screening fee will be debited upon the successful submission of an online application.

10.2 Evaluation Fee

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

10.2.1 Change of Evaluation Route

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

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application. The screening fee is not refundable. Applicants may wish to seek clarification on the appropriate application type or evaluation route via the Pre-Market Consultation (section 3) prior to the submission.

CHAPTER C NEW CTGTP APPLICATION SUBMISSION

This chapter applies to new CTGTP application.

11 APPLICATION TYPES

There are three types of applications for a new class 2 CTGTP:

NDA-1: For the first strength of a product containing a new CTGTP. This means the CTGTP is currently not a registered in Singapore.

NDA-2: For the first strength of a product containing:

- New combination of registered CTGTP
- Registered CTGTP in either of the following:
  - New dosage form, such as capsules and injectables.
  - New presentation, such as single-dose vials, multi-dose vials and pre-filled syringes.
  - New formulation, such as preservative-free.
- Registered CTGTP for use by a new route of administration.

For products that do not fall under the requirements for NDA-1 or NDA-3.

NDA-3: For subsequent strengths of a product that has been registered or has been submitted as a NDA-1 or NDA-2. The product name, dosage form, indication, dosing regimen and patient population should be the same as that for the NDA-1 or NDA-2 submission.

12 EVALUATION ROUTES

There are two evaluation routes for a new CTGTP application – full and abridged 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 2 is a schematic diagram illustrating the evaluation routes for new CTGTP applications:

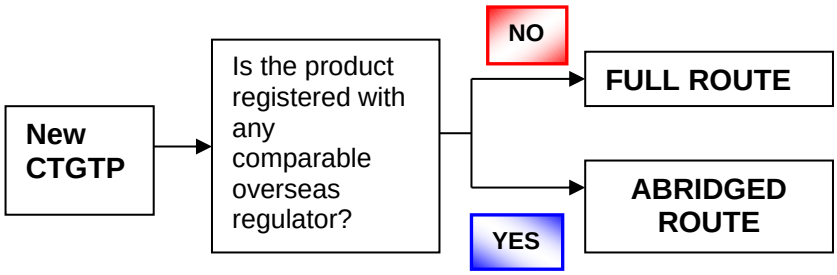

Figure 2 Schematic Diagram of Evaluation Routes for New CTGTP applications

12.1 Full Evaluation Route

Full evaluation applies to CTGTP that has not been approved by any comparable overseas regulator at the time of submission.

For a submission under the full evaluation route, the applicant is required to notify HSA via email to HSA_CTGTP@hsa.gov.sg 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.

12.2 Abridged Evaluation Route

Abridged evaluation applies to a product that has been approved by at least one of our comparable overseas regulators at the time of submission.

13 DOCUMENTARY REQUIREMENTS

Table 3 outlines the CTD Modules/Parts required for New CTGTP Applications submitted under each evaluation route:

Table 3 Dossier Submission Requirements for New CTGTP Applications

Documents	Location in		Module/Part required for	
	ICH CTD	ACTD	Full	Abridged

Administrative Documents	Module 1	Part I	Yes	Yes
Common Technical Document Overview and Summaries	Module 2	*Incorporated in Parts II, III and IV*	Yes	Yes
Quality documents	Module 3	Part II	Yes	Yes
Non-clinical documents	Module 4	Part III	Yes	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

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

13.1 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 new CTGTP applications. The following sections are to be submitted:

Cover Letter

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

Comprehensive Table of Contents

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: Applicants must complete the relevant checklist found in Appendix 3 or Appendix 4

Introduction

Applicants should give a concise summary of the application and justify the need for the application – for example, whether the product presents an advantage to patient groups in terms of improved quality, safety and efficacy compared to available alternatives.

Applicants should also justify the lack of certain documents within the dossier and deviation from the guidelines, if any.

Labelling, Package Insert (PI)

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 for the product.

