HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

**OCT 2024**

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

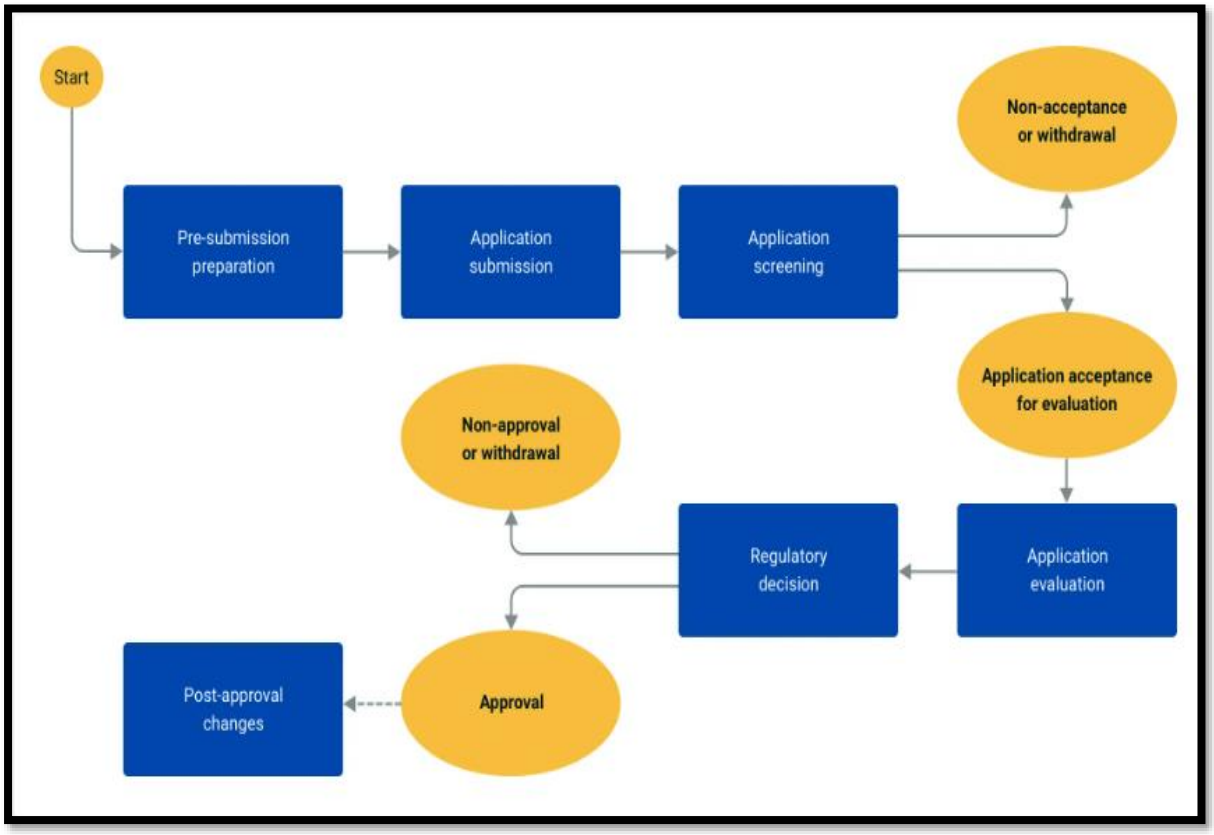
HSA Health Sciences Authority

# Table of Contents

# 1. REGISTRATION OF CLASS 2 CTGTP

## 1.1 Registration overview

Product registration is required for Class 2 CTGTP. Understand the registration process before submitting your application.



