HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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# GUIDANCE FOR INDUSTRY

## POST-MARKETING VIGILANCE REQUIREMENTS FOR THERAPEUTIC PRODUCTS AND CELL, TISSUE AND GENE THERAPY PRODUCTS

HSA Health Sciences Authority

## *PREFACE*

*This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.*

*In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.*

## REVISION HISTORY

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# TABLE OF CONTENTS

# 1 INTRODUCTION

This guidance references the Health Products Act (Chapter 122D), Health Products (Therapeutic Products) Regulations 2016 and Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021.

## 1.1 PURPOSE AND SCOPE

This guidance applies to (i) registrants, manufacturers, importers and suppliers of registered therapeutic products and cell, tissue or gene therapy products (CTGTP) and (ii) importers of unregistered therapeutic products and CTGTP for patients' use in Singapore.

The purpose of this document is to provide guidance on the **submission of relevant safety information and risk management plans** to the Vigilance and Compliance Branch of the Health Products Regulation Group (HPRG) of the Health Sciences Authority (HSA).

This guidance addresses the types of documents to be submitted at the point of application for product registration, and during the post-marketing phase of the therapeutic products and CTGTP (e.g. during variation application review or when new significant safety issues are identified).

The requirements and timelines for reporting safety information related to therapeutic products and CTGTP are also included. The topics covered in this guidance include the following:

- Records of adverse events (AE);
- Serious AE reporting;
- Risk management plans (RMP);
- Safety notification to HSA;
- Periodic benefit-risk evaluation reports (PBRER);
- Educational materials for physicians and/or patients.

## 1.2 BACKGROUND

During the clinical development of a therapeutic product or CTGTP, the patient sample size is relatively small and the patient populations recruited into clinical trials are quite homogenous due to the inclusion and exclusion criteria in the protocol for enrolment into the trials. As such, the safety and efficacy experience at the point of market approval of the product is usually limited. In spite of rigorous reviews prior to market entry, new safety issues (especially rare ones) may only be discovered and characterised with increased usage of the product following marketing authorisation. Therefore, it is important that the safety profiles of these products are monitored throughout their life cycle after they have been approved for use in the market.

In order to obtain a comprehensive picture of clinical safety and optimise a product's benefit-risk balance, careful planning of pharmacovigilance (PV) and risk minimisation activities (RMA) throughout the life cycle of the therapeutic product or CTGTP is necessary to characterise its safety profile and minimise its risks. The PV activities provide assurance that any new signals are promptly detected, while the RMA are targeted at mitigating known risks associated with these products.

## 1.3 DEFINITIONS

**Adverse effect and Adverse event (AE)**

Under the Health Products Act, an adverse effect, in relation to a health product, means any debilitating, harmful, toxic or detrimental effect that the health product has been found to have or to be likely to have on the body or health of humans when such health product is used by or administered to humans. In this guidance, the term 'adverse event' is being used in place of 'adverse effect'.

**Causality assessment**

Determination of whether there is reasonable possibility that the product is aetiologically related to the AE. Causality assessment includes assessment of temporal relationships, dechallenge or rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and biological plausibility.

**Cell, tissue or gene therapy product (CTGTP)**

"Cell, tissue or gene therapy product", as defined in the First Schedule of the Health Products Act, refers to a category of health products that is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose. Its scope includes viable or non-viable human cells or tissues, viable animal cells or tissues, and 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).

The category of CTGTP excludes the following:

*(a)* a recombinant vaccine for a preventive purpose;

*(b)* an *in-vitro* diagnostic product;

*(c)* bone marrow, peripheral blood or umbilical or placental cord blood from a human that is minimally manipulated and intended for homologous use;

*(d)* 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;

*(e)* organs and tissues that are minimally manipulated and intended for transplant;

*(f)* reproductive cells (sperm, eggs) and embryos intended for assisted reproduction;

*(g)* whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders.

**CIOMS I form**

An AE reporting form developed by the Council for International Organisations of Medical Sciences (CIOMS), intended for notifying the regulatory authorities (available at http://cioms.ch/index.php/cioms-form-i).

**Company**

Company refers to the manufacturer, importer, supplier or registrant of a registered therapeutic product or CTGTP.

**Data lock point**

The date designated as the cut-off date for data to be included in a Periodic benefit-risk evaluation report (PBRER).

**Homologous use**

Homologous use means the use of a CTGTP to repair, reconstruct, replace or supplement the cells or tissue of an individual (called the recipient) if the CTGTP performs the same basic function(s) in the recipient as the original cells or tissue in the donor in the same anatomical or histological environment.

