swissmedic

Guidance document
RMP ICH E2E information submission HMP

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List of contents

1 Abbreviations

AIPS	Swissmedic product information publication platform
Art.	Article
CD	Calendar Days
DHPC	Direct Healthcare Professional Communication
DLP	Data log point
eCTD	Electronic Common Technical Document (ICH)
EMA	European Medicines Agency
EU	European Union
GVP	Guideline on good pharmacovigilance practices
HCP	Healthcare professional
ICH	International Conference of Harmonisation
ICH E2E	ICH Harmonised Tripartite Guideline on Pharmacovigilance Planning E2E
KAS	Known active substance
KAS with innovation	Known active substance with innovation
KAS without innovation	Known active substance without innovation
Let.	Letter
NAS	New Active Substance
No.	Number
PAES	Post-Authorisation Efficacy Study / Studies
Para.	Paragraph
PASS	Post-Authorisation Safety Study / Studies
PSUR/PBRER	Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report
PVP	Pharmacovigilance Plan
REMS	Risk Evaluation and Mitigation Strategy
Rev.	Revision
RMM	Risk minimisation measures
RMP	Risk Management Plan
TPA	Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA; SR 812.21)
TPO	Ordinance on Therapeutic Products (Therapeutic Products Ordinance – TPO, SR 812.212.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products on the Simplified Licensing of Therapeutic Products and the Licensing of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products on the Licensing Requirements for Therapeutic Products (Therapeutic Products Licensing Requirements Ordinance, TPLRO; SR 812.212.22)

2 Objective

This Guidance document describes the requirements for submitting RMPs, RMP Updates, and RMP Summaries. It instructs marketing authorisation holders on the formal and regulatory aspects that apply in this regard.

3 Introduction

The Risk Management Plan (RMP) for a therapeutic product describes the primary risks (safety concerns) derived from the safety profile (safety specifications) of this therapeutic product, the pharmacovigilance activities that are required for further characterisation of the safety concerns (pharmacovigilance plan), and the risk minimisation measures for reducing the probability that the primary risks will come into effect. The RMP is part of the authorisation dossier.

4 Risk Management Plan (RMP)

4.1 Legal basis

Art. 11 para. 2 let. a no. 5 of the Therapeutic Products Act (TPA) states that applications for authorisation of a therapeutic product with indication must include an assessment of the risks and, if applicable, a plan for their systematic recording, investigation and prevention (pharmacovigilance plan). This mandatory submission is described in more detail in Art. 4 TPO.

4.2 Mandatory submission

Pursuant to Art. 4 TPO, applications for authorisation of human medicinal products containing at least one new active substance (NAS) (including orphan drug NAS) and applications for authorisation for a new indication of such a medicinal product must include a Risk Management Plan. Applications for authorisation of a medicinal product that do not qualify for the simplified authorisation procedure under Art. 12 let. a-e TPLO (vaccines, sera and toxins, blood products, medicinal products containing genetically modified organisms, biologicals as well as ATMP [Advanced Therapy Medicinal Products] and gene therapy medicinal products) must also be accompanied by an RMP.

Biosimilars are not required to include an RMP.

RMPs are not to be submitted for any other authorisation applications. Swissmedic will not review, and therefore not approve, any RMPs that are presented in the absence of a submission requirement.

4.3 Specific authorisation procedures

4.3.1 Ordinary procedure according to Art. 11 TPA

An RMP must be submitted in accordance with the remarks in section 4.2, “Mandatory submission”. As a rule, under Art. 11 para. 1 TPA all information and documents that are relevant for the decision must be submitted; this can also include the submission of RMP-related assessment reports from other agencies.

4.3.2 Simplified procedure according to Art. 14 TPA

Pursuant to Art. 4 para. 1 TPO, submission of an RMP is required for the authorisation process only in the case of those applications listed in this provision (let. a to c). No RMP is needed when applying for authorisation of medicinal products that qualify for the simplified procedure under Art. 14 TPA.