## 1.2 Application types

There are three application types to register a Class 2 CTGTP:

| Application types | Conditions |
|---|---|
| NDA-1 | For the first strength of a product containing a new CTGTP. This means the CTGTP is currently not registered in Singapore. |
| NDA-2 | 1. For the first strength of a product containing:<br>• New combination of registered CTGTP or<br>• Registered CTGTP in either of the following:<br>o New dosage forms, such as suspension for intravenous infusion and powder for injection<br>o New presentation, such as single-dose vials, freezing bags and pre-filled syringes<br>o New formulation<br>o New route of administration<br>OR<br>2. For products that do not fall under the requirements for NDA-1 or NDA-3. |
| NDA-3 | For subsequent strengths of a CTGTP that has been registered or submitted as an NDA-1 or NDA-2.<br><br>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. |

If your application is identified to be more appropriately submitted under a different application type during screening, you will be informed of the change via an input request.

### 1.3 Evaluation routes

Applications are processed via a specific evaluation route, which will determine the documents required, fees and evaluation turnaround time:

| Evaluation route | Conditions |
|---|---|
| **Full** | Any new CTGTP that has **not been approved by any** of HSA's comparable overseas regulators[1] at the time of submission.<br><br>**Pre-submission notification** is required for this route (details in Section 1.4). |
| **Abridged** | Any new CTGTP that has been **approved by at least one** of HSA's comparable overseas regulators[1] at the time of submission. |

### 1.4 Pre-submission notification

Notify us **at least two months before** you submit your **full evaluation application** via email to HSA_CTGTP@hsa.gov.sg with the following information:

- Product name
- Active ingredients
- Summaries of quality, non-clinical and clinical data e.g. Module 2.4 Non-clinical Overview, Module 2.5 Clinical Overview
- Planned submissions in other countries
- Planned date of submission to HSA

*[1]HSA's comparable overseas regulators are: Therapeutic Goods Administration (TGA, Australia), Health Canada (HC, Canada), Food and Drug Administration (FDA, United States of America), European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom)*

### 1.5 Fees and turnaround time

Refer to CTGTP fees and turnaround time.

You are encouraged to make payment via GIRO (apply eGIRO). GIRO deductions will be triggered as follows:

**Screening fee**, payable upon successful online application.

**Evaluation fee**, payable upon dossier acceptance for evaluation.

A notification on the successful GIRO deductions will be sent to the applicant's email indicated in the application. All fees paid are non-refundable.

For non-GIRO applicants, an invoice will be sent to the applicant's email indicated in the application.

### 1.6 GMP conformity assessment of overseas manufacturers

All new overseas manufacturers who intend to register CTGTP in Singapore will be subjected to a Good Manufacturing Practice (GMP) conformity assessment by us.

### 1.7 RMP submission

A risk management plan (RMP) must be submitted as part of the application dossier for all NDA-1 for CTGTP.

For other application types, including NDA-2/3 or variation applications, an RMP is to be submitted only upon HSA's request during application review.

### 1.8 Environmental Risk Assessment (ERA)

The Genetic Modification Advisory Committee (GMAC) recommendation is required for CTGTP containing genetically modified organisms, e.g. viral vectors. You need to submit documentation of your GMAC application for ERA with the NDA application dossier and provide the GMAC assessment outcome once it is available.

# 2. APPLICATION SUBMISSION

## 2.1 Application dossier

Application dossiers are the collections of technical documents supporting your application. You need to **submit all documents in English.**

Your application dossier must be organised in either an **International Council for Harmonisation Common Technical Document (ICH CTD) or ASEAN CTD (ACTD) format**. These formats use the modular framework described by the ICH Topic M4 and the ASEAN guidelines on the Common Technical Document for Registration of Pharmaceuticals for Human use: Organisation of the Dossier, respectively. The table below summarises the organisation of each dossier format:

| Documents | Location in ICH CTD | Location in ACTD |
|---|---|---|
| Administrative documents | 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 |

> The dossier format used in registering the CTGTP will determine the submission format for future variation applications of your registered CTGTP.

## 2.2 Application checklists

Application checklists provide guides on the documentary requirements for the respective applications.