One PI should be registered for each product application. If multiple manufacturing sites are proposed for registration, information for all sites should be included in one PI. If there are different strengths or dosage forms, the submission of one common PI for all strengths or dosage forms is encouraged. If separate PIs are to be registered for different strengths or dosage forms, the content should be consistent across the PIs, except for strength/dosage form-specific information.

All artwork and drafts should be legible. 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.

Handwritten information is not acceptable, with the exception of statements such as ‘batch number and expiry dates will be printed’ or similar on the outer carton or inner/blister labels. Movable text boxes/pictures placed over other hidden information/text are also not acceptable.

The product labels, PI 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.

Approved SPC/PI

In this section, the applicant should submit the approved SPC/PI from the drug regulatory agency as a proof of approval.

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

Description of Batch Numbering System

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.

Proof of Approval

Proof of approval is not required for CTGTP new applications undergoing a full evaluation.

For an abridged evaluation route, proof of approval from the comparable overseas regulators is required. Proof of approval must come in the form of:

- an official approval letter, or equivalent document (e.g. Certificate of Pharmaceutical Product; CPP), which certifies the registration status of the drug product; and
- the SPC, PI approved by the drug regulatory agency that issued the approval letter.

If the SPC is in a non-English language, applicants should refer to section 4.1.2 *Language and Translation* for more information on acceptable translations.

Note that all aspects of the CTGTP 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 approval letter.

CPP should be valid at the time of submission and should comply with WHO format (refer to Appendix 8). It is not required for information such as the product formula, manufacturing sites, etc. to be reflected on the CPP, but if such information are present in the CPP, the information should be consistent with that proposed for the Singapore market. Note that 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 4.1.2 *Language and Translation* and 4.1.3 *Certifying Non-Original Documents* for more details. Reference to drug regulatory authority websites in the form of website screenshot and URL (for the website) for confirmation of the approval status of the products by that regulatory authority are acceptable, provided that the product's identity and product's ownership can be confirmed from that website.

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 that both products marketed under the different brand names are **identical** in all aspects of quality, safety and efficacy except for the brand name.

Authorisation Letters

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:

(a) *from Product Owner to the Applicant (Company)* – this letter authorises the local applicant to apply for and be the product registrant for CTGTP and be responsible for all matters pertaining to the registration of this product in Singapore.

(b) *from Product Owner to Manufacturer*– this letter authorises the specified manufacturer to produce, pack and/or label CTGTP intended for Singapore. If there are multiple CTGTP 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 CTGTP (such as the manufacturing operation of each manufacturer in relation to the product being submitted).

(c) *from Product Owner to Batch Releaser* – this letter authorises the specified company to batch release the CTGTP. 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 CTGTP intended for Singapore.

Applicants are to ensure that all names and addresses in the authorisation letters are consistent with the information provided in 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 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.

GMP Certification/Proof of GMP Compliance

Documentary evidence must be provided to certify that the manufacturer(s) complies with current applicable GMP standards. An applicant may submit one of the of the following document as supporting evidence:

- GMP certificate issued by a regulatory agency for all CTGTP manufacturing sites including, but not limited to, bulk product manufacturer(s), primary packer(s) and secondary packer(s);
- CPP that bears the manufacturer's name(s) and address(es) and states that the certifying authority conducts periodic inspection of the manufacturing plant in which the dosage form is produced; or
- Reference to EudraGMP, the database of the European Community of manufacturing authorisations and of certificates of good manufacturing practice.

Applicants referring to the EudraGMP as the proof of GMP compliance should provide a screen capture of the EudraGMP 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 should be consistent throughout the application – i.e. GMP certificate, Letter of Authorisation and CTD sections.

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

Proof of GMP compliance must be valid at the time of submission to HSA and must be in English. Applicants should refer to section 4.1.2 *Language and Translation*.

If the submitted proof of GMP compliance is no longer valid or has less than 1 month's validity at the time of acceptance of the application for evaluation, HSA reserves the right to request for a commitment letter from the applicant to submit an updated and valid proof of GMP compliance by a specified date post-acceptance.