This applies in particular to authorisation applications for a medicinal product with known active substance (Art. 14 para. 1 let. a TPA), regardless of whether the authorisation is being requested as a KAS with innovation, i.e., with a new or additional indication, pharmaceutical form, dosage strength, dosage recommendation and/or new route of administration or as a KAS without innovation. Authorisation applications for medicinal products under let. a$^{bis\text{-}quater}$ should not include an RMP either.

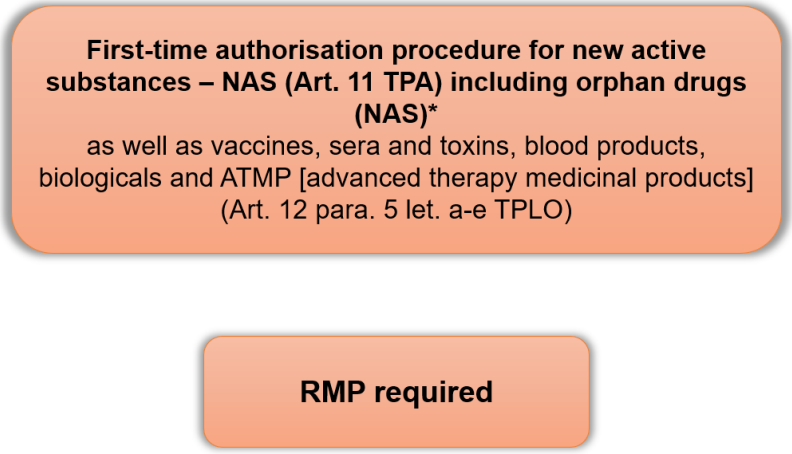
4.3.3 Authorisation under Art. 13 TPA

If an authorisation application is submitted under Art. 13 TPA, the requirements of Art. 16 et seq. TPO also apply; accordingly, the documentation filed with Swissmedic must correspond to the documentation that was submitted to the reference authority. This means that the documentation submitted would also have to include any RMP filed with the reference authority.

For authorisation applications in accordance with Art. 13 TPA that pertain to medicinal products under Art. 4 TPO (human medicinal products that contain at least one new active substance [NAS] or a new indication for this medicinal product), under Swiss Module 1.8.2 an RMP to be approved by Swissmedic must also be submitted. The latest RMP (meaning the RMP with the most recent DLP, which does not necessarily need prior approval by an authority) must be submitted; if there is no newer version of the RMP contained in the reference dossier, then the RMP in Swiss Module 1.8.2. will be identical to this.

4.3.4 Summary of mandatory RMP for first-time applications for authorisation

Figure 1: Medicinal products requiring an RMP (authorisation under Art. 11 and orphan drugs)



* also applies to NAS and orphan drugs (NAS) with temporary authorisation (Art. 9*a* TPA)

Figure 2: Medicinal products requiring an RMP (Art. 13)

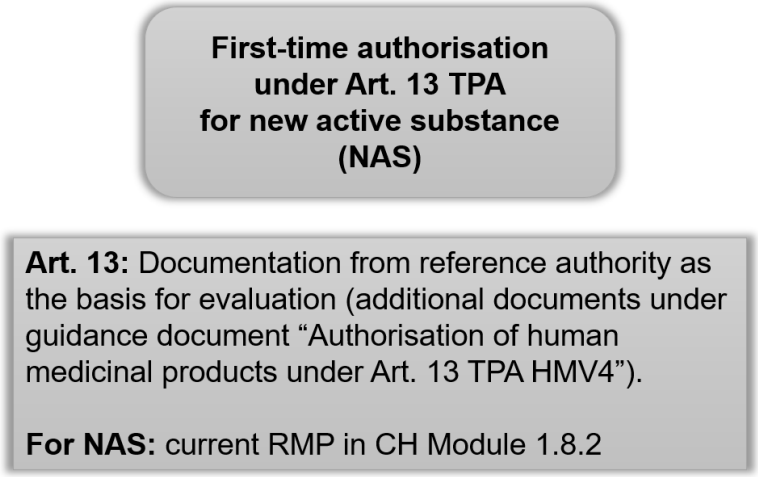
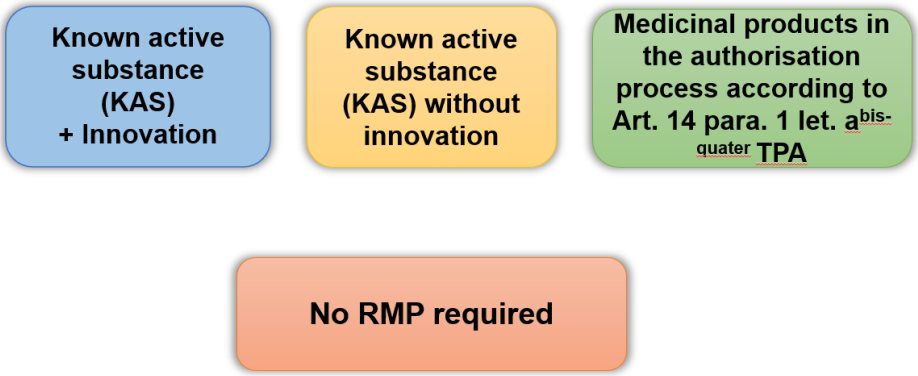


