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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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** 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);
- Periodic benefit-risk evaluation reports (PBRER);
- Updates on actions taken by other regulatory authority or company in response to safety issues.

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, careful planning of pharmacovigilance (PV) and risk minimisation activities (RMAs) throughout the life cycle of the therapeutic product or CTGTP is necessary to characterise its safety profile. The PV activities provide assurance that any new signals are promptly detected, while the RMAs 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 which are designed to identify, characterise, prevent or 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. implementation of RMPs and other follow-up actions, 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 HSA_TP_Enquiry@hsa.gov.sg (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, reporting of AEs in special situations and informing on regulatory actions arising from significant safety issues associated with the product as set out in Sections 3, 5 and 8 in 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 description of the risk management system that is put in place to identify, characterise, prevent or minimise risks relating to a therapeutic product or CTGTP, so that patients are allowed continued safe access to the product. The RMP consists of a safety overview of the product, the proposed pharmacovigilance (PV) activities, and the risk minimisation activities (RMAs).

To minimise risks relating to unsafe and inefficacious use of therapeutic products or CTGTP, HSA may direct the registrant to implement an RMP for the product, which includes, but is not limited to the following:

- Production and distribution of educational material(s);
- Production and distribution of safety information;
- Conduct of clinical studies;
- Implementation of active surveillance programmes;

- Implementation of programmes to restrict the supply of the product.

6.1 REQUIREMENTS FOR THE SUBMISSION OF AN RMP

All new drug applications type 1 (NDA-1) and biosimilar applications must have an accompanying RMP submitted.

For other application types such as NDA-2 or 3, major variation application (MAV) or generic drug application (GDA), RMP documents may be requested by HSA on a case-by-case basis:

(i) For NDA-2, the request for RMPs may be in response to a new safety concern arising from a new route of administration;

(ii) For MAV, the request may arise as a result of a new safety concern associated with a new indication that may require additional PV activities and/or RMAs;

(iii) For GDA, an RMP may be required if the innovator or reference therapeutic product has safety concerns that have been identified to require additional local PV activities and/or RMAs.

Please refer to the *Guidance on Therapeutic Product Registration in Singapore* (for therapeutic products) or *Guidance on Cell, Tissue and Gene Therapy Products Registration in Singapore* (for CTGTP) for details on the various application types.

6.2 RMP DOCUMENTS REQUIRED FOR SUBMISSION

The RMP documents are to be provided as part of the application dossier at the point of application submission and should include the following:

- Singapore-Specific Annex (SSA) (refer to section 6.2.1);
- Latest version of the approved EU-RMP and/or US REMS (where available); and
- Proposed local RMP materials (e.g. draft educational materials, if any; refer to section 6.4.2).

For therapeutic product applications, the required RMP documents should be attached in PRISM, Section 7 (Supporting Attachments) under Other Supporting Documents. For CTGTP applications, the RMP documents should be submitted to the Advanced Therapy Products Branch via the CTGTP online form or email to HSA_CTGTP@hsa.gov.sg.

Submission of the RMP documents in hardcopy is not required for both therapeutic product and CTGTP applications.

For applications submitted via the full or abridged route, if the applicant is unable to submit the complete RMP documents before the acceptance of the application, a letter of commitment to provide these documents within 40 working days from the date of application acceptance will be required. If the documents are not received within the 40 working days, an Input Request (with corresponding stop-clock imposed) will be sent to the applicant for the submission of the RMP documents. For applications submitted via the verification route, the complete set of RMP documents has to be submitted prior to the acceptance of the application.

During HSA's review of the application, if an updated version of the EU-RMP and/or US REMS becomes available, it should be submitted to the Therapeutic Products Branch (for therapeutic products), or Advanced Therapy Products Branch (for CTGTP). Submission of the updated EU-RMP and/or US REMS should be made as soon as possible upon receipt of the updated documents to facilitate the timely review of the application. The relevant updates to the EU-RMP and/or US REMS should be highlighted in a cover letter.

It is not necessary to submit updated versions of the EU-RMP and/or US REMS after the product applications have been approved, unless otherwise requested by HSA.

