Contents

1 Abbreviations

ADR	Adverse Drug Reaction
AID	Application ID
AP	Administrative proceedings
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
FeeO-Swissmedic	Ordinance of 14 September 2018 on the Fees charged by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic; SR 812.214.5)
GVP	Guideline on good pharmacovigilance practices
GVP Module IX	Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management
MAH	Marketing authorisation holder
TPA	Therapeutic Products Act (SR 812.21)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TPO	Therapeutic Products Ordinance (SR 812.212.21)

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2 Requirements for signal reports

The duty to report drug safety signals and the time limits for reporting signals to the Agency are anchored in the Therapeutic Products Act (TPA) (Art. 59) and the Therapeutic Products Ordinance (TPO) (Art. 61, 62 and 63).

The European *Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management* describes the requirements pertaining to the scientific, quality-related and regulatory aspects of signal management. The main definitions used in the context of signal management are summarised in *GVP Module IX Addendum 1*.
For the purpose of uniform understanding in relation to signal management, Swissmedic employs the definitions agreed by the European Union in the valid *GVP Module IX* and its Addendum.

3 Introduction

In the context of signal and risk management, every safety signal relating to a medicinal product or active substance authorised by Swissmedic is considered to be potentially relevant to the benefit-risk profile of the medicinal product, irrespective of whether the signal is reported in Switzerland or abroad.

Marketing authorisation holders (MAH) of medicinal products are obliged to report findings and evaluations that are relevant to the benefit-risk profile of the medicinal product to the Agency (Art. 59 TPA). Moreover, on the basis of Art. 28 of the Therapeutic Products Ordinance (TPO), the MAH are obliged to update their product information in line with the latest scientific and technical findings, new incidents and evaluations.

As part of its work on pharmacovigilance inspections, Swissmedic regularly checks compliance with the reporting obligations by the MAH.

If necessary, Swissmedic can also at any time initiate a review of the benefit-risk profile of medicinal products, individually or by groups, in connection with administrative proceedings according to Art. 16c TPA and Art. 14 TPO.

4 Objective

This Guidance document describes the signal reporting obligations of MAH and the timely implementation of risk-minimising measures (e.g. including modification of the product information) arising from the signal evaluation.
Information on the duty to report adverse drug reactions is not the subject of this Guidance document.

5 Scope

This Guidance document applies to the Swissmedic Division Safety of Medicines in regard to the duty to report signals for human medicines and the implementation of risk-minimising measures by the MAH.

6 Company signals (signals evaluated by the MAH)

Incidents or observations (both nationally and internationally) that concern the benefit-risk profile of a medicinal product and/or that can have a relevant impact on public health should be reported to Swissmedic as soon as they become known (Art. 59 TPA, Art. 61 para 4 and 5 TPO, Art. 62 para. 2 TPO)

6.1 Signals involving a serious risk potential (*emerging safety issues* as per the definition in GVP Module IX)

If the MAH classes a signal as a signal with a serious risk potential (*emerging safety issue)*, the following reporting time limits apply:

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- The signal must be reported to Swissmedic at once, and at the latest within five days, if measures for maintaining drug safety are required in the short term (e.g. informing the public immediately, market withdrawal at short notice) (Art. 62, para. 2 let. a TPO).

- A reporting time limit of 15 days is appropriate if there are other serious drug risks that are not adequately explained in the product information (Art. 62 para. 2 let. b TPO).

It should be noted that *emerging safety issues* reported for a medicinal product by the MAH to the *European Medicines Agency* (EMA) are automatically considered, in Switzerland, to be notifiable signals with a serious risk potential, provided the medicinal product/active substance is authorised in Switzerland or an application for authorisation has been submitted to Swissmedic.

The report of an *emerging safety issue* to the Agency should be accompanied by the available data on the signal in a summary assessment. In particular, the derived risk-minimising measures and a corresponding timetable for their implementation should also be submitted to the Agency.

If the *emerging safety issue* is triggered by a single case report in Switzerland, the report of the *emerging safety issue* including the above-mentioned documentation should be submitted in addition to the report on the adverse drug reaction (ADR).

