Revised Post-marketing Risk Management Requirements for Singapore – Frequently Asked Questions

General information

Q1. What are the revised post-marketing risk management requirements?

Previously, the submission of the EU-RMP and/or US REMS was required for all new drug applications (NDAs) and major variation applications (MAVs). With the revised post-marketing risk management requirements, submission of Risk Management Plan (RMP) documents will be a requirement only for NDA-1 and biosimilar applications. For other application types such as NDA-2/3, MAV or generic drug application (GDA), the submission of RMP documents will be requested by HSA on a case-by-case basis.

The RMP documents to be submitted as part of the submission dossier for NDA-1 and biosimilar applications include:

- Singapore-Specific Annex (SSA)
- Latest version of the approved EU-RMP and/or US REMS (where available)
- Proposed local RMP materials (e.g. draft educational materials, where applicable)

Q2. If the product has a long history in the international market and its safety profile is well-established, does it still require submission of RMP documents for registration in Singapore?

The submission of RMP documents is a requirement for all NDA-1 and biosimilar applications regardless of its history in the international market. However, for products with well-established safety profiles, routine pharmacovigilance activities (e.g. adverse reactions reporting to HSA) and routine risk minimisation activities (e.g. product labelling) will be sufficient.

Q3. When will the discussion on the final local RMP implementation be conducted? Will it affect the current approval lead time?

The discussion between the company and HSA on the final local risk management activities to be implemented will be done as part of the evaluation of the product application and will be within the current application approval timelines.

Q4. At what point should the RMP documents be submitted during the NDA-1/biosimilar application process? Is a hardcopy or softcopy required? If a softcopy is required, under which section of PRISM should I attach these documents?

RMP documents required in support of NDA-1/biosimilar applications should be provided as part of the application dossier at the point of application submission. Soft copies of the RMP documents are mandatory and should be attached in PRISM, Section 7 (Supporting Attachments) under "*Other Supporting Documents"*. Hardcopies are not required.

Q5. If an updated version of the EU-RMP and/or US REMS becomes available during HSA's product application evaluation, is it a requirement to submit the updated version to HSA?

During HSA's product application evaluation, if an updated version of the EU-RMP and/or US REMS becomes available, it should be submitted to HSA. The relevant updates to the EU-RMP and/or US REMS should be highlighted to HSA in a cover letter. Submission of the updated EU-RMP and/or US REMS to HSA should be made as soon as possible upon receipt of the updated documents to facilitate the timely review of the application.

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

Q6. Who should we contact if we have queries on the revised post-market risk management requirements?

For enquires on RMP submission requirements, please contact the Therapeutic Products Branch at HSA_TP_Enquiry@hsa.gov.sg. For other enquiries on the post-marketing risk management requirements, please contact the Vigilance and Compliance Branch at HSA_productsafety@hsa.gov.sg.

Singapore-Specific Annex (SSA)

Q7. What is the purpose of the SSA?

The SSA serves as documentation of the RMP to be implemented for the therapeutic product in Singapore. It is required as part of the application dossier for all NDA-1 or biosimilar applications.

The aim of the SSA is to outline the safety concerns (e.g. important identified risks and important potential risks) of the therapeutic product seeking product approval in Singapore, as well as the local pharmacovigilance and risk minimisation activities that the company is proposing to be put in place to monitor and mitigate the safety concerns identified. If routine pharmacovigilance and risk minimisation activities are sufficient, this can be stated as such in the SSA.

HSA will review the SSA in conjunction with the EU-RMP and/or US REMS submitted with the application dossier (where available) before deciding on the pharmacovigilance plan and/or risk minimisation activities to be implemented in Singapore.

Q8. Will HSA be providing a template for the SSA?

HSA has provided a SSA template under Annex I of the Guidance for Industry - Post-marketing Vigilance Requirements for Therapeutic Products. Companies are recommended to follow the template when drafting the SSA.