Figure 3: Medicinal products not requiring an RMP



4.4 Content and format

The structure of the RMP must follow Guideline E2E of the ICH (pharmacovigilance planning) or GVP Module V Rev. 2 (risk management systems) from the EMA (Art. 11 para. 4 TPA in conjunction with Art. 5a para. 1 TPLRO in conjunction with Annex 3 para. 1 let. a. TPO).

The ICH E2E Guideline describes two main aspects of the RMP, namely the safety specifications and the pharmacovigilance plan (PVP). GVP Module V is aligned to the ICH E2E Guideline and defines additional content and formatting requirements for the RMP.

Any RMP that complies with the aforementioned legal requirements can be submitted. Submission of an EU RMP is preferable. The EMA's "Guidance on the format of the risk management plan (RMP) in the EU – in integrated format" provides additional details on the content and format of the EU RMP.

In addition to this, a Switzerland-specific annex can be submitted to describe deviations from the submitted RMP that apply exclusively to Switzerland (see section 6 - Switzerland-specific annex to the RMP). If additional risk minimisation measures are no longer deemed necessary at a later point in time due to changes in the risk assessment, the marketing authorisation holder can file an application to revoke the requirement.

5 RMP Update

5.1.1 Preconditions for submission

An RMP Update under this guidance document refers to any RMP that is submitted in order to replace a previously approved RMP. RMP Updates are to be submitted only if the first submitted RMP was approved by Swissmedic.

No RMP Updates are to be submitted for medicinal products that are no longer subject to mandatory RMP submission (see section 4.3.4 Fig. 3) under this guidance document. RMP-specific requirements and the mandatory implementation of educational materials still apply to these medicinal products. If the additional risk minimisation measures are no longer deemed necessary at a later point in time due to changes in the risk assessment, the marketing authorisation holder can file an application to revoke the requirement.

5.2 Specific procedures

5.2.1 Applications for indication extensions

Under Art. 4 para. 1 let. c TPO, applications for additional indications for an NAS (including orphan drug) must always include an RMP Update. The RMP Update will be reviewed and approved as part of this application. The cover letter must indicate the most recent version of the RMP that was approved by Swissmedic.

5.2.2 RMP Updates in the context of other applications

RMP Updates should be submitted in the context of other applications if at least one of the following aspects of the RMP content is affected by the update:

Safety concerns: addition, modification or deletion of risks
Additional pharmacovigilance activities: addition, modification (e.g. of milestones or design of PASS) or deletion of PV measures and/or
Additional risk minimisation measures: introduction, modification or deletion of additional RMM.

If there is a need for an RMP Update due to other applications, such as applications for modifications to medicinal product information, applications to remove requirements or the submission of PSUR/PBRER, this update must be included with the relevant application. The RMP will be evaluated and approved as part of this application. An EU RMP Update can be submitted even if not yet approved. The cover letter must indicate the most recent version of the RMP that was approved by Swissmedic.

5.2.3 RMP Updates as a standalone application

RMP Updates that are not directly associated with an application must be submitted as a standalone “AMS RMP Update” application with a cover letter.

Submissions must be made via the Swissmedic Portal with the delivery type “communication”, if eCTD delivery type “variation/new application” or CD by post.

