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## 1 Abbreviations

ADR	Adverse Drug Reaction
AID	Application ID
AP	Administrative proceedings
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
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)
TPO	Therapeutic Products Ordinance (SR 812.212.21)

## 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. 35, 36 and 37).

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. 16 of the Ordinance of 17 October 2001 (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. 16 para. 2 and 3 TPA and Art. 13 TPO.

### 4 Objective

This Information sheet 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 Information sheet.

### 5 Scope

This Information Sheet 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).

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

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

- The signal must be reported to Swissmedic within five days if measures for maintaining drug safety are required in the short term (e.g. informing the public immediately, short-term market withdrawal) (Art. 36 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. 36 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. 16 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).

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

The available data and findings relating to the signal or process must be submitted to Swissmedic in an evaluative summary.

In individual cases, Swissmedic can, after the initial notification of the signal/procedure, agree on a specific timetable for exchanging information with the MAH.

- Swissmedic should also be informed by the MAH about the results and resulting measures within five 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 Ordinance on Fees for Therapeutic Products, HGebV).

In connection with signal processing, time-based fees are also charged for AP for medicinal products with an "Orphan Drug Status".<sup>1</sup>

## 9 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 "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]

<sup>1</sup> Art. 6 para. 1 in conjunction with Annex 2 B, no. 1 of the HGebV specifies a fee reduction for marketing authorisation applications relating to medicinal products for rare diseases according to Art. 14 para. 1 f of the TPA. Fee reduction does not apply for market surveillance (in this case PA in the context of signal processing).

- 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

**Change history**

Version	Valid and binding as of	Modified without version change	Description, comments (by author)	Author's initials
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