Guidance document
Drug Safety Signals HMP

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1 Abbreviations

ADR	Adverse Drug Reaction(s)
AID	Application ID
AP	Administrative proceedings
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
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
HMP	Human medicinal products
MAH	Marketing authorisation holder
MHRA	Medicines & Healthcare products Regulatory Agency
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)

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 document “GVP Annex I - Definitions” contains definitions of the main terms in pharmacovigilance.
In the interest of consistency in relation to signal management, Swissmedic employs the definitions agreed by the European Union in the valid “*GVP Module IX”* and the definitions in the current “*GVP Annex I – Definitions”*.

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 potentially relevant to the benefit-risk profile of the medicinal product, irrespective of whether the signal is reported in Switzerland or abroad.

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, based on 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-minimisation measures (e.g. modification of the product information) arising from the signal evaluation.
Information on the mandatory reporting of 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-minimisation measures by the MAH.

6 Company signals (signals evaluated by the MAH)

Safety and efficacy signals (both national and international signals) that concern the benefit-risk profile of a medicinal product and/or that can have a relevant impact on public health must 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 Company 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:

- 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.

Following the report of the *emerging safety issue*, further analyses and investigations of the signal by the MAH and by Swissmedic are usually needed, in order to define the definitive measures for risk minimisation (signal evaluation procedure). To this end, Swissmedic conducts administrative proceedings according to Art. 58 para. 3 in conjunction with Art. 66 TPA.

The Signal Notification Form should be used for reporting safety signals. The report of an *emerging safety issue* to the Agency should be accompanied by all the existing available data on the signal in a summary assessment. In particular, the planned derived risk-minimisation measures and a corresponding timetable for their implementation should also be submitted to the Agency. If this information is incomplete, a date by which further information will be submitted to Swissmedic should be stated.

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). A cross-reference to the report submitted via E2B should be appended to the signal report.

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

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

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

If the company internal 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 for modification of the product information (type C.I.4) shortly after the signal is closed (by the MAH), but at the latest after 6 months (Day 0 = closure of the signal evaluation by the MAH).

For these signals (company signals without a serious risk potential) the obligation of the MAH to report the signals is fulfilled with the timely submission of the corresponding application of the variation of the product information.

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

If no risk-minimisation 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.

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

On expiry of the PSUR obligation in Switzerland, company signals without a need for risk minimisation measures (e.g. modification of the product information) do not have to be reported as standalone notification, but they should continue to be tracked as part of the company's in-house signal management process.

7 Signals evaluated by foreign authorities (signals from authorities)

7.1 Reporting of signals and safety- and efficacy-related procedures of foreign authorities

The signals that must be reported according to TPO Art. 61 include signals and safety- or efficacy-related procedures (referrals) evaluated by foreign authorities (countries with a comparable drug regulatory authority) and potentially involving medicinal products authorised in Switzerland.

- Swissmedic should be informed by the MAH about the initiation of the signal evaluation and about safety- or efficacy-related procedures (*referrals*) by the following authorities within 30 days[1]:
  - EMA
  - FDA
  - MHRA

Interim reports should be submitted after the initial signal notification only if these are requested by Swissmedic. If the MAH does not receive a specific request for the submission of interim reports, only the signal/referral closure of the corresponding authority needs to be notified again to Swissmedic.

- Swissmedic should be informed by the MAH about the results and resulting measures within 30 days[1] following the closure of the signal evaluation / referral procedure by the corresponding authority.

The time limit for reporting signals of foreign authorities that are classified as emerging safety issues (e.g. EU referral procedures for safety reasons: urgent EU procedures) is reduced to 5 or 15 days respectively[1] for reporting the opening or conclusion of the signal/procedure:

- The signal must be reported to Swissmedic at once, and at the latest within five days[1], 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[1] 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).

The Signal Notification Form should be used for the initial signal report and for closure reports relating to signals. A cover letter is not required.

Additional documentation relating to the signal report, such as assessment reports, detailed statements, references, etc., should be appended to the signal notification form.

The signal notification form should not be used for signal reports for which a Swissmedic signal number (Signal ID) has already been opened. For these signals, a cover letter should be attached, clearly stating the Signal ID in the subject line (see section 10).

[1] Definition of day 0:
Signals/procedures of foreign authorities (EMA, FDA, MHRA):
Day 0 = MAH informed of the start/conclusion of the foreign authority's signal evaluation/referral procedure (information provided by the evaluating authority to the MAH or, if this does not apply, publication of the information by the respective authority)
Risk minimisation measures ordered by foreign authorities in connection with PSUR/PBRER/PSUSA procedures:
Day 0 = day on which the MAH was informed about the necessary measures by the evaluating authority.

