1 Abbreviations

ADR  Adverse Drug Reaction
CD   Calendar days
DLP  Data lock point
MAH  Marketing authorisation holder
PSUR Periodic Safety Update Report
SMP  Signal Management Process
SPC  Summary of product characteristics
TPA  Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act; SR 812.21)
TPO  Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance; SR 812.212.21)
VGVP Guideline on Veterinary Good Pharmacovigilance Practices
VICH Veterinary International Conference on Harmonisation

2 Introduction

Swissmedic uses this guidance document primarily as a resource for applying the legal provisions in a uniform and equitable manner. For applicants, the document is intended to make clear the specific requirements that must be fulfilled so that Swissmedic can process corresponding applications as quickly and efficiently as possible.
This guidance document explains the submission obligation relating to PSURs/annual reports arising from the Signal Management Process (SMP) and the form in which they are submitted to the EU pharmacovigilance database.

3 Objective

The guidance document describes the requirements pertaining to the submission of PSURs/annual reports arising from the Signal Management Process and explains the formal and regulatory aspects.

4 Scope

This guidance document applies to the submission of PSURs/annual reports arising from the Signal Management Process for veterinary medicinal products.

5 Procedure

5.1 General

According to Art. 60 TPO, marketing authorisation holders of a medicinal product with a new active substance must periodically and spontaneously submit Periodic Safety Update Report (PSUR) for this medicinal product to Swissmedic for 4 years after authorisation. The observation period covered by the report must include the date of the official decision and continue without any gaps for at least 4 years after the official decision on the authorisation application.

According to para. 1bis of the same article, for veterinary medicinal products, the update report according to paragraph 1 can be submitted in the form of an annual report with the results and conclusions on the benefit-risk balance, and include references to the relevant specialist scientific literature that are entered in the pharmacovigilance database of the European Union in connection with the signal management process (report from the Signal Management Process).

In case of variations of the authorisation after the PSUR obligation has expired, Swissmedic may – subject to a proviso (Art. 16 para. 1 TPA) – extend the 4-year period stated in Art. 60 TPO or start a new one.

The end date of the PSUR obligation is communicated to the marketing authorisation holder with the respective decision.

5.2 Content and format of the reports

A. For periodic reports according to Art. 60 para. 1 TPO (PSURs)

The format is based on point V of Guideline VICH GL29 and the annex of this guidance document.

1. Veterinary medicinal products that are authorised exclusively in Switzerland:
   a) The specific period covered by the report
   b) Sales figures for this period
   c) Incidence of reported adverse drug reactions
   d) Description of the observed adverse drug reactions (ADRs / side effects)

2. Veterinary medicinal products that are authorised both in Switzerland and abroad

The following information must be included in the report:

   a) Adverse reactions internationally: The required details are defined in Guideline VICH GL 29 and the annex of this guidance document
   In summary, the following key information is required:
b) Adverse reactions in Switzerland, sales figures and the incidence of reported ADRs in Switzerland for the period concerned.

B. For annual reports arising from the Signal Management Process according to Art. 60 para. 1bis TPO

Swissmedic basically accepts the same format required in the EU for reports arising from the Signal Management Process. Deviations can be approved at the request of the authorisation holder.

During the Signal Management Process (SMP), data have to be continuously evaluated for signals, and any confirmed signals that lead to a change in the benefit-risk profile and/or require measures are to be reported to Swissmedic.

The annual report arising from the SMP aims to provide an overview of the benefit-risk profile of a medicinal product, as well as an overview of confirmed signals, including signals for which no immediate measures were required or that did not lead to any recommendation for such measures. The marketing authorisation holder must confirm in the annual report that the SMP has been carried out continuously and that all signals requiring measures have been communicated to Swissmedic.

The latest guidelines relating to Veterinary Good Pharmacovigilance Practices (VGVP) can be found under point 2 of Annex 3 TPO (SR 812.212.21).

5.3 Time limits and periodicity

As regards periodicity, Swissmedic complies with the periods to be observed for the submission of PSUR reports as stated in Art. 60 para. 1, which are based on those stated in Guideline VICH GL 29, as follows:

- Every 6 months for the first 2 years after authorisation
- Once a year for the next 2 years

The intervals and periods for the PSUR can be submitted according to the "international birthday" (date of first authorisation abroad) of the product. The international birthday for the submission and periodicity of the PSUR report is applied at the request of the respective authorisation holder.

The reports based on the Signal Management Process are submitted once a year. The submission date can be based on the date that applies in the EU. The request must be submitted by the marketing authorisation holder.

As a rule, all reports should be submitted within 90 CD of the data lock point (DLP).

5.4 Documentation

A covering letter must accompany the submitted report. If a PSUR is submitted as part of an authorisation application (e.g. a change to the product information), this must be mentioned in the covering letter.

