Guidance document
Drug Safety Signals VPM

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1 Abbreviations

ADR	Adverse Drug Reaction
AE mB	Variation with assessment
AE oB	Variation without assessment
AID	Application ID
AP	Administrative proceedings
AR	Assessment Report
CVMP	Committee for Veterinary Medicinal Products (EMA)
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)
FO	Form
MAH	Marketing authorisation holder
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Medically Important
NW	Side effect
OD	Official decision
PSUR	Periodic Safety Update Report
ROR	Reporting odds ratio
SMC	Swissmedic
SMP	Signal management process (acc. to Art. 81 EU 2019/6)
TPA	Federal Act on Medicinal Products and Medical Devices (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)
VeDDRA	Veterinary dictionary for drug regulatory activities
VGVP	Veterinary Good Pharmacovigilance Practice
VGVP module	Guideline on Veterinary Good Pharmacovigilance Practices Module: Signal Management (EMA/399713/2020)[1]
VMP	Veterinary medicinal product
VMPC	*Tierarzneimittelkompendium der Schweiz* (Compendium of veterinary medicinal products in Switzerland)
WL	*Wegleitung* [Guidance document]

[1] EMA/522332/2020, 18 November 2021

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).

In the present context, a signal is defined as any information from one or more sources, including observations and experiments, that points to a new potential causal relationship or a new aspect of a known causal relationship between an intervention and an adverse event or a series of contiguous adverse events such that closer investigation of potential causality is deemed to be appropriate[2].
The European *Guideline on veterinary good pharmacovigilance practices (GVP) Module Signal Management* describes the requirements pertaining to the scientific, quality-related and regulatory aspects of signal management. The document "V*GVP Annex – Glossary"*[3] contains definitions of the main terms in pharmacovigilance for veterinary medicinal products.

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.

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, 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 (WL) 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.
Swissmedic uses this Guidance document first and foremost as a resource for applying the legal provisions in a uniform and equitable manner. For MAH, the document is intended to clarify the specific requirements that must be fulfilled so that risk minimisation measures can be processed and implemented as quickly and efficiently as possible.

[2] Art. 1c, Implementing Regulation (EU) 2021/1281
[3] EMA/118227/2021, 18 November 2021

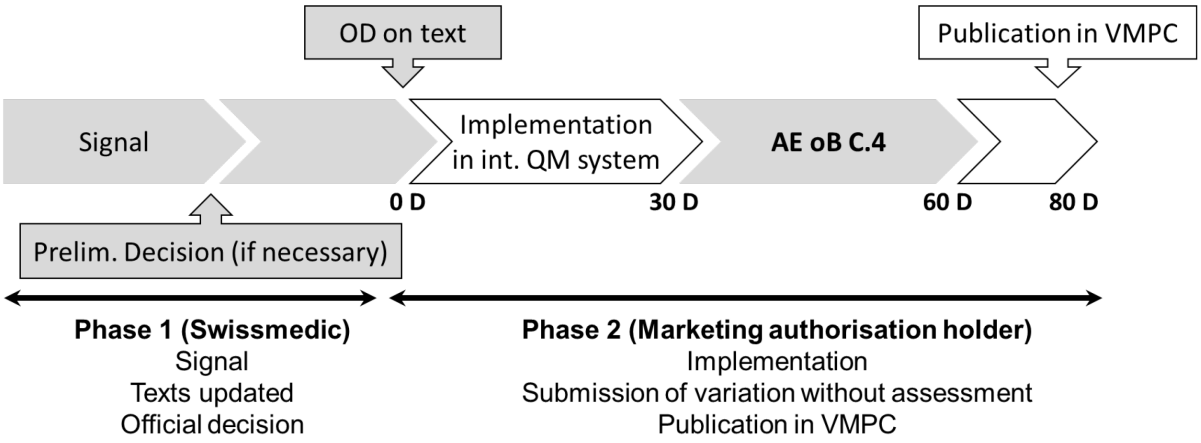
5 Scope

This WL applies to all veterinary medicinal products authorised by Swissmedic in regard to the duty to report signals for veterinary medicinal products and the implementation of risk-minimising measures by the MAH.