Please refer to the *Guidance on Therapeutic Product Registration in Singapore – Appendix 16 Guideline on Submission Requirements for Risk Management Plan Documents* (for therapeutic products), or *Guidance on Cell, Tissue and Gene Therapy Products Registration in Singapore – Appendix 9 Guideline on the Submission of Risk Management Plan Documents* (for CTGTP) for details.

6.2.1 SINGAPORE-SPECIFIC ANNEX

The SSA serves as documentation of the RMP to be implemented for the therapeutic product or CTGTP in Singapore. An SSA template is provided in Annex I.

The SSA template includes the following sections:

- Product information (product name and active ingredient[s]);
- Safety concerns (important identified risks and important potential risks);
- Description of the proposed local PV activities (refer to section 6.3);
- Description of the proposed local RMAs (refer to section 6.4); and
- Additional information (if applicable).

6.3 PHARMACOVIGILANCE ACTIVITIES

6.3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine PV activities are those that should be conducted as part of continued efforts to detect safety signals in therapeutic products or CTGTP. Routine PV activities include, but are not limited to the following:

- Reporting of local serious AEs to the Vigilance and Compliance Branch in accordance with the stipulated timeline;
- Timely update on significant safety issues that may influence the overall benefit-risk profile of the product;
- Timely update on safety-related regulatory actions taken by other agencies (in particular, HSA’s reference agencies*);

- Submission of PBRERs (for selected products if required under registration conditions) (refer to section 7).

***** *Reference regulatory agencies refer to Australia TGA, EMA, Health Canada, UK MHRA and US FDA.*

6.3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional PV activities may be required for therapeutic products or CTGTP with important identified or potential risks, in order to provide more timely evidence on the benefit-risk profile of the product. These may include, but are not limited to the following:

- Implementation of active surveillance programme;
- Post-marketing safety studies (applicable to local context);
- Conduct of additional clinical studies (where required);
- Leveraging data from established local or overseas patient registries.

For CTGTP, in particular gene therapy products that may present long-term risks to patients (e.g. evidence of product persistence, potential for reactivation from latency), the proposed plan for long-term follow-up observations of delayed AEs should be discussed. The discussion may include, but is not limited to 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. registry, clinical studies);
- 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 report.

6.4 RISK MINIMISATION ACTIVITIES

6.4.1 ROUTINE RISK MINIMISATION ACTIVITIES

Routine RMAs are activities that should be conducted for therapeutic products or CTGTP to reduce the probability or severity of AEs. These include, but are not limited to the following:

- Provision of warnings and precautions in the package insert (PI);
- Timely safety updates to labelling and packaging.

6.4.2 ADDITIONAL RISK MINIMISATION ACTIVITIES

Additional RMAs are required for therapeutic products or CTGTP with important identified or potential risks that require an extra level of risk minimisation, in order to strengthen the benefit-risk balance of the product. These may include, but are not limited to the following:

- Provision of physician educational material by the company (refer to section 6.4.3.1);
- Provision of patient medication guide by the company (refer to section 6.4.3.2);
- Issuance of Dear Healthcare Professional Letter;
- Implementation of Restricted Access Programme (RAP) (refer to section 6.4.4);
- Implementation of controlled distribution, e.g. supply to selected physicians/specialists/pharmacies;
- Implementation of pregnancy prevention programme.

6.4.3 EDUCATIONAL MATERIALS FOR PHYSICIANS AND/OR PATIENTS

Educational materials for physicians and/or patients may be requested as part of RMAs when significant safety issues are identified with the use of the therapeutic product or CTGTP during risk assessment at either pre- or post-marketing phases. The objective of such materials is to inform physicians

and/or patients of potential risks associated with the use of these products and to educate them on the early detection and management of AEs.

Where the applicant considers educational materials as part of the local RMAs, the draft educational materials should be submitted together as part of RMP documents at the point of application for product registration. The draft educational materials will be reviewed during application evaluation and approved at the point of product registration. Following approval, the applicant should submit the finalised artwork of the educational materials to HSA for publication on the HSA website.