Each application must be accompanied by the chosen CTD application checklist, completed by the applicant:

- NDA Checklist for Class 2 CTGTP (ICH CTD Format)
- NDA Checklist for Class 2 CTGTP (ACTD Format)
- Checklist for the Registration of Class 2 CTGTP containing materials of animal origin (if applicable)

### 2.3 How to apply

Submit your applications through SHARE.

Ensure you have the following before proceeding:

- CRIS company account and note your client code for billing
- Corppass

**Schedule a pre-market consultation with us, if necessary.**

You may request for a pre-market consultation if it is necessary to discuss **specific areas related to your application**, including the need for an overseas Good Clinical Practice (GCP) inspection.

Your **meeting request must be made at least five months before the proposed meeting date** (details in Section 2.4).

### 2.4 Pre-market consultation

You can book a consultation with us to discuss specific regulatory requirements relevant/unique to your CTGTP or seek feedback on the appropriateness of specific supporting documents for your application.

Each consultation is limited to one CTGTP registration application and up to 1 hour in duration. Pre-market consultation fee applies.

**Pre-market consultation does not constitute a scientific evaluation** of the CTGTP and does not guarantee CTGTP registration.

Advice given is based on the information provided up to the point of consultation. Evaluation will be based on information and dossier submitted during application.

## Step 1: Book appointment online

- **When: Five months before** the consultation. For example, an appointment for a consultation on 31 August must be booked by 1 April.
- **How:** Complete the **online booking form.**
    - You will receive an acknowledgement email with a *Response ID*. Please quote this *Response ID* for all correspondence with us regarding this request.
    - An invoice will be sent to you within 5 working days. Please make the payment within 3 working days from the date of invoice. Otherwise, this request will be void.
    - You will receive a confirmation email upon payment processing.

**Rescheduling or cancelling your appointment**

To change or cancel the appointment, email with subject *[Response ID] Rescheduling/Cancelling Pre-Market Consultation* to HSA_CTGTP@hsa.gov.sg.

Fees paid are not refundable. Only one rescheduling is allowed per booking reference, subject to availability at the point of processing.

## Step 2: Documents submission

- **When to submit**: **At least 30 working days before the consultation**, to allow us ample time to review them before the consultation.
- **What to submit:**
    - Completed **Pre-Market Consultation Form**
    - Relevant information/documents described in the form
- **How to submit:** Reply the confirmation email or email to HSA_CTGTP@hsa.gov.sg with subject *[Response ID] Document Submission*.

**Check before submitting**

Check that you have attached the required documents for consultation. Incomplete information may result in the appointment being rescheduled or cancelled. Fees paid are not refundable.

# 3. SCREENING, EVALUATION AND REGULATORY DECISION

## 3.1 Screening stage

Application screening involves us checking that the application type is correct and that the dossier is complete. The screening timeline starts from the date of receipt of the application dossier.

Screening will not commence if:

- The entire dossier sections are not submitted.
- The submitted dossier does not comply with either the ICH CTD or ACTD format.

Input request(s) will be sent to the applicant if clarification or additional information is required. The applicant will be given **20 working days** to respond to each input request. The application will be put on a stop-clock, starting from the date of input request until the date of receipt of a complete and satisfactory response to the query.

Screening input requests will generally be capped at two cycles.

Failure to address the deficiencies raised during screening will render the dossier incomplete for evaluation. Applicants will be requested to withdraw the application. Future submission will be processed as a new application.

- Screening fees paid are non-refundable.
- If your application is identified to be more appropriately submitted under a different application type, you will be informed to change via an input request.
- The screening process only checks for completeness of the application dossier for evaluation. The acceptance of the dossier for evaluation does not constitute the adequacy of the data for regulatory approval.

## 3.2 Evaluation stage

If the dossier is screened to be complete for evaluation, an acceptance notice will be issued, marking the start of the evaluation timeline. The evaluation stage ends when a regulatory decision is issued.

Input request(s) will be sent to the applicant if clarification or additional information is required. The applicant will be given **20 working days** to respond to each input request. The application will be put on a stop-clock, starting from the date of input request until the date of receipt of a complete and satisfactory response to the query.