6 Application types, procedure and deadlines

6.1 General procedure for signals

The diagram below shows the general procedure for signals.



Grey boxes: responsibility of Swissmedic, white boxes: responsibility of marketing authorisation holder

The majority of phase 1 of the procedure takes place at Swissmedic (deadlines for information exchange and comments are not shown for the sake of simplicity). Phase 2 comprises the implementation of the modifications in the MAH's QM system, submission and assessment of the variation without assessment C.4 and publication of the modified medicinal product information in the Compendium of veterinary medicinal products in Switzerland (VMPC). A preliminary decision is not required.

Important: Once an official decision has been issued for a signal, the text with the necessary modifications is known. For this reason, no subsequent changes should be expected.

The following applies to implementation of the modifications:

- The implementation date is the date on which the modifications to the texts are entered in the MAH's QM system
- This date must be no more than 30 days after the official decision on the signal
- This date must also be prior to submission of the variation without assessment C.4

6.2 Application types and deadlines

Source of identified risks	Procedure / application type

Signal (internally at MAH or as part of SMP)	FO Signal Notification VMP, OD signal, AE oB C.4
Signal in the EU (CVMP, referral)	FO Signal Notification VMP, OD signal, AE oB C.4 or AE mB G.I.4 (**with** documentation only: AR and/or EMA decision, incl. text officially approved in the EU)
Signal opened by SMC	OD signal, AE oB C.4
Foreign PSUR	AE mB G.I.4 (**with** documentation only: AR and/or EMA decision, incl. text officially approved in the EU)
Swiss PSUR (requested by SMC)	AE mB G.I.3

Each letter connected with a signal lists the deadlines and variation types to be submitted.

Important: Given the differing deadlines, safety-relevant variations may not be submitted as part of a multiple application.

7 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 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).

7.1 Prioritisation of company signals

7.1.1 Company signals involving a serious risk potential (*emerging safety issues* as per the definition in VGVP module Signal Management, EMA/399713/2020)

Company signals involving a serious risk potential (emerging safety issues) are signals that require immediate regulatory action and communication. Examples of *emerging safety issues* include:

- Signals involving a serious risk potential that are associated with ongoing or recently completed clinical studies, e.g. an unexpected increase in deaths or serious adverse reactions;
- Signals involving a serious risk potential that are discovered by spontaneous reporting or a literature search and which might result in modifications to contraindications or restrictions on use or even in suspension or revocation;
- Regulatory action in other countries resulting in restrictions on use or suspension or revocation of authorisation.

In this context, reports of serious adverse reactions to veterinary medicinal products in humans[4] should be regarded as signals involving a serious risk potential. Use for intended suicide is excluded for this purpose.

[4] The criteria for serious adverse reactions in humans apply here: *Serious adverse reactions* are those which result in death, are life-threatening, require inpatient hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or are a birth defect or congenital anomaly.

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) or a national authority 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. To this end, Swissmedic conducts administrative proceedings according to Art. 58 para. 3 in conjunction with Art. 66 TPA.

The Signal Notification Form VMP 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-minimising 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).

7.1.2 Signals with Medically Important (MI) terms in VeDDRA terminology

A list of *Medically Important terms* based on VeDDRA has been drawn up and is available in Appendix 1 of the VGVP Signal Management module. Reports involving *Medically Important terms* should always be prioritised, even if there is insufficient evaluation of incidence (e.g. ROR, reporting odds ratio) or insufficient information on the number of cases (except where such cases are adequately described in the approved version of the medicinal product information).

However, a report containing an MI term must not be automatically regarded as a safety signal. In general, signals require more than one single report; nevertheless, signals can, in exceptional cases, also result from individual reports.