The SSA template includes the following sections:

I. Product information (product name and active ingredient(s))
II. Safety concerns (important identified risks and important potential risks)
III. Description of the proposed local pharmacovigilance activities*
IV. Description of the proposed local risk minimisation activities*
V. Additional information (if applicable)

** Please refer to section 6.3 and 6.4 of the Guidance for Industry - Post-marketing Vigilance Requirements for Therapeutic Products for examples of routine and additional pharmacovigilance and risk minimisation activities.*

Periodic Benefit-Risk Evaluation Report (PBRER)

Q9. Is there a need to submit PBRERs for all NDA-1/biosimilar applications to HSA on a routine basis since it is a routine pharmacovigilance activity as outlined in the ICH E2E guidelines?

PBRERs do not have to be submitted to HSA on a routine basis, except when requested by HSA as part of the post-approval licensing conditions.

Q10. What are the criteria for the products that will be identified to require submission of PBRERs?

The request for PBRERs is on a case-by-case basis depending on the safety concerns identified for each product. Should significant safety concerns be identified during pre-market review and assessed to require further close monitoring following marketing of the product, HSA may request for routine submission of PBRERs for that product as part of post-approval licensing conditions, and the company will be informed of this at the point of product approval.

In the event where new significant safety concerns emerge during post-market that may impact the benefit-risk profile of the product, PBRER submission may be requested by HSA.

Q11. For selected therapeutic products that require routine submission of PBRERs to HSA (as stated under licensing conditions), what is the frequency of routine submission?

The frequency for routine submission of PBRER will be at intervals of six months commencing from the date of registration of the product, or its International Birth Date, for a period of two years; and thereafter, annually, for the next three years. Companies who have difficulty in meeting the submission timeline should inform HSA at the point of PBRER request and HSA will work with the company on a mutually agreeable submission frequency for the affected product.

Educational materials for physicians and/or patients

Q12. What are the key elements or components that should be present in the educational materials?

The key elements in the educational materials should include, but are not limited to the following:

- Local approved indication(s) of the product
- Contraindication(s) (if any)
- Important identified and/or potential risks associated with the use of the product
- Monitoring parameters to manage the adverse reactions
- Scenarios under which medical attention needs to be sought

Please refer to section 6.4.3 of the Guidance for Industry - Post-marketing Vigilance Requirements for Therapeutic Products for further details.

Q13. Is there a need to develop a patient medication guide if a patient information leaflet (PIL) is already available for the product?

The patient medication guide is different from the PIL that is available with the product inserts of some products. The patient medication guide, which can come in the form of reading materials, is developed in consultation with HSA to address specific safety concerns with the intention of risk mitigation. The patient medication guide will be requested on a case-by-case basis, following evaluation of the safety concerns associated with the product, and is to be submitted for review and approval by HSA before being provided to healthcare professionals for distribution to all patients who have been prescribed the product.

Q14. How long should the educational materials be implemented?

In general, educational materials may need to be implemented throughout the life span of the product. Companies are encouraged to assess the need for the continued provision of educational materials based on local market experience with their products after 5 years and to provide justification to HSA should they wish to propose to discontinue the existing materials.

Q15. What type of distribution records should the company maintain for the distribution of educational materials?

HSA will require companies to keep records of the distribution of the educational materials to healthcare professionals. The distribution records should include:

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

The distribution records should be submitted to HSA when requested.

Q16. If there are changes made to the educational materials after the product is granted registration in Singapore, does the company need to submit the amended materials to HSA? Who should we submit these amendments to?

Revisions affecting the clinical use and/or safety content of the approved educational materials should be submitted for review and approval by HSA prior to distribution to the healthcare professionals. These amendments should be submitted to HSA_TP_Enquiry@hsa.gov.sg.

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 to HSA with the soft copy of the revised materials will be sufficient. The revised materials may be distributed following the notification to HSA.

Implementation of revised post-marketing risk management requirements

Q17. When will the revised post-marketing risk management requirements be implemented?

The revised post-marketing risk management requirements have been implemented since **1 June 2016.**