**International birth date**

The date of the first marketing approval for any product containing the active substance granted to any company in any country in the world.

**Minimally manipulated**

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 are not altered, such as by cutting or sizing; grinding; shaping; centrifugation; soaking in an antibiotic or antimicrobial solution; sterilisation or irradiation; cell separation, concentration or purification; filtration; lyophilisation; freezing; cryopreservation; or vitrification.

**Periodic benefit-risk evaluation report (PBRER)**

A PBRER is intended to present a periodic, comprehensive, concise and critical analysis of new or emerging information on the risks of the health product, and on its benefits in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

**Risk management plan (RMP)**

A detailed description of the risk management system which includes a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent and minimise risks relating to a therapeutic product or CTGTP.

**Serious adverse reaction and Serious adverse event**

Under the Health Products (Therapeutic Products) Regulations, a serious adverse reaction for a therapeutic product means an AE that is unintended and occurs in association with the use or administration of a therapeutic product at doses normally used in humans for prophylaxis, diagnosis or therapy of a disease or for the restoration, correction or modification of a physiological function, and that

(*a*) may result in a person's death;

(*b*) may threaten a person's life;

(*c*) results in a person being hospitalised or prolong a person's existing stay in hospital;

(*d*) results in a person's persistent or significant disability or incapacity;

(*e*) results in a congenital anomaly or birth defect; or

(*f*) is judged to be medically important even though the effect might not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the person's health or may require intervention to prevent the person's death or one of the other outcomes referred to in sub-paragraphs (*c*), (*d*) and (*e*).

Under the Health Products (Cell, Tissue and Gene Therapy Products) Regulations, a serious adverse reaction for a CTGTP means an AE that is unintended and occurs in association with the administration of a CTGTP in

humans, and that may result in the outcomes mentioned in sub-paragraphs *(a)* to *(f)* above.

Serious adverse event is an AE that may result in the outcomes mentioned in sub-paragraphs *(a)* to *(f)* above.

When an AE threatens a person's life, it means that the person was at risk of death at the time of event. It does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the person's health should be considered as serious.

**Therapeutic product**

"Therapeutic product", as defined in the First Schedule of the Health Products Act, refers to a category of health products that is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose. Its scope includes chemical and biological therapeutic products.

## 2 RESPONSIBILITIES OF THE COMPANY

The company is responsible for its products in the market and must have proper systems and processes in place to take appropriate action, when necessary. This includes having written procedures for the receipt, evaluation of AEs and the reporting of serious AEs.

The company is responsible for matters relating to product safety and should provide a point of contact on safety matters and updates to the Vigilance and Compliance Branch.

The responsibilities of the company include:

- Report all relevant safety information relating to the therapeutic product or CTGTP to HSA, in accordance with the local requirements stipulated in this guidance;
- Be aware of and ensure compliance with any local post-marketing requirements, obligations or commitments relating to the safety of the product, e.g. implementing RMP and other follow-up actions, and complying with safety restrictions imposed on use of the products;
- Respond promptly to any request from HSA for the provision of information necessary for the benefit-risk evaluation of the product, e.g. sales data and list of purchasers; and
- Provide prompt inputs, when required by HSA, on significant safety concerns so that timely and appropriate regulatory action(s) can be taken, e.g. communications to healthcare professionals or patients, or issuance of press releases.

The company should contact the Vigilance and Compliance Branch proactively whenever there are any changes in its contact details, such as the name of the contact person, his/her designation, telephone number, fax number, email address and mailing address. The contact details should be kept up to date at all times.

## 3 RECORDS OF ADVERSE EVENTS

The manufacturer, importer, supplier or registrant of a therapeutic product or CTGTP must maintain records of every event that concerns any AE arising from the use of the product and produce such records for inspection by HSA, when required.

The record must contain all of the following information:

- the proprietary name of the product;
- the date on which the manufacturer, importer, supplier or registrant first became aware of the event;
- the lot, batch or serial number of the product; and
- the nature of the AE.

The record must be **retained for at least 2 years** after the expiry date of the therapeutic product or CTGTP. This will facilitate traceability and retrospective review of emerging signals arising from safety and/or quality issues by HSA.

## 4 SERIOUS ADVERSE EVENT REPORTING

Upon becoming aware of any serious AE, the company must report the event to the Vigilance and Compliance Branch as soon as possible **and no later than 15 calendar days**. The initial report of a serious AE should contain as much detail as available but should not be delayed for the sake of gathering more information.

The clock for reporting starts as soon as any personnel in the company, including sales representatives, are made aware of the serious AE. If there is uncertainty about whether the serious AE is reportable, the company should still submit a report within 15 calendar days.