7.1.3 Prioritisation criteria for further types of signal

Additional criteria have to be applied to exclude false positive signals and categorise further types of signal by priority. The following criteria can be used to categorise by priority new signals that are not *emerging safety issues* or do not contain *Medically Important terms*:

- **Recency of the identified association** between medicinal product use and reaction. The focus should be placed on recently discovered associations or new aspects of a known

association (e.g. change in frequency, severity, duration or persistence and changes in post-reaction outcome or mortality rate).
- **Evidence level** for an association between use and reaction plus number of reports.
- **Severity, outcome, reversibility** of the incident and potential for prevention
- **ROR** (not solely conclusive, i.e. the significance of the ROR cannot be used to directly determine whether a report constitutes a signal)
- **Impact on public health, animal health and the environment**
- **Species-specific incidents**

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

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

Based on 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 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 form Signal Notification VMP or an application for modification of the product information (see table in section 6.2) shortly after the signal is closed (by the MAH), but at the latest after 60 days (Day 0 = closure of the signal evaluation by the MAH).

Important: It is not possible to submit a safety-relevant variation as part of a multiple application owing to the differing deadlines. The safety-relevant variation must be submitted as a separate type C.4 application after an official decision on the signal has been issued.

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.

7.2.2 Company 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 or as part of the next scheduled equivalent annual report.

During its assessment of the PSUR or equivalent annual report, 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.

On expiry of the PSUR obligation in Switzerland, company signals without a need of 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 and may be examined in the course of inspections.

8 Signals evaluated by foreign authorities

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

The signals that must be reported according to Art. 61 TPO include both signals and safety- or efficacy-related procedures (referrals) evaluated by foreign authorities 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 foreign authorities within 30 days5:

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 Signal Notification Form VMP should be used for the initial signal report and for closure reports relating to signals (see also section 10). 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 information on signal reports that already have a Swissmedic Signal/SA ID. For these signals, a cover letter should be attached, clearly stating the Signal/SA ID in the subject line (see section 10).

In connection with the signal reports, specific measures scheduled for Switzerland (including a timetable for implementation) should be defined by the MAH (see Signal Notification Form VMP). 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 VMP in the correspondence language. The texts are then reviewed and the final wording decided by Swissmedic as part of the signal evaluation procedure. Subsequently, the changes to the product information texts must be submitted to Swissmedic as an application for a **variation without assessment C.4** within 30 calendar days.

[5] Definition of day 0:
Signals/procedures of foreign authorities (EMA, FDA, MHRA):
Day 0 = MAH informed of the procedure status 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.

Important: It is not possible to submit the C.4 variation as part of a multiple application owing to the differing deadlines. The variation without assessment C.4 must be submitted as a separate application after an official decision on the signal has been issued.

If the MAH considers that a risk-minimising measure required by a foreign authority is not appropriate for Switzerland, the MAH must clearly justify this to Swissmedic (see Signal Notification Form VMP). 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.

As a general rule: if the MAH announces risk minimisation measures in the signal report and their implementation in Switzerland (e.g. submission of an application for a variation of the product information for a specified date), Swissmedic will open a signal procedure under which the proposed measures will be reviewed and an official decision issued..

8.2 Reporting of safety- and efficacy-related results from PSUR or equivalent procedures of foreign authorities

Risk-minimising measures imposed by foreign authorities in connection with PSUR or equivalent procedures must be notified to Swissmedic within three months, using the “Signal Notification Form VMP”. The intended measures for Switzerland must be set out. The application for a type G.I.4 variation with assessment for modification of the product information or for other risk-minimising measures may be submitted at the same time. In this case, the Signal Notification Form VMP should include the corresponding application ID or a note in regard of the planned submission of the variation.