Post-approval revisions affecting the clinical use and/or safety content of the educational materials should be submitted for review and approval by HSA prior to distribution to the healthcare professionals. However, for revisions that do not affect the clinical use and/or safety content of the educational materials (e.g. editorial changes, administrative changes, corrections of typographical errors, and changes in address), a notification of the soft copy of the revised materials to HSA will be sufficient (i.e. approval from HSA is not needed). The revised materials may be distributed following the notification to HSA. All revised educational materials should be submitted to the Therapeutic Products Branch via the online form (for therapeutic products) or to the Advanced Therapy Products Branch via the CTGTP online form or email to HSA_CTGTP@hsa.gov.sg (for CTGTP). The revised materials will replace the existing version published on the HSA website.

As part of ongoing post-marketing benefit-risk review for registered therapeutic products or CTGTP, educational materials may be requested by HSA at any point in time throughout the product life cycle when new significant safety issues are identified in the post-market setting.

6.4.3.1 PHYSICIAN EDUCATIONAL MATERIALS

Physician educational materials may be requested when risk assessment shows that safety concerns identified with the use of a therapeutic product or

CTGTP may be mitigated under situations that may include, but are not limited to the following:

- Physicians are made aware of the risks and can therefore make informed decisions to select appropriate patients who may benefit from the therapy;
- Physicians are reminded to adhere closely to the recommended dosing information and advisories;
- Physicians are made aware of the need for regular monitoring and/or laboratory testing that could affect the decision to continue or modify the patient therapy;
- Physicians receive adequate information regarding the monitoring of early signs of AEs that could require discontinuation or modification of patient therapy;
- Physicians are made aware of the potential risk for medication error;
- Physicians are made aware of the need to conduct long-term safety monitoring for delayed AEs (where applicable).

The key information to be stated in the physician educational material may include, but is not limited to:

- Local approved indication(s) of the product;
- Contraindications (if any);
- Important AEs associated with the product;
- Monitoring parameters to manage the AEs;
- Patient counselling and information;
- For biosimilar products, there should also be a generic paragraph to remind physicians of the following:
    - Information regarding interchangeability;
    - The importance of keeping good records of patients prescribed the biosimilar product (including the batch number) for traceability purposes in the event of safety/quality concerns; and
    - To report AEs (including brand name and batch and/or lot number) associated with the biosimilar product to the registrant and HSA.

6.4.3.2 PATIENT MEDICATION GUIDES

Patient medication guides may be requested when risk assessment shows that safety concerns identified with the use of a therapeutic product or CTGTP may be mitigated under situations that include, but are not limited to the following:

- Patients are able to monitor themselves for early signs of AEs;
- Patients know when to seek medical attention;
- Important food-drug interactions that the patients need to be aware of;
- Patients are required to adhere closely to the directions for use of the prescribed medication;
- Patients are aware of lifestyle modifications required while on the medication (e.g. drugs that are associated with teratogenicity).

The key information to be stated in the patient medication guide may include, but is not limited to:

- Local approved indication(s) of the product;
- Contraindications (if any);
- Important AEs associated with the product;
- Scenarios under which medical attention may need to be sought.

6.4.3.3 DISTRIBUTION OF EDUCATIONAL MATERIALS

The registrant must ensure that all healthcare professionals who will be prescribing the therapeutic product or CTGTP are provided with a copy of the latest HSA-approved physician educational materials. Copies of the latest approved patient medication guides, where applicable, must also be made available to healthcare professionals for distribution to all patients who will be supplied with the product.

The registrant must keep records of the distribution of the educational materials to healthcare professionals. The distribution records must include:

- Names of the healthcare institutions/clinics/pharmacies receiving the educational material(s); and

- Date of distribution of the educational material(s).

The distribution records must be submitted to HSA when requested.

The registrant must also ensure that the latest copy of the HSA-approved educational materials is provided to HSA for publication on the HSA website.

6.4.4 RESTRICTED ACCESS PROGRAMME

A therapeutic product or CTGTP may be subjected to the requirements of a Restricted Access Programme (RAP) following a benefit-risk assessment by HSA, when it is assessed to be associated with significant safety issue(s) that affect(s) its overall benefit-risk profile but is still beneficial for a selected group of patients with no suitable therapeutic alternatives. The RAP allows for continued safe use of the product in the local market while ensuring that adequate measures are put in place to mitigate its risks.