It is **mandatory** for companies to report all serious AEs. This includes reports where the company does not agree with the reporting healthcare professional's assessment and reports where the healthcare professional has not provided a causality assessment.

Serious AEs which are not suspected of being product-related by the healthcare professional should not be reported unless the company has reasons to suspect a causal association.

## 4.1 REPORTING REQUIREMENTS

To report serious AEs, the company is to complete the CIOMS I form and submit it via online reporting or to the Vigilance and Compliance Branch via HSA_productsafety@hsa.gov.sg.

Reports of serious AEs should be as complete as possible and contain essential information to facilitate causality assessment. The minimum information required for the submission of an initial report is:

- an identifiable reporter or healthcare professional;
- an identifiable patient;
- an AE; and
- a suspected product.

The name, profession and place of practice of the reporter or healthcare professional making the report should be included to facilitate the detection of duplicate reports.

The company is to comment on whether there is a causal association between the suspected product(s) and AE(s) and explain how the causality assessment was made.

## 4.2 FOLLOW-UP REPORTS

When additional medically relevant information is received for a previously reported case, the company is required to submit the follow-up report as soon as possible within 15 calendar days. The reports are to be clearly labelled as follow-up reports (with appropriate cross-referencing).

## 4.3 LOCAL NON-SERIOUS ADVERSE EVENTS OR OVERSEAS ADVERSE EVENTS

Local non-serious AEs or overseas AEs occurring outside of Singapore need not be reported to HSA. However, records of the events must be maintained and made available upon request.

## 4.4 REPORTING BY CONSUMERS

Consumers who report AEs should be encouraged to seek medical attention and get the attending healthcare professional to report the AE. Medical confirmation is strongly encouraged for the purpose of submission to the Vigilance and Compliance Branch. If a consumer is unwilling or unable to seek medical attention, the company should attempt to obtain as much information as possible from the consumer about the AE.

For serious AEs, voluntary informed consent must be obtained from the consumer before the company contacts the treating healthcare professional for relevant information, such as medical documentation. This is to facilitate causality assessment of such reports by the company.

## 4.5 SCIENTIFIC LITERATURE AND OTHER POST-MARKETING SAFETY INFORMATION

Any scientific or medical literature or information from unpublished or published study reports, surveys and registries that could change the benefit-risk balance of the registered therapeutic product or CTGTP must be communicated to the Vigilance and Compliance Branch within 15 calendar days after first knowledge.

A copy of the relevant report should be provided. If the report is not in English, the company must submit a summary or translation in English.

# 5 ADVERSE EVENT REPORTING IN SPECIAL SITUATIONS

## 5.1 NEW SAFETY INFORMATION ON PRODUCTS PENDING HSA'S REVIEW

Where a therapeutic product or CTGTP registration application is pending HSA's review, the applicant must ensure that any new safety information which may impact the benefit-risk balance of the product is immediately submitted to the Therapeutic Products Branch via PRISM (for therapeutic products) or the Advanced Therapy Products Branch via HSA_CTGTP@hsa.gov.sg (for CTGTP). The applicant is to submit a tabulation of the new or unexpected serious AEs that have not been previously submitted and are not mentioned in the proposed Singapore package insert.

The new information may include but are not limited to the following examples:

(i) Safety reports of unexpected or new serious AEs with evidence of causal relationship;

(ii) Safety reports where there is suspicion of a change in the frequency or severity of a known effect;

(iii) Results from studies which may negatively impact the efficacy of the product.

## 5.2 ADVERSE EVENTS OF UNREGISTERED PRODUCTS IMPORTED VIA SPECIAL ACCESS ROUTE

Importers of unregistered therapeutic products or CTGTP for named patients' use must report all suspected cases of local serious AEs to the Vigilance and Compliance Branch if the information is made available to them, as set out in Section 4. They should also follow the requirements on maintaining records of AEs and reporting of AEs in special situations as set out in Sections 3 and 5 of this guidance respectively. It should be indicated that the suspected product reported is not registered in Singapore.

## 5.3 LACK OF EFFICACY OF A PRODUCT

When the therapeutic product or CTGTP fails to produce the expected pharmacological or therapeutic benefit and results in an adverse outcome for the patient, including a worsening of the condition for which the product is being taken or administered, such events should be reported. Clinical judgment should be used when reporting the event, taking into consideration the local product labelling and disease being treated.

Examples of classes of products where lack of efficacy **must** be reported are those that are used for the treatment of life-threatening or serious diseases, vaccines and contraceptives.