9 Fees

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

10 Formal requirements for signal reporting

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

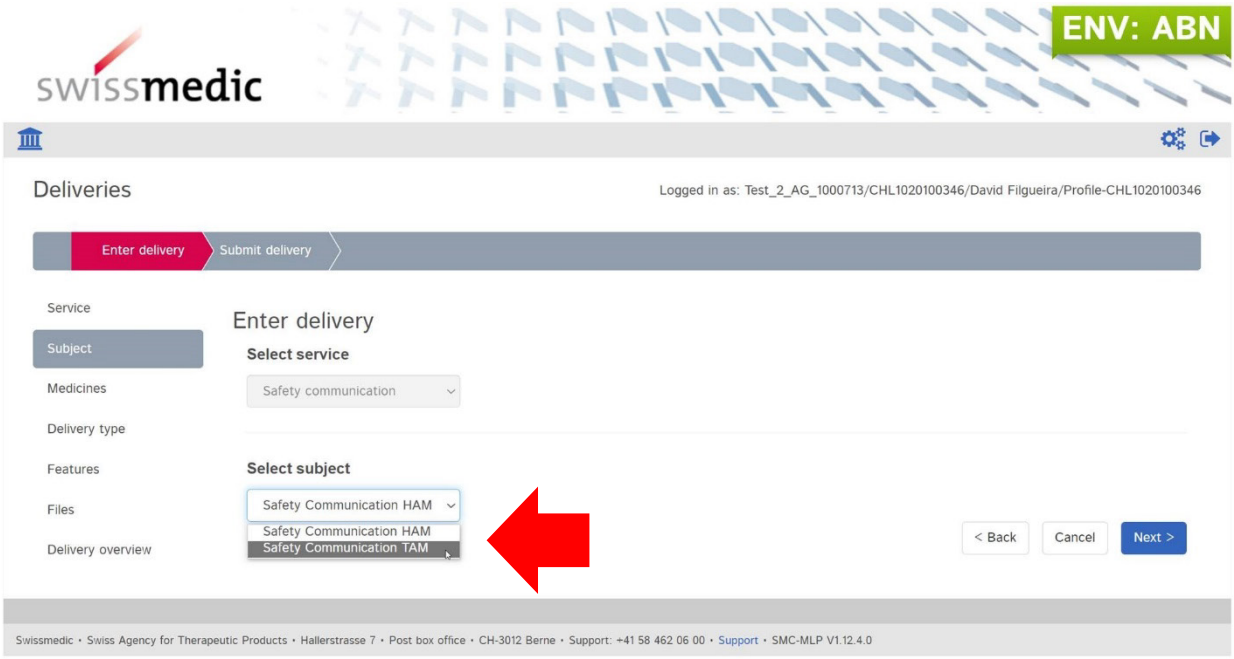
- Address: Veterinary Medicinal Products Division
- The signal reports can be submitted by post or via the Swissmedic Portal (see section 10.1).
- Form ZL404_00_002e_FO_Signal_Notification_Form_VMP should be used both for initial signal reports and for follow-up reports on signals *without Swissmedic Signal ID*. 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/SA ID that is known to you, please do not use the notification form. A covering note should be attached stating the Signal/SA ID in the subject line as follows:
  Subject: Signal ID_Active substance _adverse reaction (*VedDRA* term)
  Example: SA123456789_Penicillin_Anaphylaxis

10.1 Submission via Safety Portal

The form “Signal Notification VMP” should be submitted via the Safety Portal. Please note that separate **specific registration is required for this portal**.
The following points must be noted:

- Please submit the signal documentation under “safety communication”. For signals concerning veterinary medicinal products (subject of this Guidance document), the subject selected must be “Safety communication TAM”, as shown in the screenshot below.



- 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 that decision.

Once an official decision has been issued, the text modifications should be submitted to Swissmedic within 30 calendar days as a **variation without assessment C4**. The legal framework is provided by Art. 21 TPO. The updated product information texts must be published promptly, but at the latest by 80 days after the official decision on the signal.

Important: It is not possible to submit the variation without assessment C.4 as part of a multiple application owing to the differing deadlines. The variation without assessment C.4 must be submitted as a separate application after an official decision on the signal has been issued.

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 VMP, Swissmedic will review these and, if the wording is acceptable, issue its official approval directly. In case of corrections of the wording is needed, Swissmedic will inform the MAH by a letter.
- If medicinal product information has to be modified in the course of Swissmedic's evaluation of a signal, MAH will be sent the wording of the modified text by letter (signals with signal ID). They will then have an opportunity to comment on the measures and the wording of the modification.
  If they agree with Swissmedic's proposal in its entirety, an official decision for the measure and wording can be issued immediately. If they do not agree with Swissmedic's proposal, the company's response will be assessed again and the outcome communicated in a preliminary 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 or official decision. An official decision on the final text will be issued once the MAH has/have 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 within 30 days as a variation without assessment C.4. Whenever you submit an application, please reference the corresponding signal ID.

Change history

Version	Description	sig
1.0	First version, new layout, no content adjustments to the previous version.	hem