The cover letter must indicate the most recent version of the RMP that was approved by Swissmedic.

5.2.4 Summary of the RMP Update requirement

Figure 4: Applications for indication extensions for an NAS (including orphan drug NAS)

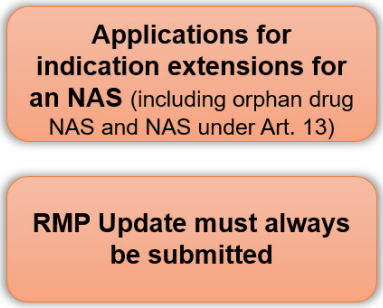
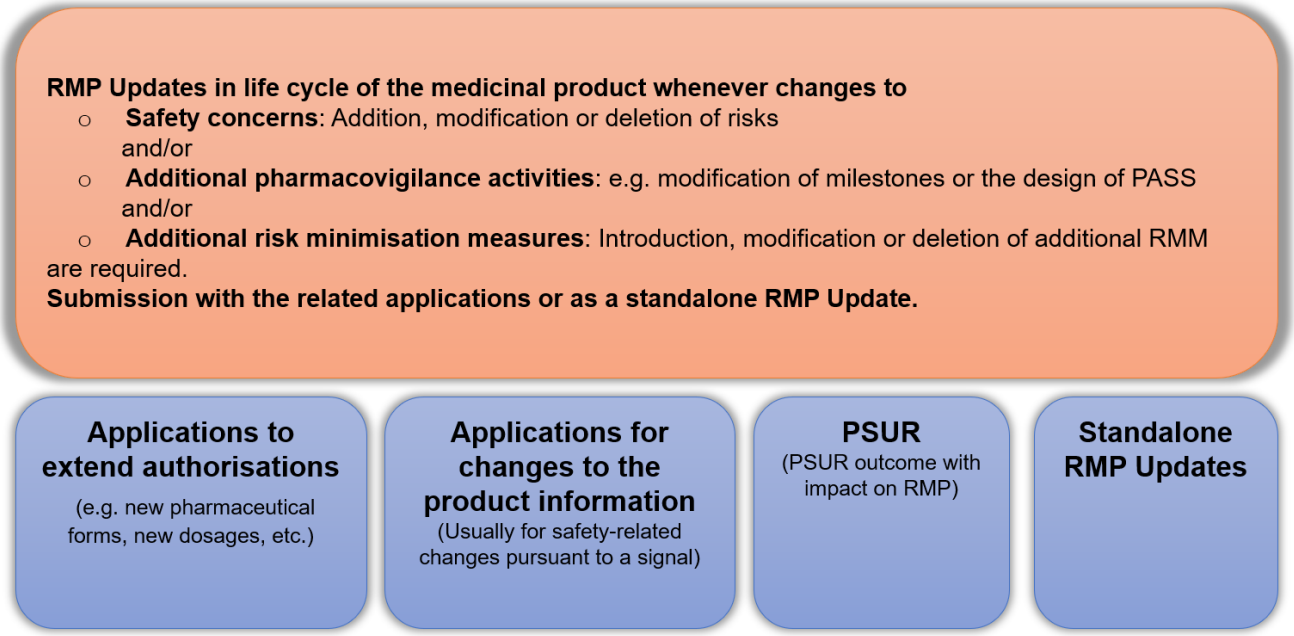


Figure 5: RMP Updates during the life cycle of a medicinal product



5.3 Content and format

RMP Updates required in accordance with the aforementioned criteria must meet the specifications of Guideline E2E by the ICH (pharmacovigilance planning) or GVP Module V Rev. 2 (see section 4.4 - Content and format). Submission of an EU RMP is preferable. The RMP Update can include a specific annex for Switzerland (see section 6 - Switzerland-specific annex to the RMP).

5.4 Time limits and fees

RMP Updates relating to an application must be presented at the same time as the application; the time limits for the respective application apply in addition thereto.

The time limits for submitting standalone RMP Updates are as follows:

EU RMP: within 3 months after approval of the RMP Update by the EMA (“CHMP opinion date”).
If an EU RMP is not involved: within 3 months after the "final sign off" of the RMP Update.