## 5.4 OUTCOMES OF USE DURING PREGNANCY

The company should follow up with the doctor on the pregnancy outcome when the company is aware that a pregnant woman has consumed or been administered a therapeutic product or CTGTP that is not recommended during pregnancy.

If the pregnancy results in an abnormal outcome and the reporting doctor considers that it might have been due to the product, the company must submit the serious AE report to the Vigilance and Compliance Branch within 15 calendar days upon first knowledge.

## 5.5 DRUG OVERDOSES AND MEDICATION ERRORS

Serious AEs caused by accidental or deliberate overdoses and medication errors need not be reported.

# 6 RISK MANAGEMENT PLANS

A risk management plan (RMP) is a detailed description of the risk management system that is put in place to identify, characterise, prevent and minimise risks relating to a therapeutic product or CTGTP. The RMP comprises the product's:

- **Safety concerns**, which include the product's important identified risks or potential risks, and missing information.
- **Proposed pharmacovigilance (PV) activities** to identify and characterise safety signals and clinically relevant risks.
- **Proposed risk minimisation activities (RMA)** to reduce the probability or severity of adverse events.

**Routine** PV activities and RMA should be conducted for all products registered in Singapore.

**Additional** PV activities and RMA may be necessary for products requiring extra level of monitoring and risk minimisation to ensure that their benefit-risk profiles remain acceptable for the approved indication(s).

## 6.1 SAFETY CONCERNS

The safety concerns to be included in the RMP outline the important risks that could impact the benefit-risk balance of a therapeutic product or CTGTP. These safety concerns are classified into three categories based on the strength of evidence of a causal association with the product and knowledge about its safety profile:

- **Important identified risks** are adverse reactions with adequate evidence of an association with the product.
- **Important potential risks** are safety concerns with suspected but unconfirmed association with the product.
- **Missing information** are clinically significant gaps in knowledge about the product's safety profile or its use in particular patient populations.

## 6.2 PHARMACOVIGILANCE (PV) ACTIVITIES

**Routine** PV activities include:

- Monitoring the safety profile of registered products, including signal detection and evaluation
- Reporting local **serious** adverse events to HSA in accordance with the stipulated timeline (refer to Section 4)
- Providing timely notifications to HSA on significant safety issues that may influence the overall benefit-risk profile of the product (refer to Section 8.1)
- Preparation of the product's Periodic Benefit-Risk Evaluation Reports (PBRER). HSA may request for the submission of PBRER for selected products on a routine or ad hoc basis (refer to Section 8.2)

**Additional** PV activities can include:

- Conducting and submitting the results of post-market safety studies e.g. monitoring of long-term safety from clinical studies
- Conducting active surveillance programmes
- Regular review and submission of data from established local or overseas patient registries

For CTGTP, in particular gene therapy products that may present long-term risks to patients, the proposed plan for long-term follow-up observations of delayed adverse events should be discussed in the RMP. The discussion may include the following:

- Objective(s) of the long-term follow-up (e.g. to monitor for insertional mutagenesis and secondary malignancy)
- Safety endpoint(s)
- Proposed long-term follow-up plan (e.g. conduct of observational studies and/or randomised controlled trials, leveraging existing registries)
- Patient population
- Data source (e.g. clinical studies, patient registries)
- Duration of follow-up (e.g. 15 years for products using integrating vectors, or products with potential for reactivation from latency)

- Frequency of submission of the long-term follow-up reports

## 6.3 RISK MINIMISATION ACTIVITIES (RMA)

**Routine** RMA include:

- Provision of warnings and precautions in the package insert
- Timely safety updates to labelling and packaging

**Additional** RMA can include:

***a) Provision of physician and/or patient educational materials***

Educational materials may be developed to provide the necessary information to help physicians and/or patients mitigate or manage safety concerns that may be significantly reduced through tighter patient selection, closer monitoring, or earlier detection and management of adverse events (refer to Section 7.1.4).

***b) Issuance of Dear Healthcare Professional Letter (DHCPL)***

A DHCPL is a communication tool intended to alert healthcare professionals about important new or updated safety information regarding a product and any actions they may need to take. A DHCPL may be initiated by the product registrant or HSA.

***c) Implementation of controlled access programme***

A controlled access programme may be required for products with significant safety concerns when used by the general population, but have a place in therapy for certain patient populations (e.g. treatment of conditions without alternative therapies). Under this programme, supply of the product may be restricted to selected physicians/ specialists/pharmacies, and patient access is contingent on fulfilment of one or more requirements (refer to Section 7.1.5).