Components of the RAP may include, but are not limited to the following:

- Supply of products only to healthcare professionals who have enrolled in the RAP;
- Letter of undertaking by physicians to indicate that they are aware of the serious safety issue(s) associated with the use of the product, will discuss the risks involved with the patients and obtain their informed consent before prescribing and/or dispensing the product;
- Letter of undertaking by pharmacists in charge of institutions or clinics who will be dispensing the product to indicate that they are aware of the serious safety issue(s) associated with the use of the product and conduct proper counselling;
- Patients' informed consent that they understood the potential risks involved with the use of the product;
- Submission of updated list of healthcare professionals enrolled in the RAP to HSA;
- Regular submission of sales data of the product to HSA.

7 PERIODIC BENEFIT-RISK EVALUATION REPORTS

The preparation of periodic benefit-risk evaluation reports (PBRERs) for regulatory authorities is a routine pharmacovigilance activity outlined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2E guidelines. The guidance on the format and content of the PBRER can be referenced from the latest version of ICH E2C (R2): Periodic Benefit-Risk Evaluation Report, available at http://www.ich.org/.

7.1 REPORTING REQUIREMENTS FOR PBRERs

HSA may require any registrant of a therapeutic product or CTGTP to submit, within the timelines specified by the Authority, a benefit-risk evaluation report relating to the product should significant safety concerns be identified during pre- and/or post-marketing phases of the product and assessed to require further close monitoring. PBRERs may be submitted to the Therapeutic Products Branch via the online form (for therapeutic products) or to the Advanced Therapy Products Branch via the CTGTP online form or email to HSA_CTGTP@hsa.gov.sg (for CTGTP).

The registrant must submit the PBRER:
(*a*) for an initial period of 2 years, at intervals of 6 months commencing from either the date of registration of the product, or its international birth date; and
(*b*) annually, for the next 3 years.

Each PBRER should cover the period of time since the last updated report and must 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.

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

8 UPDATE OF ACTIONS TAKEN BY OTHER REGULATORY AUTHORITIES OR THE COMPANY

The registrant must inform the Vigilance and Compliance Branch as soon as possible, of any regulatory actions taken by other regulatory authorities, or action(s) taken by the company arising from significant safety issues of the therapeutic product or CTGTP.

Significant safety issues are those which may influence the overall benefit-risk profile of the product and may include, but are not limited to the following:

- Product withdrawal;
- Product recall and product defects;
- Removal of approved indications by regulatory agencies;
- Failure to obtain a product registration renewal due to safety reasons;
- Dissemination of Dear Healthcare Professional Letter related to safety issues.

The safety-related reasons that led to these actions should be described and notified to HSA with supporting documents, where appropriate. Each notification should be accompanied with an assessment by the registrant, of the significance of the regulatory action in the local context and recommendation(s) on follow-up action(s) to be undertaken locally. Any intention of voluntary local withdrawal/discontinuation of a registered therapeutic product or CTGTP from the market by the registrant arising from safety issues should be discussed with HSA at an early stage.

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; Fax: (65) 6478 9069

Email: HSA_productsafety@hsa.gov.sg

ANNEX I

RISK MANAGEMENT PLAN - SINGAPORE-SPECIFIC ANNEX TEMPLATE

I Product Information

Product name:	e.g. ABC123
Active ingredient(s):	e.g. safetyzumab

II Safety Concerns

To list the important safety concerns relevant in the Singapore context.

Important identified risks (an untoward occurrence for which there is adequate evidence of an association with the therapeutic product)	e.g. • Drug-induced liver injury (DILI) • Severe cutaneous adverse reactions (SCAR) • Heart failure • Elevated liver enzymes (ALT and AST)
Important potential risks (an untoward occurrence for which there is some basis for suspicion of an association with the therapeutic product)	e.g. • Malignant cell growth • QT prolongation • Potential medication error/ dispensing error • Unknown safety in special populations (e.g. elderly, immunocompromised patients, patients who are renally impaired or with hepatic dysfunction)

III Description of the Proposed Local Pharmacovigilance (PV) Activities

To describe the PV activities (routine and/or additional), relevant to the local context, that are planned to address the safety concerns.