The fee for reviewing standalone RMP Updates is charged according to the actual time spent (CHF 200/hour) pursuant to Art. 1 in conjunction with Art. 4 of the Ordinance on the fees charged by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic; SR 812.214.5) dated 14 September 2018. As a rule, the application will be processed within three months of submission.

6 Switzerland-specific annex to the RMP

6.1 Legal basis

Pursuant to Art. 11 para. 2 let. a no. 5 TPA, as a rule an RMP must be submitted with an application for authorisation; if adaptations must be made to the submitted RMP to account for the situation in Switzerland, a Switzerland-specific annex to the RMP can also be filed. The option to submit country-specific annexes is an efficient means of accounting for national situations and corresponds to international practice.

6.2 Procedure

There is no specific procedure for submitting a Switzerland-specific annex. The Switzerland-specific annex can be submitted along with an RMP for an authorisation application or with an RMP Update. If a Switzerland-specific annex to the RMP has been approved, it must always be submitted together with the RMP Update.

6.3 Content and format

In the event of significant deviations from the submitted RMP that apply exclusively to Switzerland, a Switzerland-specific annex with details of the deviations can be filed. Such deviations include in particular:

Safety concerns,
Additional pharmacovigilance activities and/or
Additional risk minimisation measures.

However, the Switzerland-specific annex may be needed due to other deviations, such as a significant difference in indication or significantly different epidemiology of the illness or condition to be treated in Switzerland. The deviations should be listed as well as described and/or substantiated.

While there is no legally required form of the Switzerland-specific annex, the structure should – where possible and reasonable – be aligned to Guideline E2E of the ICH (pharmacovigilance planning) and GVP Module V.

An approved Switzerland-specific annex shall be considered an integral part of the underlying RMP; the activities for the pharmacovigilance plan and risk minimisation measures listed therein must be implemented in full.

7 RMP Summary

7.1 Legal basis

Submission of an RMP Summary is mandatory under Art. 5a para. 2 TPLRO. On the basis of Art. 68 para. 1 let. e. no. 2 TPO, Swissmedic publishes RMP Summaries for authorised medicinal products on its home page; these RMP Summaries are also linked on the medicinal product information platform of Swissmedic (AIPS; www.swissmedicinfo.ch). RMP Summaries are intended for healthcare professionals and third parties seeking information, and are a supplement to the publicly available medicinal product information. Approval of an application that includes an RMP is subject to submission of an RMP Summary.

7.2 Submission

The RMP Summary must be submitted to Swissmedic as a standalone document with cover letter (not as a separate application) (submission via Swissmedic Portal delivery type “communication”, if submitted via eCTD delivery type “variation/new application” or CD by post).

The RMP Summary should be submitted in English; publication will also be in English in accordance with Art. 68 para. 3 sentence 2 TPO. A translation into the Swiss national languages is not envisaged.

Following a formal review of the RMP Summary submitted, it will be published as described above. No separate correspondence is conducted with the marketing authorisation holder. In the event of a complaint, the marketing authorisation holder will be contacted.

7.3 Content and format

The form of the RMP Summary should correspond to the EMA's "Guidance on format of the risk management plan in the European Union" (Part VI)". When drafting the summary, ensure that it is complete (list all risks and risk minimisation measures) and easily comprehensible.

The following should be added to the document intended for publication:

Title page – stating the name of the medicinal product, active substance, version number of the underlying RMP, name of the marketing authorisation holder, date, and the following disclaimer word for word:

> The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP Summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.
>
> The RMP summary of "Bezeichnung des Arzneimittels" is a concise document and does not claim to be exhaustive.
>
> As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
>
> Please note that the reference document which is valid and relevant for the effective and safe use of "Bezeichnung des Arzneimittels" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Name of the marketing authorisation holder" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Bezeichnung des Arzneimittels".

7.4 Time limits

The RMP Summary must be sent to Swissmedic within 60 calendar days (CD) after approval of the application for authorisation or the RMP Update. As a rule, the application will be published on the website within 30 days of submission.