***d) Implementation of pregnancy prevention programme***

A pregnancy prevention programme may be required for products with known or potential teratogenic effects. It lays out a set of interventions that aim to minimise the likelihood of pregnancy during treatment and drug exposure during pregnancy (refer to Section 7.1.6).

# 7 RMP SUBMISSIONS FOR PRODUCT REGISTRATION

An RMP must be submitted for all New Drug Applications type 1 (NDA-1) for therapeutic products or CTGTP. This requirement will also apply to products with a long history in the international market. Companies may propose to implement only routine PV activities and RMA if the product has been shown to have an acceptable and well-established safety profile.

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

Companies must continue to comply with the routine PV activities and RMA, regardless of RMP submission to HSA.

## 7.1 RMP DOCUMENTS FOR NDA-1 APPLICATIONS

The following RMP documents are to be submitted as part of the NDA-1 application dossier:

- Singapore-Specific Annex
- Reference RMP (e.g. EU-RMP, US REMS, Core RMP)
- Other RMP documents (where relevant)

### 7.1.1 SINGAPORE-SPECIFIC ANNEX

The Singapore-Specific Annex (SSA) describes the product's proposed RMP for Singapore and includes the following information:

- **Product information**, i.e. product name and active ingredient(s)
- **Safety concerns**, i.e. important identified risks, potential risks and missing information
- **Proposed local PV activities and RMA**
- **Supporting documents**, e.g. the list of RMP documents that have been submitted in the application

The SSA interactive PDF form can be downloaded here.

### 7.1.2 REFERENCE RMP

For products that are registered in the EU or USA, the latest approved EU-RMP and/or US REMS should be included in the application dossier. If the product does not have an EU-RMP or US REMS, an alternative reference RMP may be submitted, such as the company's core RMP or RMP(s) approved by other overseas regulators (translated into English, where applicable).

If the EU-RMP or US REMS is pending approval at the point of the application submission in Singapore, their draft versions may be submitted first and the final approved EU-RMP or US REMS is to be submitted as soon as available.

If an **updated version** of the reference RMP(s) becomes available during HSA's application review, it should be submitted as soon as possible to facilitate the timely review of the application. The relevant updates to the RMP(s) and an impact assessment of these updates on the proposed local RMP should be highlighted in a cover letter. An updated SSA should also be submitted if there are any changes to the proposed local RMP.

To submit an updated EU-RMP, US REMS and/or alternative RMP during application review:

- For **therapeutic products**, the updated reference RMP should be uploaded in PRISM, Section 7 (Supporting Attachments) under Other Supporting Documents.

- For **CTGTP**, the updated reference RMP should be submitted to the Advanced Therapy Products Branch via HSA_CTGTP@hsa.gov.sg, indicating the product name and application reference number.

### 7.1.3 OTHER RMP DOCUMENTS

If additional PV activities or RMA are proposed for the product, all relevant RMP documents should be included in the NDA-1 application dossier as part of the product's proposed local RMP. Further details of these documents are provided in the next few sections.

### 7.1.4 EDUCATIONAL MATERIALS FOR PHYSICIANS AND/OR PATIENTS

Educational materials for physicians and/or patients may be proposed to highlight specific safety concerns associated with therapeutic products and CTGTP, and provide advice on the actions required to optimise their safe and effective use.

Key information in educational materials include the product's local approved indication(s), contraindications and the important adverse events to note. Educational materials may also highlight important information such as:

| Physician Educational Material | Patient Medication Guide or Patient Alert Card |
|---|---|
| ▪ Risks in certain patient population(s), allowing physicians to make informed decisions when | ▪ Need to closely adhere to the directions for use of the |

| | |
|---|---|
| selecting patients who may benefit most from the therapy<br>▪ Recommended dosing information and advisories to adhere closely to<br>▪ Need for regular monitoring and/or laboratory testing that could affect the decision to continue or modify the patient therapy<br>▪ Any monitoring parameters to manage the adverse events<br>▪ Need to monitor for early signs of adverse events that could require discontinuation or modification of patient therapy<br>▪ Potential risk for medication error<br>▪ Need to conduct long-term safety monitoring for delayed adverse events<br>▪ Information to aid patient counselling | prescribed medication<br>▪ Early signs of adverse events and when to seek medical attention<br>▪ Important food-drug interactions or lifestyle modifications required while on the medication (e.g. drugs that are associated with teratogenicity) |

The proposed educational materials should be submitted in the application dossier. HSA will review the submitted draft material(s) during application evaluation in conjunction with the dossier to determine the additional activities required for implementation in the local RMP.

The HSA-approved educational materials will be published on the HSA website.