5.5 Enquiries

Any enquiries should be sent to vetvigilance@swissmedic.ch
6 Miscellaneous

New national or international safety signals must be reported to Swissmedic on an ad hoc basis without delay (Art. 59 TPA / Arts. 61 and 62 TPO). This obligation continues to apply after the end of the 4-year period according to Art. 60 para. 1.
7 Annex: Contents and structure of the reports according to Art. 60 para. 1 TPO (PSURs)\(^1\)

The PSUR should include information on the following types of adverse reaction reports/case histories received during the period of review:

- All adverse reactions in animals and in humans, sent spontaneously to the MAH
- All adverse reactions forwarded to the MAH by the Competent Authority.
- Reports from post-authorisation studies
- Any available information on investigation of insufficient withdrawal period, lack of expected efficacy, adverse reactions related to off-label use or any potential environmental problems, caused by the product under the normal conditions of use.
- Information about any adverse reactions in humans as a result of administering or exposure to the veterinary medicinal product

The report should be structured as follows:

1. **Marketing Authorisation Holder (MAH) and product details**

2. **SPC**
   The latest version of the relevant SPC must be included for reference in the report.

3. **Narrative review of individual case histories**

4. **Incidence of Adverse Reactions**

   4.1 **Sales volume**

   4.2 **Calculation of Incidence of adverse reactions**

   It is suggested that MAHs adopt a two-tier approach to calculation of incidence of adverse reactions.

   **Step 1**

   In the first instance, the ratio of the number of animals reacting during a period to the amount of product sold during that period should be computed:

   \[
   \frac{\text{No of animals reacting during period}}{\text{No of doses sold during period}}
   \]

   This calculation is based on data that tends to be accurate and can be used reliably to monitor trends from one PSUR to the next. Any increase in this ratio relative to previous PSURs may signal a problem and the need for more detailed evaluation of the pharmacovigilance data. Sales volume should be broken down by calendar year and the ratio of the number of animals adversely reacting to the amount of product sold should be computed for each of the years concerned by the report.

   **Step 2:**

   The incidence (%) of adverse reactions should be calculated by dividing the total number of animals reacting during the period by an estimate of the number of animals treated during the period of the report and multiplying by 100.

   \[
   \% \text{ Incidence} = \frac{(\text{No of animals reacting during period} \times 100)}{(\text{Estimated No of animals treated during the period})}
   \]

   In the first instance, it is expected that % incidence will be calculated based on the total number of animals reacting during a period derived from all A, B and O/O1 coded reports. This calculation may

\(^1\) As specified in section 6 of the earlier Guideline EMEA/CVMP/183/96-Rev. 1
then be revised to exclude O/O1 coded reports, that is, this final calculation focuses on A “probable” and “B possible” coded reports only.

The values included in the calculation of incidence must be justified. It is expected that the values used for estimation of the number of animals treated would be representative of the conditions of use of the veterinary medicinal product. When calculating the number of animals treated during a period, the following points should be taken into consideration:

- For some veterinary medicinal products, the number of doses (individual units) sold is equivalent to the number of animals treated (e.g. anthelmintic bolus, flea collars). For veterinary medicinal products formulated as pastes, aerosols, eye/ear preparations or other formulations where it is likely that each unit of product (for example, syringe, single dose pipettes) will be dispensed for the treatment of an individual animal, the number of individual units sold should be considered equivalent to the number of animals treated.

- For the majority of pharmaceutical veterinary medicinal products, the number of animals treated will be a function of:
  - **Recommended treatment regimen** (daily recommended treatment dose (mg/kg) x duration of treatment (days)), as detailed on the authorised SPC. Where a range for dose or duration of therapy is indicated on the SPC, it is appropriate to calculate incidence based on a ‘worst case’ scenario (that is, use the upper limit of the dose range and/or duration of therapy). Following from the worst case calculation, it is acceptable to propose alternative assessments of incidence based on known conditions of use of the product. Any such alternative calculations should be justified.
  - **Average weight of target population (kg)**
  - **Amount of product sold**

A proportion of veterinary medicines are indicated for more than one target animal species. Where this situation pertains, it is recognised that it is difficult to calculate individual species incidence of adverse reactions. However, it is suggested that the ratio be computed for each species based on the estimated conditions of use of the product (sales/species). This information is of importance to competent authorities although the arbitrary nature of such theoretical calculation is recognised.

A number of PSURs will show no reports of adverse reactions. In these cases it is not possible to calculate any incidence of adverse reactions.

5. Reports from other sources

6. Overall safety evaluation
The PSUR should include a concise critical analysis and opinion on the risk/benefit profile of the product written by a suitably qualified expert for pharmacovigilance. This section should include:

- information on any previous action taken by either regulatory authorities or the Marketing Authorisation Holder as a result of safety issues, and

- any new important information on the following:
  - evidence of previously unidentified toxicity
  - increased frequency of known toxicity
  - drug interactions
  - overdose and its treatment
  - adverse reactions associated with off-label use
  - adverse reactions in humans related to the use of the product.

For each of these points, lack of significant information should be reported.

7. Important information received after data lock point

8. If available: Individual case histories (PSUR line listings)