8 Implementation of the RMP

As a rule, approval of the RMP requires the marketing authorisation holder to implement the RMP upon introduction of the medicinal product in Switzerland. This applies in particular to:

- The pharmacovigilance plan with the activities described therein (e.g. specific / targeted follow-up questionnaires), post-authorisation safety studies [PASS], etc.),
- Risk-minimisation measures (appropriate warnings in the information for healthcare professionals and patients, design of the packaging material, additional measures such as patient information cards, educational material, etc.)

Any intended deviations must be described and substantiated in the Switzerland-specific annex (see section 6 – Switzerland-specific annex to the RMP) (this does not apply to differences between the product information given in the RMP and the text of the Swiss medicinal product information, which will be reviewed independently of the RMP).

Swissmedic will review the full implementation of the RMP by way of pharmacovigilance inspections, among other things.

8.1 Implementation of the pharmacovigilance plan (PVP)

As a rule, the complete pharmacovigilance plan must be adopted in a manner suitable for Switzerland. This means, for example, that risk-related questionnaires (targeted questionnaires and follow-up questionnaires) must be provided in all of the official languages.

A routine submission of study reports is not envisaged. Study reports on studies that were performed for an RMP must be submitted only if submission of these study reports was expressly stipulated as a condition.

However, if the results of studies mentioned in the PVP lead to changes in the product information or further risk minimisation measures, the study reports should be submitted in the context of the corresponding variation application. On the basis of Art. 28 TPO, marketing authorisation holders are obliged to update their product information in line with the latest scientific and technical findings, new incidents and evaluations.

8.2 Implementation of risk minimisation measures (RMM)

The provisions of GVP Module V, XVI and XVI Addendum must be applied as appropriate when creating any additional materials (additional RMMs) such as patient information cards, educational materials, educational videos, etc. For instance, these cannot contain any promotional content; the documents submitted cannot be inconsistent with the product information and must be adapted continuously to the approved product information.

RMMs must be implemented in accordance with the Switzerland-specific rules, which means that alongside the product information (general RMMs) any additional materials (additional RMMs) such as patient information cards, educational materials, educational videos, etc. must be provided in all official Swiss languages.

The legal responsibility for the content of the materials rests with the marketing authorisation holder. The materials must be submitted to Swissmedic on request.

8.2.1 Implementation of additional risk minimisation measures for medicinal products that do not require an RMP

Additional risk minimisation measures, such as those approved or recommended by other authorities, can be adopted in Switzerland even for medicinal products that do not require an RMP.

If Swissmedic considers that additional risk minimisation measures are needed for medicinal products that do not require an RMP, the marketing authorisation holder will be advised accordingly during the application review process, e.g. in the LoQ. Conversely, the marketing authorisation holder can request the adoption of additional risk minimisation measures without an underlying RMP.

If the need for additional risk minimisation measures is confirmed, implementation will be prescribed as a condition. If additional risk minimisation measures are no longer deemed necessary at a later point in time due to changes in the risk assessment, the marketing authorisation holder can file an application to revoke the requirement.

9 Queries

Please submit queries in writing to riskmanagement@swissmedic.ch. We also welcome suggestions for improvement to this guidance document.

- **Change history**

Version	Description	sig
5.0	Section 4: Additional information on which applications or medicinal products are subject to mandatory submission; details on specific authorisation procedures Section 5: Additional information on submission of an RMP Update; details on specific procedures Section 6: Additions to the Switzerland-specific annex Section 7: Comprehensive information on the RMP Summary Section 8: New section on implementation of the RMP Section 8.2.1: New section on implementation of additional risk minimisation measures for medicinal products that do not require an RMP Additional, comprehensive edits in all sections	wue
4.0	Section 6: Additional information on the RMP obligation in the context of authorisation procedures Section 7: Additional information on the preconditions and the procedure for submitting RMP Updates New: Subsection 8.1: Switzerland-specific annex (SSA) to the RMP Section 9: Additional information on the submission of the results of studies in the pharmacovigilance plan and on educational materials Section 10 Additional information on RMP Summaries Other editorial changes in various sections	dst
3.0	Update: submission via eCTD (section 10)	dst
2.0	Additional information on submission via Swissmedic Portal; delivery type “communication” (section 10)	dst
1.0	Implementation of HMV4	dst