Applicants are reminded that the submission of additional supporting data not requested by HSA following the acceptance of the application will not be considered in the evaluation.

## 3.3 Regulatory decision

You will be notified of the regulatory decision after evaluation:

### 3.3.1 Approval

An approval decision means the application satisfies the registration requirements for quality, safety and efficacy.

The product will be added to the Register of Class 2 CTGTP. As the CTGTP registrant, you are responsible for ensuring the CTGTP's quality, efficacy and safety throughout its life cycle, and must notify us of any changes to these profiles.

### 3.3.2 Rejection

A rejection decision means your response failed to address the major deficiencies specified in the non-approvable notice.

A rejection decision is final.

# 4. RETAIN, CANCEL OR TRANSFER CTGTP REGISTRATION

## 4.1 Retain CTGTP registration

Registered CTGTP will remain in the Register of Class 2 CTGTP, unless:

- The registration is suspended or cancelled by HSA
- The registration is cancelled by the registrant (see Section 4.2) OR
- The annual retention fee **payment is not completed within 60 days** after the retention due date[2].

A retention notice will be sent to the registrant 60, 45 and 30 days before the retention due date.

The SHARE system will automatically create a retention application one day after the retention due date, and payment reminder notices will be sent 15 and 30 calendar days after the retention due date.

> Your CTGTP registration will be automatically cancelled if we do not receive your retention fee payment within 60 days after the retention due date. Cancellation of registration is irreversible.

If your company has an existing GIRO account with us, GIRO deduction will be triggered and a notification on the successful GIRO deduction will be sent to you.

If your company does not have an existing GIRO account with us, an invoice will be sent via email to you, with the payment instructions.

> You are advised to update your contact information through SHARE to ensure that you receive your retention notifications without delays.
>
> HSA will not be responsible for failure in the delivery of the retention notices due to outdated email records with us.

[2] The retention due date for each registered CTGTP will fall on the anniversary of the CTGTP registration date.

## 4.2 Cancel CTGTP registration

Submit your ***cancellation*** applications via SHARE, if you no longer intend to retain the CTGTP registration.

A supplier **cannot continue to supply** the CTGTP after its registration is cancelled.

> **Cancellation is immediate upon submission and is irreversible.**
> Requests for reinstatements of cancelled CTGTP registrations will not be entertained. You will need to submit a new registration application for the CTGTP.

## 4.3 Change of Registrant (Transfer of CTGTP registration)

A new registrant can submit a ***change of registrant*** application via SHARE to transfer CTGTP registration(s) from the current registrant. Change of registrant fees apply.

### 4.3.1 New registrant eligibility and submission requirements

The new registrant must be a Singapore registered company and have the following to access SHARE:

- CRIS company account and note your client code for billing
- Corppass

**Submission requirements:**

1. Letter of Authorisation from the product owner (using the product owner's company letterhead) containing:
    a. Full name of the CTGTP and its Singapore product registration number, the name and address of the new registrant
    b. A statement authorising the new registrant
    c. A statement to withdraw the authorisation granted previously to the current registrant
    d. The proposed effective date for the transfer
2. Written confirmation that arrangement has been made with the current registrant for the handing over of the relevant product registration files.

### 4.3.2 Current registrant responsibilities

Before the change of registrant application is submitted by the new registrant, the current registrant should ensure:

- There are no pending or outstanding variation applications for the CTGTP to which the transfer relates
- Payment of the annual retention fee due (if applicable) has been completed

The application cannot be processed if either of the above are pending.

# 5. VARIATION APPLICATIONS

## 5.1 Variation overview

### 5.1.1 Variation types

There are three types of variation applications for a registered CTGTP. All variation applications require approval before changes can be implemented.