Non-English version(s) of educational materials will not be vetted by HSA. If the applicant wishes to distribute the non-English version(s), a copy of these materials should be submitted to HSA for documentation purposes, together

with a letter of declaration or translation certificate stating that the content and meaning in the non-English version(s) is consistent with the HSA-approved English version.

### 7.1.5 CONTROLLED ACCESS PROGRAMME

A controlled access programme may be proposed for a product where the benefit has been assessed to outweigh the risks for a selected group of patients.

The RMP documents to be submitted for HSA's review should comprise:

- A description of the objectives and requirements of the programme, including the conditions to be fulfilled before the product is prescribed and/or dispensed
- The proposed educational materials to be distributed under the programme

Forms used in the programme should also be submitted for documentation purposes. These may include:

- Letter of undertaking from prescribing physicians
- Letter of undertaking from dispensing pharmacists
- Patient informed consent form

### 7.1.6 PREGNANCY PREVENTION PROGRAMME

A pregnancy prevention programme may be considered for products with known or potential teratogenic effects.

The RMP documents to be submitted for HSA's review should comprise the proposed conditions of the programme, such as:

- Exclusion of pregnancy before starting treatment and during treatment

- Mandatory patient counselling prior to treatment initiation about the risk of teratogenicity and the need for effective contraception throughout treatment
- Acknowledgement by physicians/pharmacists regarding their understanding of the programme
- Acknowledgement by patients that the appropriate advice regarding risk of teratogenicity has been given and understood
- Provision of educational materials for physicians and/or patients

## 7.2 HOW TO SUBMIT RMP DOCUMENTS

The RMP documents should be **submitted in softcopy** as part of the product registration application dossier:

- For **therapeutic products**, the RMP documents should be uploaded in PRISM, Section 7 (Supporting Attachments) under Other Supporting Documents.

- For **CTGTP**, the RMP documents should be submitted in a CD/DVD to Advanced Therapy Products Branch, Medicinal Products Pre-Market Cluster, Health Products Regulation Group, Health Sciences Authority at 11 Biopolis Way, #11-01, Singapore 138667. More information on the submission of CTGTP applications is available here.

For **therapeutic products**, if the complete set of RMP documents is not available at the point of application submission, they must be submitted within the following time frame:

- **Applications submitted via the full or abridged route**

  The application must be accompanied by a letter of commitment to provide the complete set of RMP documents within 40 working days from the date of application acceptance for evaluation. A stop-clock may be imposed on an application under evaluation if the documents are not submitted to HSA.

- **Applications submitted via the verification route**
  The complete set of RMP documents must be submitted for the application to be accepted for evaluation.

For **CTGTP**, all RMP documents required in support of NDA-1 applications should be provided as part of the application dossier at the point of application submission.

## 7.3 POST-SUBMISSION OF RMP DOCUMENTS

HSA will review the submitted RMP documents together with the application dossier.

HSA may discuss with the applicant or request for additional PV activities or RMA to be implemented in Singapore. Applicants should submit all the requested additional RMP materials and supporting documents as soon as possible to prevent unnecessary delays in the product application process.

The additional PV activities or RMA to be implemented as part of the local RMP will be stipulated in the product registration conditions upon application approval.

# 8 POST-REGISTRATION RMP OBLIGATIONS

Registrants are responsible for the implementation and continued compliance with the RMP requirements to characterise or minimise the risks associated with their products. These include routine PV activities and RMA, as well as additional PV activities and RMA stipulated in the product registration conditions. Other information, such as data on local product utilisation, may also be requested by HSA on an ad hoc basis.

## 8.1 SAFETY NOTIFICATION TO HSA

The registrant must notify HSA of actions taken by HSA's comparable overseas regulators* or the registrant to address significant safety issues which may influence the overall benefit-risk profile of the product as soon as possible.

Examples of such actions include:

- Update to warnings or safety information in the overseas product labelling requested by HSA's comparable overseas regulators, including removal of approved indications
- Company-initiated risk minimisation measures related to newly emerging safety issues that were not mandated by HSA, e.g. dissemination of local DHCPL
- Product withdrawal/suspension due to safety concerns
- Failure to obtain a product registration renewal due to safety reasons

Ongoing assessments for potential safety signals with no interim measures planned by the registrant or HSA's comparable overseas regulators do not need be notified to HSA. This could include requests by the regulator to perform a cumulative review of a potential signal.

The safety notification should describe the safety-related reasons that led to the actions being taken, with supporting documents where appropriate. Each notification should be accompanied by the registrant's assessment on the significance of the safety issue in the local context and recommendation(s) on follow-up action(s) to be undertaken locally. If the assessment by the overseas regulator or registrant is still ongoing, the anticipated timelines for the assessment outcomes should be provided in the interim, followed by the final outcomes when available.