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

For products manufactured in the USA or Canada, if the applicant is unable to obtain any proof of GMP compliance (in the form of a CPP or GMP certificate) from either US FDA/Health Canada or other regulatory agencies, the applicant is required to submit the latest Establishment Inspection Report (EIR) issued by US FDA or Inspection Exit Notice issued by Health Canada, and any other relevant supporting documents[1] as proof of GMP compliance. The applicant is also required to provide the following information if not found in the inspection reports:

- the last date of audit by US FDA/Health Canada;
- the approved dosage forms;
- any licensing conditions or restrictions;
- the scope of the inspection; and/or
- objective evidence and the date of a satisfactory close-out of the latest inspection conducted by US FDA/Health Canada.

For products manufactured in Switzerland, if the applicant is unable to obtain any proof of GMP compliance (in the form of a CPP or GMP certificate) from either

[1] Any other supporting document which declares GMP compliance of the manufacturing site in the US and signed by an official of the US FDA.

SwissMedic or other regulatory agencies, the Manufacturer's Licence issued by SwissMedic is an acceptable documentary GMP evidence.

If the drug product is manufactured by a new overseas **CTGTP manufacturing site** not previously registered with HSA before Feb 2021, a GMP Conformity Assessment will be conducted by HSA. Thus, 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 Advanced Therapy Products Branch (as part of the product registration application) as stipulated in the *Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer*.

Overseas CTGTP manufacturers, including manufacturers of active substance, finished product and critical starting materials such as viral vector, who intend to register CTGTP products in Singapore may be subject to GMP Conformity Assessment. Each assessment is generally applicable to a specific site, product, company and manufacturing activities. Multiple application forms are expected to be submitted if there are more than one manufacturing site.

HSA has the prerogative to perform on-site GMP inspection(s) of the overseas manufacturers to assess their GMP compliance based on HSA Guidelines on GMP for Cell, Tissue and Gene Therapy Products. Overseas manufacturers which have been previously inspected and found to conform to GMP standards by at least one Pharmaceutical Inspection Co-operation Scheme (PIC/S) member authority may submit GMP evidence such as valid GMP certificate for evaluation via GMP Documentary Evidence Verification Application (DEVA). If the submitted evidence is found to be acceptable to demonstrate that the overseas manufacturer compiles with the required GMP standards, an on-site GMP inspection may not be performed.

HSA reserves the right to request for a GMP Conformity Assessment if deemed necessary, or to request for additional or updated documents as evidence of GMP compliance during the course of the registration process. HSA also 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 in doubt whether a GMP Conformity Assessment by HSA is required for the manufacturing sites included in the submission, applicants are encouraged to complete and submit applications to request for GMP Conformity Assessment with the product registration application, and HSA will advise accordingly whether the GMP Conformity Assessment would be required.

Declaration on Rejection, Withdrawal and Deferral

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

Registration Status in Other Countries

The full details should be attached in softcopy (PDF) in the format shown in Table 4:

Table 4 Example of a Table of Information on Registration Status in Other Countries

Country	Application status	Status Date	Approved application indication/dosing regimen details
Country 1	*Approved*	*12 Jan 2020*	*Adjuvant treatment of colorectal cancer stage III (Dukes C) following complete resection of primary tumour.*
Country 2	*Approved*	*2 Feb 2020*	*Adjuvant treatment of colorectal cancer following surgery*

Country	Application status	Status Date	Approved application indication/dosing regimen details
Country 3	*Withdrawn by applicant*	*14 Apr 2019*	*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 2018 with completed phase III data for 'Adjuvant treatment of colorectal cancer following surgery'.*
Country 4	*Approved*	*21 Nov 2019*	*Adjuvant treatment of colorectal cancer stage III (Dukes C) following complete removal of primary tumour.* *Notice of Compliance with Conditions issued on 16 April 2019 based on promising efficacy results with condition to furnish confirmatory efficacy data.*
Country 5	*Pending*	*Submitted: 15 Jun 2020*	*Adjuvant treatment of colorectal cancer stage III (Dukes C) following surgery.*

13.2 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

13.3 Quality Documents

The quality documents relate to Module 3 of the ICH CTD or Part II of the ACTD. Please refer to the Appendix 8 for details.