- **Major variation 1 (MAV-1) application** i.e., Any variation that involves:
  - Change(s) to the approved indication, dosing regimen or patient group(s) OR
  - Inclusion of clinical information extending the usage of the CTGTP e.g. clinical trial information related to an unapproved indication, dosing regimen or patient population.

  See section 5.2 for submission details.

- **Minor variation (MIV-1 and MIV-2) applications** i.e., Any variation that is specified under the MIV Checklist for Class 2 CTGTP where:
  - Part A refers to an **MIV-1 application**
  - Part B refers to an **MIV-2 application**

  See section 5.3 for submission details.

> HSA may notify the applicant to withdraw and resubmit the application under a more appropriate variation type, where necessary. Screening fees paid for MAV-1 applications are non-refundable and non-transferable to application resubmissions.

### 5.1.2 Fees and turnaround time

Refer to CTGTP fees and turnaround time.

### 5.1.3 How to apply

Submit your applications through SHARE. Ensure you have the following before proceeding:

- CRIS company account and note your client code for billing
- Corppass

## 5.2 Major variation 1 (MAV-1) application

### 5.2.1 Evaluation routes

There are two evaluation routes for an MAV-1 application with different documentary requirements, fees and evaluation turnaround times:

| Evaluation route | Conditions |
|---|---|
| **Full** | A variation that has **not been approved by any** of HSA's comparable overseas regulators[1] at the time of submission.<br><br>Like for NDA, **pre-submission notification** is required for this route (see details in section 1.4) |
| **Abridged** | The proposed variation is the same as that evaluated and **approved by at least one** of HSA's comparable overseas regulators[1] at the time of submission. |

### 5.2.2 MAV-1 submission requirements

Each application must be accompanied by a completed application checklist with the relevant specified documents:

- **MAV-1 Checklist for Class 2 CTGTP (ICH CTD Format)**
- **MAV-1 Checklist for Class 2 CTGTP (ACTD Format)**

> Your application dossier must be organised in the **same ICH CTD/ACTD format submitted in the original NDA** for your CTGTP registration.
> **All documents must be in English.**

## 5.3 Minor variation (MIV-1 and MIV-2) applications

### 5.3.1 Organising your MIV applications

At any one time, you may submit up to **four concurrent MIV-1 applications** and **only one MIV-2 application** for each registered CTGTP.

If there are multiple changes, follow the guide below to organise your submission(s):

| Change category | Submission options |
|---|---|
| MIV-1 only | MIV-1 changes should be grouped and submitted as one MIV-1 application if the changes are consequential. A consequential change is an unavoidable and direct result of another change e.g. a change of specifications is consequential to a change of manufacturing process.<br><br>Grouping of non-consequential MIV-1 changes under one application is not allowed. You will be requested to withdraw and resubmit separate applications. |
| MIV-2 only | Multiple MIV-2 changes can be bundled in one MIV-2 application. |
| MIV-1 and MIV-2 | If your variation involves an MIV-1 change and an MIV-2 change, you can bundle both changes and submit as one MIV-1 application. |

Your application dossier must be organised in the **same ICH CTD/ACTD format submitted in the original NDA** for your CTGTP registration.
**All documents must be in English.**

### 5.3.2 MIV submission requirements

You will need to submit the following in your online application:

- Table of contents
- Cover letter
- Table of summary of changes which must include all of the following:
    - Section(s) of the original dossier affected by the change(s)
    - Approved and proposed condition(s)
    - Reason(s) for the change(s)
    - Registration status and date of approval of the proposed change(s) in other countries/agencies
- Relevant **MIV Checklist for Class 2 CTGTP** and their specified supporting documents

You need to disclose all proposed changes in the Table of summary of changes. Any undisclosed variation embedded in the submitted data, or any follow-on changes not requested, will not be considered for evaluation.

## REVISION HISTORY

| Version | Date of publication | Amendment Summary |
|---|---|---|
| 1 | Oct-2024 | This document GN-ATPB-1-1 Version 1 replaces the previous guidance GN-ATPB-001 Revision 2 dated January 2024. |

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