(A) Routine PV Activities *[required for all products]*
Please refer to the *Guidance for Industry – Post-marketing Vigilance Requirements for Therapeutic Products and Cell, Tissue and Gene Therapy Products* on the respective timelines for the following routine PV activities.

✓	Reporting of local serious adverse reactions to the Vigilance and Compliance Branch, HSA in accordance with stipulated timeline
✓	Timely update on significant safety issues that may influence the overall benefit-risk profile of the product
✓	Timely update on safety-related regulatory actions taken by other agencies, particularly HSA's reference agencies (i.e., Australia TGA, EMA, Health Canada, UK MHRA and US FDA)

(B) Additional PV Activities

Where applicable, to include planned date for such activities. If no additional PV activities are considered to be required, it should be indicated as such (i.e. "Nil").

Examples: Active surveillance programme, post-marketing safety studies (applicable to local context), etc.

e.g. To conduct active soliciting of local serious adverse reaction reports associated with the use of ABC123 from physicians who prescribe the product. Solicited local serious adverse reaction reports will be compiled on a quarterly basis and submitted to the Vigilance and Compliance Branch, HSA. (e.g. end of March, June, September, December)

IV Description of the Proposed Local Risk Minimisation Activities (RMAs)

To describe RMAs (routine and/or additional), relevant to the local context, that are planned to address the safety concerns.

(A) Routine RMAs *[required for all products]*

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

(B) Additional RMAs

If no additional RMAs are considered to be required, it should be indicated as such (i.e. "Nil").

Examples: Provision of physician educational materials and patient medication guides, provision of sales data, issuance of Dear Healthcare Professional Letter, implementation of restricted access programme, controlled distribution, pregnancy prevention programme

e.g.

- Physician educational material is developed to highlight the identified safety concerns, signs and symptoms to look out for and to highlight on the potential risk of medication error/dispensing errors
- A patient medication guide is developed to highlight the identified safety concerns, signs and symptoms to look out for and when to seek medical attention
- A Dear Healthcare Professional Letter will be issued to reinforce the significant safety concerns at product launch

V Additional Information

To list the RMP documents enclosed in this application and to provide other comments (if any)

e.g.
The following RMP documents are enclosed in this application for your perusal:

- Latest version of the approved EU-RMP (i.e. version 2.1)
- Draft physician educational materials and patient medication guides
- Draft Dear Healthcare Professional Letter

Last updated: 01 March 2021

ANNEX II

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	Submit to
Local adverse event (AE) reports (spontaneous) *Sections 3 and 4*	Serious AEs	Initial and Follow-up Reports: No later than 15 calendar days after first knowledge by the company.	VCB*
	Non-serious AEs	Not required on a routine basis. However, need to maintain records and produce for inspection when required.	-
Overseas AE reports (spontaneous) *Section 4*	Serious and Non-serious AEs	Not required on a routine basis.	-
Risk management plans (RMPs) *Section 6*	Submission of RMP documents is required for new drug applications type 1 (NDA-1) and biosimilar applications. RMP documents include: 1) Singapore-specific annex 2) Latest version of the approved EU-RMP and/or US REMS (where available) 3) Proposed local RMP materials	RMP documents should be provided as part of application dossier for NDA-1 and biosimilar application.	TPB or ATPB

Periodic benefit-risk evaluation reports (PBRERs) *Section 7*	For selected products only	For an initial period of 2 years, at intervals of 6 months commencing from either the date of registration of the therapeutic product or CTGTP or its international birth date, and annually for the next 3 years.	TPB or ATPB**

ATPB: Advanced Therapy Products Branch
CTGTP: Cell, tissue or gene therapy product
TPB: Therapeutic Products Branch
VCB: Vigilance and Compliance Branch

* Submit to VCB 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

** Submit to TPB via the online form (for therapeutic products) or to ATPB via the CTGTP online form or email to HSA_CTGTP@hsa.gov.sg (for CTGTP)

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

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HSA Health Sciences Authority