13.4 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: Nonclinical guidelines for detailed information on the contents of non-clinical documents for the application dossier.

13.5 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 Guideline 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 CTGTP formulation submitted in the application and in the appropriate patient population for the indication(s) and/or dosing regimen(s) as requested in the new application.

The submission of risk management plans (RMPs) in support of all new CTGTP applications is mandatory. Guidance on RMP submission requirements can be found in Appendix 9.

13.6 Specific Documentary Requirements for Each Evaluation Route

13.6.1 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 CTGTP active substance and final 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.

13.6.2 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 comparable overseas regulators that issued the proof of approval.

The technical documents required include:

- complete quality documents for both the CTGTP active substance and final 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).

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

- the product;
- the extent of characterisation which is possible to undertake when using state-of-the-art analytical methods; and

- the clinical experience with the product class.

A case-by-case approach is needed for each CTGTP product.

CHAPTER D 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.

14 APPLICATION TYPES

There are two types of variation applications: major variation 1 (MAV-1) and minor variation applications (MIV-1 and MIV-2).

MAV-1	Major variation 1 application for an existing registered product.
	Any variation to the approved indication(s), 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.
Minor Variation	MIV-1 application and MIV-2 application for an existing registered product
MIV-1	Minor variation that • Is specified under Part A of Appendix 10. • Requires prior approval before the change(s) can be implemented.
MIV-2	Minor variation that • Is specified under Part B of Appendix 10; • May be implemented within 40 days upon application submission if there are no objections raised by HSA

HSA may re-categorise the application type if appropriate. Applicants will be notified if they are required to withdraw and resubmit the application according to the correct category.

Please refer to Chapters E and F for more information on MAV-1 and minor variation application, respectively.

15 VARIATION APPLICATION PROCESS

Figure 3 is a schematic diagram illustrating the variation approval process:

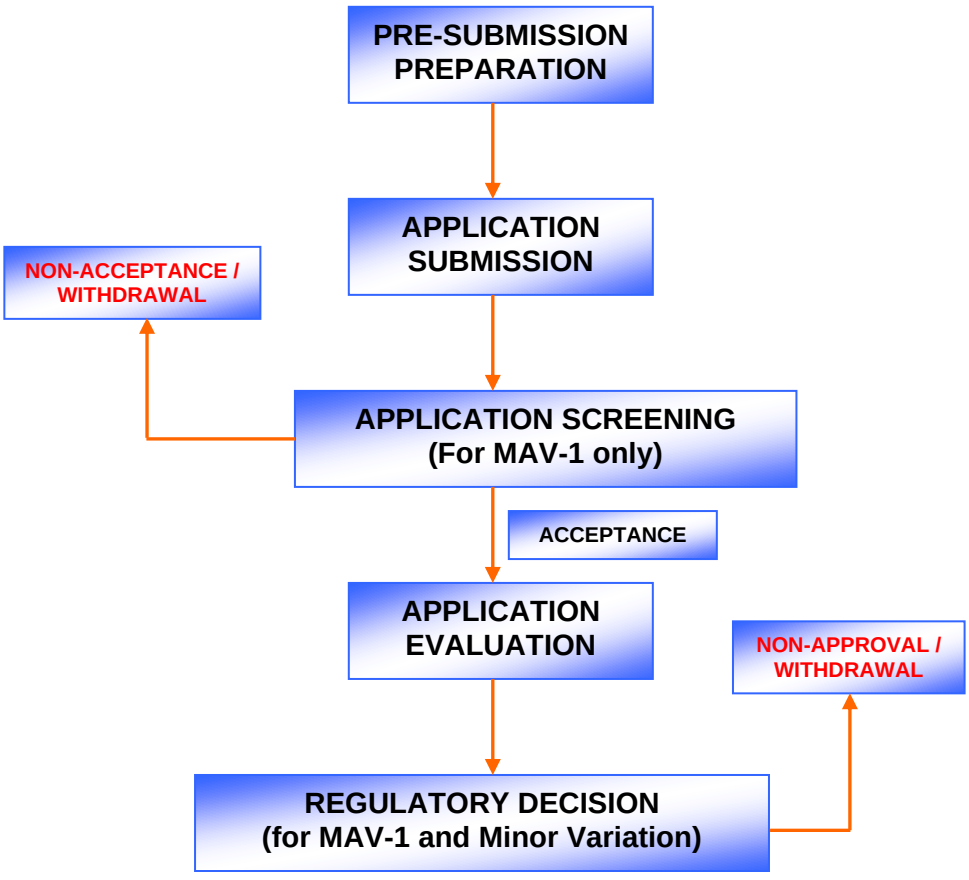

Figure 3 Schematic Diagram of the CTGTP Variation Application Process.

For information on the variation application processing time, refer to Appendix 6 .

15.1 Pre-Submission Preparation

Applicants are encouraged to contact HSA prior to the submission of a variation application if there are questions regarding the application.

15.1.1 Pre-Submission Consultation

An applicant may request for a pre-submission consultation with us if it is necessary to discuss specific areas of concerns related to your MAV-1 application. Your meeting request to us must be made via e-mail to HSA_CTGTP@hsa.gov.sg at least four weeks before the proposed meeting date, with the meeting agenda clearly stated. Relevant documents such as presentation slides and briefing documents should be provided at least one week before the meeting. You may change or cancel the appointment by notifying via e-mail to HSA_CTGTP@hsa.gov.sg.

15.1.2 Pre-Submission Notification

For a MAV-1 submission under the full evaluation route, the applicant is required to notify HSA via email to HSA_CTGTP@hsa.gov.sg 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 substance(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.

15.1.3 Query for Variation Submissions

For issues relating to variation submissions, the applicant should submit a completed enquiry form Appendix 11 via email to HSA_CTGTP@hsa.gov.sg.

15.2 Application Submission

15.2.1 Variation Application Dossier

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 MAV-1 applications should be in the **same CTD format** as that used for the original new CTGTP application.

Application checklists for both ICH CTD and ACTD dossiers are provided in Appendix 12 and Appendix 13, respectively, to guide applicants on the submission requirements and to ensure completeness of the dossier. Each MAV-1 application must be accompanied by a checklist duly completed by the applicant.

15.2.1.1 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.

Colour scanned copy of the original documents should be submitted and original hardcopy of documents are not required. However, HSA reserves the right 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 4.1.3 for more information on certifying non-original documents if the original documents cannot be provided.

All documents submitted in support of an application must be in English. For documents in original language which is not English, a certified translation or a verified translation may be acceptable. Please refer to section 4.1.2 for more information.

For submission requirements for minor variation applications, please refer to Appendix 10.

Submitting a CD or DVD

When submitting a CD/DVD, applicants are encouraged to organise the dossier (i.e. folders and subfolders) according to the CTD format and to include bookmarks in all documents to facilitate retrieval of documents.

Files containing certain scripts will not be accepted due to cybersecurity reasons. Please refer to section 4.1.1 for more information.

The CD/DVD should be properly labelled with the following information:

- Product name;
- Application type; and
- Contents of the CD/DVD (Modules 1 to 5).

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

15.3 Application Screening

MAV-1 applications will be screened to ensure 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.

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.

MAV-1 application submitted without the clinical dossier will not be screened. An Input Request will be issued to the applicant to withdraw the application.

Applicants are also advised to ensure that the dossier is compiled according to the required format. Failure to adhere to the required CTD format will lead to the non-acceptance of the dossier without screening.

If the dossier submitted is incomplete, a screening query stating the deficiencies will be issued to the applicant. The stop-clock starts when an Input Request is sent and ends upon receipt of a complete and satisfactory response to the query. For MAV-1 applications, 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 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 raised during screening, the dossier is considered incomplete for evaluation. An Input Request will be issued to the applicant to withdraw the application. 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 minor variation applications, applicants will receive an “Acceptance” notification sent within 3 working days after submission. For applications submitted under an incorrect application type (e.g. MAV-1 changes submitted as minor variation applications), applicants will be requested to withdraw the application during evaluation.