7.1.1 Implementation of risk-minimisation measures (signals from authorities)

Specific measures planned for Switzerland (including a timetable for implementation) should be defined by the MAH in the signal report (see Signal Notification Form). If the risk minimisation measures, particularly the modification of product information texts, are already defined, these should be presented directly in the Signal Notification Form in the correspondence language (template for wording in the correspondence language).

The submitted wording is then reviewed and decided by Swissmedic as part of a signal evaluation procedure.

Subsequently, following the decision on the wording as part of the signal evaluation procedure, the changes to the product information texts must be submitted to Swissmedic as a **C.I.1 a) type IA$_{IN}$** application within 30 calendar days. The wording of the change of the C.I.1 a) type IA$_{IN}$ application must be identical to the wording used in the signal.

If risk-minimisation measures are planned in Switzerland but the final version is not available to the MAH at the time of notification of the signal closure (wording of the change is not yet submitted with the signal notification), the MAH may indicate the submission of an application for modifying the product information within a specific timeframe (must be indicated). This will be considered by Swissmedic to be a binding commitment to implement the corresponding measures. If Swissmedic agrees with the measures and the indicated timeframe, no further correspondence with the MAH follows. The marketing authorisation holder is then obligated to submit the announced modification as a C.I4 (type II) application. The content of the modification will be reviewed and an official decision issued on the application. If Swissmedic reaches a different result from the action plan proposed by the MAH, this will be communicated to the MA as part of a signal evaluation procedure.

If the MAH considers that a risk-minimisation measure required by a foreign authority is not appropriate for Switzerland, the MAH must clearly justify this to Swissmedic (see “Rationale for any discrepancies” in Signal Notification Form). The statement by the MAH is evaluated by Swissmedic. If Swissmedic agrees with the divergent measures, no further correspondence follows. If Swissmedic does not agree with the action plan proposed by the MAH, this will be communicated to the MAH in of a signal evaluation procedure.

7.2 Reporting of safety- and efficacy-related results from PSUR/PBRER/PSUSA procedures of foreign authorities

Risk-minimisation measures imposed by the authorities listed in section 7.1 in connection with PSUR/PBRER/PSUSA procedures must be notified to Swissmedic within three months. However, it is not necessary to provide notification of the opening of a PSUSA procedure or submit interim reports.

This notification should be made using the “Signal Notification Form”. The intended measures for Switzerland must be set out. The application for the variation of the product information or for other risk-minimisation measures may be submitted at the same time. In this case, the Signal Notification Form should include a reference to the corresponding application ID or a note in regard of the planned submission of the variation.

7.3 Reporting requirements of signals for medicinal products with the authorisation status "Known active substance (KAS)"

For medicinal products with the authorisation status "KAS", the findings on the efficacy and safety of the respective reference medicinal product are generally considered transferable.

In order to avoid duplication, signals evaluated by foreign authorities as listed in sections 7.1 and 7.2 should be reported *a priori* by the MAH of the reference products.

Any measures derived by Swissmedic from the results of the specific active substance signal evaluation are usually transferable to all authorised medicinal products containing the relevant active substance.

MAH of medicinal products with the authorisation status "KAS without innovation" are obliged to implement the adaptation of the product information to the reference product without delay.

For medicinal products with the authorisation status "KAS without innovation", the obligation to report signals evaluated by foreign authorities is fulfilled with the timely submission of the application for a variation of the product information (adaptation to the reference product).

If the reference product is no longer authorised, the primary responsibility for following up international signals under evaluation by foreign authorities is transferred to the MAH(s) of the medicinal product/s "KAS without innovation", as is also the initial obligation to report the signal within the periods stated in sections 7.1 and 7.2.

Company signals must be reported to Swissmedic as per section 6, regardless of the authorisation status of the medicinal product.

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 and, in certain cases, by substance class. If several MAH are concerned 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.*
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 and official decision if additional risk minimisation measures are required, such as a DHPC or the introduction of training material.

MAH 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 in line 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 a signal report providing clear scientific justification for not aligning the texts.

Swissmedic expects to receive the variations for alignment to the reference medicinal product within three months after the updated product information texts for the reference medicinal product have been published.