Following the report of the *emerging safety issue*, further analyses and investigations of the signal by the marketing authorisation holder and by Swissmedic are usually needed in order to define the definitive measures for risk minimisation. This takes place in the context of administrative proceedings according to Art. 58 para 3 in conjunction with Art. 66 TPA.

6.2 Signals without a serious risk potential (not meeting the definition of an *emerging safety issue*)

6.2.1 Signals without a serious risk potential: Implementation of changes to the product information

On the basis of Art. 28 of the TPO, the MAH is obliged to update its product information in line with the latest scientific and technical findings, new incidents and evaluations.

If the signal evaluation by the MAH reveals the need for modification of the product information, this should be submitted without a specific request from Swissmedic (application submission).
If the MAH identifies a new signal (nationally or internationally) that necessitates a change to the product information, the following specific procedure is indicated:

- The MAH is explicitly requested, in the interests of drug and patient safety, to submit the application shortly after the signal is closed (by the MAH).
- Submission of a corresponding application to Swissmedic after 6 months at the latest (Day 0 = closure of the signal evaluation by the MAH).

6.2.2 Signals without a serious risk potential: no modification of the product information necessary

If no risk-minimising measures are indicated (at this stage) (e.g. because further investigations are needed) for a signal validated by the MAH, the signal should be reported to Swissmedic as follows:

- Inclusion of the signal evaluation in the next scheduled PSUR/PBRER.

If risk-minimising measures emerge from the subsequent signal investigation by the MAH, these should be submitted to Swissmedic independently by the MAH as described in Chapter 6.2.1 (application submission).

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During its assessment of the PSUR/PBRER, Swissmedic can request further information relating to an ongoing signal and implement any risk-minimising measures in connection with administrative proceedings according to Art. 66 TPA.

7 Signals evaluated by foreign authorities

It should be noted that Swissmedic basically classifies signals evaluated by foreign authorities (countries with a comparable drug regulatory authority) and potentially involving medicinal products authorised in Switzerland, as signals that must be reported to the Agency.

- Swissmedic should be informed by the MAH about the initiation of the signal evaluation or about safety- or efficacy-related procedures (*referrals*) by the following authorities within 15 days:
  - EU and EFTA countries
  - USA

Data and findings available to date regarding the signal and/or the procedure must be reported to Swissmedic in an evaluative summary together with the expected timetable for having the signal processed by the authority concerned.

Following the initial signal report, no interim reports need be submitted unless requested by Swissmedic.

- Swissmedic should also be informed by the MAH about the results and resulting measures within 15 days following the closure of the signal evaluation / procedure by the corresponding authority.

In connection with this information sharing, specific measures scheduled for Switzerland (including a timetable for implementation) should be defined by the MAH. If the MAH considers that a risk-minimising measure required by a foreign authority is not appropriate for Switzerland, the MAH should clearly justify this to Swissmedic. The scheduled measures / statement are evaluated by Swissmedic. If this evaluation leads to differing results in respect of risk-minimising measures or the timing of their implementation (e.g. wording of the change to the product information, the time limit for submitting the corresponding application and any further measures (e.g. DHPC)), the Agency specifies the requirements in connection with administrative proceedings according to Art. 66 TPA.

Risk-minimising measures imposed by foreign authorities listed above in connection with the evaluation of PSUR/PBRER must be notified to Swissmedic within three months, where the date on which the authority in question completes its evaluation of the PSUR/PBRER counts as day 0. The intended measures for Switzerland must be set out. The application to modify the product information or for other risk-minimising measures can be submitted at the same time.

8 Fees

Time-based fees are charged for administrative proceedings, specifically AP in connection with signal processing (e.g. implementation of a change to the PI, DHPC, suspension, revocation) (Art. 1 in conjunction with Art. 4 FeeO-Swissmedic).

9 Implementing risk minimisation measures for medicinal products containing known active substances, biosimilars and co-marketing medicinal products

Swissmedic generally evaluates safety signals by active ingredient or, in certain cases, by substance class. Where several MAH are affected by a signal, communication on content-related aspects and planned risk minimisation measures associated with the signal generally takes place with the MAH of the reference medicinal products in question (also with regard to biosimilars) and with the MAH of medicinal products containing known active substances *with innovation.*

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If the reference medicinal product is no longer authorised, communication takes place with the MAH of biosimilars and of known active substances with and without innovation.