15.4 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 whenever HSA issues a query and ends upon the receipt of a complete and satisfactory response from the applicant.

In situations where the applicant is unable to provide a complete response within the specified timeframe, the applicant should notify HSA as soon as possible after

receiving HSA's queries. The application will be considered withdrawn if the applicant fails to observe the specified response deadline.

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.

Upon approval/notification of a variation application, applicants will be informed and the product registration information (including registration conditions and post-approval commitments) will be updated to reflect the changes (as applicable).

15.5 Target Processing Timelines

Please refer to Appendix 6 for information on target processing timelines for the different application types and evaluation routes.

15.6 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.

NOTE: Applicants are strongly encouraged to apply for a GIRO account (refer to GIRO application form) with HSA to facilitate payments for future submissions and subsequent payment for retention fee for the registered products.

15.6.1 Screening Fee

The screening fee is only applicable for MAV-1 applications and is payable at the time of online submission. The screening fee is non-refundable once the application is submitted. The screening fee will be debited upon the successful submission of an online application.

A screening fee is not applicable for minor variation applications.

15.6.2 Evaluation Fee

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.

An evaluation fee for minor variation application is payable upon the submission of the application and is non-refundable. The evaluation fee will be debited upon the acceptance of the application.

15.6.2.1 Change of Evaluation Route

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

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application. The screening fee is not refundable. Applicants may wish to seek clarification on appropriate application type or evaluation route via email to HSA_CTGTP@hsa.gov.sg prior to the submission.

CHAPTER E MAJOR VARIATION 1 APPLICATION SUBMISSION

This chapter applies to major variation 1 applications for currently registered CTGTP.

16 MAV-1 APPLICATIONS

A MAV-1 application applies to variations to any of the following:

(a) approved indication(s);

(b) approved dosing regimen(s);

(c) approved patient group(s); and/or

(d) 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 CTGTP registration, applicants may submit up to a maximum of three concurrent MAV-1 applications at any one time.

16.1 Evaluation Routes

There are two evaluation routes for a MAV-1 – full and abridged. The eligibility criteria and documentary requirements are different for each evaluation route.

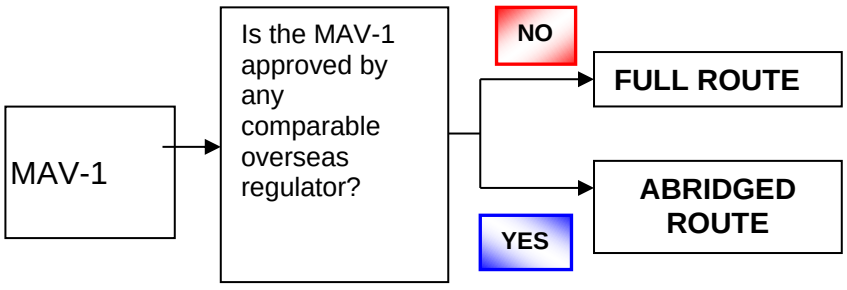

Figure 4 Schematic Diagram of Evaluation Routes for MAV-1

16.1.1 Full Evaluation Route

Full evaluation will apply to a MAV-1 that has not been approved by any comparable overseas regulator at the time of submission.

For a submission under the full evaluation route, the applicant is required to notify HSA via email to HSA_CTGTP@hsa.gov.sg 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.

16.1.2 Abridged Evaluation Route

Abridged evaluation applies to a major variation that has been evaluated and approved by at least one of our comparable overseas regulators. The proposed variation – i.e. the proposed indication(s), 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.