Any intention of voluntary local withdrawal/discontinuation of a registered product from the market by the registrant arising from safety issues should be discussed with HSA at an early stage.

** HSA's comparable overseas regulators are Australia TGA, EMA, Health Canada, UK MHRA and US FDA.*

## 8.2 SUBMISSION OF PBRER UPON HSA'S REQUEST

The Periodic Benefit-Risk Evaluation Report (PBRER) provides a comprehensive, concise and critical analysis of new or emerging information on the product's benefit-risk profile in its approved indications.

HSA may request for the routine submission of PBRER for specific products. The registrant will be informed accordingly through the product's registration conditions.

The registrant must submit the PBRER:

a) at intervals of 6 months commencing from the date of registration of the product for an initial period of 2 years; and
b) annually, for the next 3 years.

The first PBRER submitted should include data from the date of local product registration. For example, if the product was approved locally in July and the data lock period of the latest available PBRER was from January to June, this PBRER does not need to be submitted. Instead, the next PBRER with a data lock period of July to December will be considered as the first PBRER submission to fulfil the post-approval conditions for the product.

Each subsequent PBRER should cover the period since the last updated report and should be submitted within 70 days (for PBRER covering up to 12 months) or 90 days (for PBRERs covering more than 12 months) from the data lock point.

Under situations where the data lock period of the available PBRER differs from the local submission timelines, please provide HSA with the data lock period of the latest available PBRER and we will advise you on the submission schedule for the PBRER, if required under the product's registration conditions.

After the initial 5 years of registration approval, HSA may request for PBRER to be continued to be submitted if there are reasons to continue the safety monitoring of the product in the market.

HSA may also request for the submission of PBRER on an ad hoc basis e.g. when new significant safety concerns emerge during post-market surveillance.

## 8.3 HSA-APPROVED EDUCATIONAL MATERIALS

### 8.3.1 PUBLICATION AND DISTRIBUTION OF EDUCATIONAL MATERIALS

Following HSA's approval of the educational materials, the registrant should submit the finalised artwork to HSA for publication on the HSA website when available.

The registrant must also ensure that all healthcare professionals (HCP) who will be prescribing the product are provided with the latest copy of the HSA-approved physician educational materials. Copies of the latest approved patient medication guides and/or patient alert cards must also be made available to HCP for distribution to their patients who are supplied with the product.

Registrants are to keep the records of the distribution of these educational materials to the HCP and to submit these records to HSA upon request. The distribution records must include the following information:

- Names of the healthcare institutions/clinics/pharmacies receiving the educational material(s)
- Date of distribution of the educational material(s)

HSA does not dictate the mode of distribution of the educational materials (i.e. hardcopy or softcopy), as long as the materials are disseminated in accordance with the product's registration conditions. Companies who are

planning to host educational materials on digital platforms are encouraged to notify the Vigilance and Compliance Branch via HSA_productsafety@hsa.gov.sg of their intention to implement an electronic RMP.

Materials that were not requested by HSA as part of the product registration conditions (i.e. **company-initiated educational materials**) may be distributed without HSA's review and approval. The registrant should ensure that these educational materials are non-promotional, factual, and aligned with the latest approved local package insert. Hardcopies of company-initiated patient educational materials may only be distributed by the HCP to their patients and should not be displayed or made accessible in public areas. These materials will not be published on the HSA website.

### 8.3.2 SUBMISSION OF REVISED EDUCATIONAL MATERIALS

All post-approval revisions to the educational materials are to be submitted to HSA for approval or notification:

- **For approval**
  Revisions affecting the clinical use and/or safety content of the educational materials must be reviewed and approved by HSA prior to distribution to the HCP.
- **For notification**
  Revisions that do not affect the clinical use and/or safety content of the educational materials (e.g. editorial updates, artwork changes, version number or company logo changes, corrections of typographical errors, changes in address, and other administrative changes) do not require HSA's approval and may be distributed following their submission to HSA.

Following HSA's approval of the revised educational materials, the registrant should submit the finalised artwork to HSA when available. The revised materials will replace the existing version published on the HSA website.

### 8.3.3 REQUESTS FOR DISCONTINUATION OF EDUCATIONAL MATERIALS

For educational materials that have been implemented locally for at least 5 years, the registrant can review the need for continuation of these educational materials and provide justifications to HSA should the registrant wish to propose discontinuing the existing materials.