MAH of medicinal products containing known active substances *without innovation*, of biosimilars and of co-marketing medicinal products are informed of the outcome of the signal evaluation process by means of a preliminary decision/official decision if additional risk minimisation measures are required, such as a DHPC or the introduction of training material.

MAH of medicinal products containing known active substances *without innovation* and for biosimilars are subject to the universal updating obligation set out in Article 28 TPO (obligation to ensure that "Information for healthcare professionals" and "Patient information" texts are aligned with current scientific knowledge or the reference medicinal product).
The wording of "Information for healthcare professionals" and "Patient information" texts for medicinal products containing known active substances *without innovation* must be identical to that for the reference medicinal product(s) (Annex 4 no. 1 para. 5 or Annex 5 no. 1 para. 6 TPLRO).

MAH of biosimilars are also required in particular to actively monitor changes to the safety sections in the product information for the reference product (Information for healthcare professionals: Contraindications, Warnings and precautions, Interactions and Undesirable effects) and to spontaneously submit either an appropriate application for a variation requiring approval or to provide clear scientific justification for not aligning the texts.

Variations to the reference medicinal product must be submitted to Swissmedic no later than 90 days after the variations approved for the reference medicinal product have been published.

Variations to co-marketing medicinal products should be reported to Swissmedic within 30 days of the variations to the basic product being approved. The variations approved for the basic product must be adopted unchanged for the co-marketing medicinal product.

10 Formal requirements for signal reporting

Signal reports according to Chapter 6.1 and Chapter 7 should be submitted to Swissmedic as follows:

- Signal reports should be addressed to the Safety of Medicines Division, Risk Management Unit.
- The signal reports can be submitted by post (CD) or via the Swissmedic Portal.
- For portal submissions please note the following:
  - Submit under „safety communication", stating clearly that a signal report to the Safety of Medicines Division, Risk Management Unit is involved.
  - Since signals are not yet displayed on the Portal, they cannot be assigned directly to an Application ID (AID). However, if an AID exists for the signal, please refer to this in the accompanying letter.
- In the subject line of the accompany letter, please state clearly that a signal report is involved.
  - Subject: Signal report [Name of the affected medicinal product/active substance] [Signal]
- The signal report should also include the following information:
  - List of all affected preparations of the MAH
  - Summary assessment of the signal
  - Signal evaluation reports from other foreign authorities (if available)
  - Planned risk-minimising measures and timetable for Switzerland

11 Information on submitting an application for a variation "Change to the product information" (HMV IV)

Variation applications to medicinal product information in the context of signal evaluation should generally be submitted as follows:

1. **Swissmedic provides the final text for implementation in the context of the signal evaluation**

Application type: Minor variations to be reported in advance, type C.I.1 – IB.

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The legal framework is provided by Art. 22 TPO.

2. The MAH submits the proposed text for the change to the product information
Application type: Major variations, type C.I.1 – II.
The legal framework is provided by Art. 23 TPO.

3. The change to the product information must be implemented without delay
Application type: safety-relevant variation C.100 – II

Whenever you submit an application resulting from a signal, please reference the relevant signal ID.

Application types for applications for variations involving medicinal products with known active substances *without innovation*, biosimilars and co-marketing preparations can be found in the currently valid version of the relevant guidance documents.

Change history

Version	Valid and binding as of	Description, comments	Author's initials
3.0	**01.04.2019**	**New chapters added:** • **9. Implementing risk minimisation measures for medicinal products containing known active substances, biosimilars and co-marketing medicinal products** • **11. Information on submitting an application for a variation "Change to the product information" (HMV IV)**	**dst**
2.0	**01.01.2019**	**Company signals without a serious risk potential: deadline for implementation of changes to the product information extended from 3 to 6 months. (see chapter 6.2.1)** **Correction in chapter 7: 15 days timeline to report the closure of the signal evaluation / procedure by the corresponding authority**	**dst**
1.0	**01.01.2019**	**Implementation of TPO4**	**dst**

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