16.2 Documentary Requirements

Table 5 outlines the CTD Modules/Parts required for MAV-1 submitted under each evaluation route:

Table 5 Dossier Submission Requirements for MAV-1

	Location in		Module/Part required	
	ICH CTD	**ACTD**	**Full**	**Abridged**
Administrative Documents and Product Information	Module 1	Part I	Yes	Yes
Common Technical Document	Module 2	*Incorporated into Parts II, III and IV*	Yes	Yes

Overview and Summaries				
Quality documents	Module 3	Part II	No	No
Non-clinical documents	Module 4	Part III	No[§]	No[#]
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

[§] 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.

16.2.1 Administrative Documents

The two evaluation routes for a 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;

> **NOTE**: Applicants must complete the relevant checklists found in Appendix 12 or Appendix 13

(b) Introduction;

(c) Labelling and Package Insert– both the proposed and currently approved Singapore product labels and PI are required. For the proposed labelling/PI, a pristine and an annotated version (which highlights the changes made to the currently approved labelling) are required. Annotations should be made on the proposed labelling materials based on the actual text to be added, and on current approved labelling materials. Current approved text proposed for

deletion should be struck through, whereas newly added and proposed text should be underlined or highlighted. Current approved text that is not intended to be deleted should not be annotated. However, the translocation of current approved text from one section to another can be allowed in its entirety.

(d) Approved SPC/PI from the regulatory agency that issued the proof of approval and from each of HSA's reference regulatory agencies (where applicable);

(e) Proof of Approval – for a MAV-1, the official approval letter(s) must contain information on the requested Singapore variation.

(f) Declaration on rejection, withdrawal and deferral; and

(g) Registration Status in Other Countries.

16.2.2 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.

16.2.3 Quality Documents

Quality documents (Module 3/Part II) are not required for MAV-1 applications.

16.2.4 Non-clinical and Clinical Documents

Each evaluation route will have different non-clinical and clinical documentary requirements.

For MAV-1 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 in Appendix 9.

16.2.5 Specific Documentary Requirements for Each Evaluation Route

16.2.5.1 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.

16.2.5.2 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).

CHAPTER F MINOR VARIATION APPLICATION SUBMISSION

This chapter applies to minor variation applications for currently registered CTGTP.

17 APPLICATION TYPES

There are two types of minor variation applications – MIV-1 and MIV-2:

MIV-1	Minor variation that • Is specified under Part A of Appendix 10. • Requires prior approval before the change(s) can be implemented.
MIV-2	Minor variation that • Is specified under Part B of Appendix 10; • May be implemented within 40 days upon application submission if there are no objections raised by HSA.

18 APPLICATION SUBMISSION

Applicants should be familiar with the guidelines and documentary requirements described in Appendix 10 before submitting minor variation applications. The appropriate variation may be selected with the aid of this self-help tool. In the event that applicants are still unable to determine the type of variation, please complete and submit enquiry form Appendix 11 via email to HSA_CTGTP@hsa.gov.sg.

Any undisclosed variation(s) embedded in the submitted data, including any flow-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.

Applicants are strongly encouraged to submit variation applications for multiple strengths of the same CTGTP at the same time. Applicants should also indicate in the cover letter if the proposed change(s) affect multiple products and if there are other pending variation (MAV-1/Minor Variation) applications for the same CTGTP.

- Suggested guidance for further reading: Appendix 6
- Submission route – abridged route.

For each CTGTP registration, applicants may submit up to a maximum of two concurrent minor variation applications at any one time.

If one minor variation application contains multiple changes that belong to both MIV-1 and MIV-2 amendments categories, then the minor variation should be categorised as MIV-1 changes.

Minor variation application should be grouped together as one application when these are consequential changes. For instance, for a quality MIV-1 changes, variation updates to the product labelling unrelated to quality changes will not be accepted.

Unrelated consequential changes in a single application is not allowed and should be split into separate minor variation application(s).

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

CONTACT INFORMATION

Advanced Therapy Products Branch (ATPB)
Medicinal Products Pre-Market Cluster
Health Products Regulation Group
Health Sciences Authority

11 Biopolis Way, #11-01, Helios
Singapore 138667
www.hsa.gov.sg
Fax: 6478 9032
Website: www.hsa.gov.sg

HSA
Health Sciences Authority