The justifications should include:

- Summary status of safety concerns highlighted in the educational materials to support the discontinuation of the materials (e.g. changes in adverse event reporting rates or trends since implementation of the educational materials)
- New and/or emerging safety concerns associated with the product (if any) and the actions taken to manage these safety concerns over the past 5 years
- Whether educational materials were requested by HSA's comparable overseas regulators*, including an elaboration on the type of materials requested and whether these materials are still being implemented or have been discontinued
- Local annual sales data for the past 5 years
- Registrant's proposed local education action plan for new and/or emerging safety concerns as well as those highlighted in the educational materials upon discontinuation of the materials
- Any other relevant information

* *HSA's comparable overseas regulators are Australia TGA, EMA, Health Canada, UK MHRA and US FDA.*

## 8.4 HSA-APPROVED CONTROLLED ACCESS PROGRAMMES OR PREGNANCY PREVENTION PROGRAMMES

Registrants should have a system in place such that the following information can be provided to HSA upon request:

- List of authorised prescribers/pharmacies that supplied the product to patients
- Number of patients prescribed with the product
- Distribution records of the educational materials, including
  a) Name and address of the healthcare institutions/ clinics/pharmacies where the materials are distributed
  b) Date and distribution of educational materials

  The distribution records of the educational materials must be retained for two years from the date of distribution.
- Number of potential pregnancy exposures in patients and pregnancy outcomes with congenital malformations (only applicable to pregnancy prevention programmes)

New or updated forms used in the controlled access programme or pregnancy prevention programme should be provided for updating of HSA's document records when available.

## 8.5 OTHER HSA-REQUESTED RMP DOCUMENTS

The registrant may be requested to submit other RMP documents in the post-registration setting. Examples include:

- **Clinical safety study reports** to further characterise any potential and identified risks associated with the product or to evaluate the safety of the product in selected patient populations.
- **Data on local product utilisation**, such as the product sales data or cumulative data on number of patients exposed to the product.

## 8.6 HOW TO SUBMIT

| Post-registration RMP obligation | Method of submission |
|---|---|
| Safety notifications | https://go.gov.sg/safetynotification |
| PBRER requested by HSA | For therapeutic products<br>or<br>For CTGTP<br><br>Please indicate the purpose of the submission in the form (e.g. "Finalised artwork for [Product Name]") |
| HSA-approved educational materials<br>• Finalised artwork<br>• Revisions to current materials (proposed draft and clean copies)<br>• Requests for discontinuation of current materials | |
| Information related to controlled access programme or pregnancy prevention programmme | HSA will inform registrants of the method of submission |
| Other HSA-requested RMP documents | HSA will inform registrants of the method of submission |

For enquiries on this document, please contact:

**Vigilance and Compliance Branch**

**Vigilance, Compliance & Enforcement Cluster**

**Health Products Regulation Group**

**Health Sciences Authority**

**11 Biopolis Way**

**#11-03, Helios**

**Singapore 138667**

**Tel: (65) 6866 1111**

**Email: HSA_productsafety@hsa.gov.sg**

**ANNEX I**

## SUMMARY OF SAFETY REPORTING REQUIREMENTS

The summary of the reporting requirements is shown in the table below. For the detailed requirements, please refer to the relevant sections of the guidance document.

| **Types of information** | **Description** | **Reporting timeframe** | **Submission method** |
|---|---|---|---|
| Local adverse event (AE) reports (spontaneous)<br>*Sections 3 and 4* | Serious AEs | Initial and Follow-up Reports: No later than 15 calendar days after first knowledge by the company. | Refer to Footnote 1 |
| | Non-Serious AEs | Not required on a routine basis. However, need to maintain records and produce for inspection when required. | - |
| Overseas AE reports (spontaneous)<br>*Section 4* | Serious and Non-Serious AEs | Not required on a routine basis. | - |
| Safety notification<br>*Section 8.1* | Actions taken by HSA's comparable overseas regulators or the registrant to address significant safety issues affecting the product's benefit-risk profile | As soon as possible<br><br>Ongoing assessments for potential safety signals with no planned interim measures do not need to be notified. | Refer to Footnote 2 |

[1] Submit via online reporting or email to HSA_productsafety@hsa.gov.sg. Refer to https://www.hsa.gov.sg/adverse-events to find out how to report AEs to HSA

[2] Submit via https://go.gov.sg/safetynotification

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

**Contact:**

Vigilance and Compliance Branch
Vigilance, Compliance & Enforcement Cluster
Health Products Regulation Group
Health Sciences Authority

11 Biopolis Way, #11-03 Helios
Singapore 138667
www.hsa.gov.sg
**Tel**: 6866 1111
**Email**: HSA_productsafety@hsa.gov.sg

HSA
Health Sciences Authority