Variations to co-marketing medicinal products must be notified to Swissmedic within 30 days after the approval of the variations to the basic product. 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:

- Address: Safety of Medicines Division, Risk Management Unit
- The signal reports can be submitted by post (CD) or via the Swissmedic Portal.
- The Signal Notification Form MU101_10_025e_FO should be used both for initial signal reports and for follow-up reports on signals *without Swissmedic Signal ID (signal number)*. A covering note is no longer required. Any additional documents relating to the signal report, such as assessment reports from other authorities, detailed reviews, references, etc. should be appended to the fully completed notification form. If information is lacking, a date by which Swissmedic can expect to receive further details should be stated.
- If the report is submitted via the portal, an "Acceptance of delivery" is generated. Swissmedic does not send confirmations of receipt of signal reports submitted by post.
- For information on signals that already have a Swissmedic Signal ID known to you, please do not use the notification form. A covering note should be attached stating the Signal ID in the subject line as follows:
  Subject: Signal ID_Active substance _adverse reaction (MedDRA term)

When submitting material through the portal, please note the following:

- Please submit the signal documentation under “safety communication”.
- For information on signals *with Swissmedic Signal ID*: At present, signals are not yet displayed on the portal. Consequently, information on signals with Signal ID can only be properly identified if the Signal ID is stated in the covering note (see above).

11 Information on submitting an application for a variation “Change to the product information” in the context of signal evaluation by Swissmedic

In the context of signal evaluation by Swissmedic, an official decision will be issued on the final wording for modified medicinal product information and/or packaging, according to the signal process, and the signal closed with the decision.

Once an official decision has been issued, the variation to Swissmedic should be submitted within 30 calendar days as a **C.I.1 a) type IA_{IN}** application. The legal basis is provided by Art. 21 TPO.

The updated product information texts must be published promptly, but at the latest by 70 days after the official decision on the signal.

Please note, however, that these applications for a variation cannot be submitted as part of a multiple application.

The signal process in detail:

- If the MAH has already submitted the draft version of the variation of the product information in the correspondence language with the Signal Notification Form, Swissmedic will review the draft version and, if the wording is acceptable, issue its official decision directly. If the wording has to be ameneded, Swissmedic will inform the MAH by a letter.
- If Swissmedic prescribes a modification of medicinal product information in the course of its evaluation of a signal, the MAH will be sent the wording of the modified text by letter (providing the wording has not already been submitted by the MAH). They will then have an opportunity to comment on the measures and the wording of the modification.

  Unless the MAH informs Swissmedic otherwise within the specified deadline, the Agency will assume that they consent. Swissmedic will then issue its official decision on the text and complete the signal with that decision.

  If the MAH does inform Swissmedic otherwise, the Agency will review their reply and notify them of the results of the evaluation and the resulting requirements by means of a preliminary decision. The MAH then again has the opportunity to make a statement on the requirements in a response to the preliminary decision. After reviewing the statement, the measures will be ordered based on the outcome of the evaluation in the form of a decision.
- Swissmedic can propose a general wording when extensive and complex changes are required. In such cases, the MAH should submit the final text in the correspondence language, with comments. After reviewing the proposed text, Swissmedic will notify the MAH of the outcome of its review, including any text corrections, in the form of a preliminary decision.

  An official decision on the final text will be issued once the MAH has replied to the preliminary decision.

Once the official decision on the wording has been issued in the context of signal closure, the modified medicinal product information and/or packaging texts must be submitted as a C.I.1 a) type IA_{IN} application. Whenever you submit an application, please reference the corresponding signal ID. Application types for applications of 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	Change	sig
9.1	New layout, no content adjustments to the previous version.	dei
9.0	Chapter 7.2: Additions to the reporting obligation (no notification of the opening of a PSUSA procedure, no submission of interim reports)	dst
8.0	Section 7.1: Addition of reporting time lines for signals of foreign authorities that are classified as emerging safety issues. Further explanation of the implementation of risk-minimisation measures (signals from authorities) and new sub-section added: • 7.1.1 Implementation of risk-minimisation measures (signals from authorities) Other editorial changes and corrections.	dst
7.0	Revision of the document, with focus on a more detailed description of the existing procedure. New subsections added: • 7.2: Reporting of safety- and efficacy-related results from PSUR/PBRER/PSUSA procedures of foreign authorities • 7.3: Reporting requirements of signals for medicinal products with the authorisation status "Known active substance (KAS)" Modification of reporting time limits in section 7. Addition of publication deadline in section 11.	dst
6.1	Chapter 7: Harmonisation with German version: last sentence “can” replaced by “should”.	dst
6.0	Chapter 2: Correction_the specified reference “GVP Module IX Addendum 1” was replaced with “GVP Annex I - Definitions (Rev 4)”.	dst
5.0	Chapter 11: Full revision (change in the safety signal process following modification of medicinal product information as a risk minimisation measure)	dst
4.0	Editorial adaptations in different chapters. Chapter 10: introduction of the Signal Notification form	dst
3.0	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	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	Implementation of HMV4	dst