## A. Reporting of adverse reactions, incidents and quality defects, or exceptional release of OOS batches, associated with a transplant product (TpP), a gene therapy medicinal product (GT) or a medicinal product consisting of, or containing, genetically modified organisms (GMO) (Art. 59 TPA)

The recording of spontaneous reports of adverse drug reactions is designed to reliably identify safety signals – i.e. suspected important new aspects of known or new drug risks – at an early stage. The requirements pertaining to the reporting process are geared to this goal.

Article 49 of the Transplantation Act (SR 810.21) states that, in addition to the requirements of this Act, the provisions specified in Article 3 (Duty of care) and Article 59 (Mandatory reporting, reporting system and the right to report) of the Federal Act on Medicinal Products and Medical Devices (TPA) of 15 December 2000, also applies by analogy to transplant products. Accordingly, the requirements pertaining to the reporting system for TpP/GT/GMO have been approximated to those for medicinal products. Institutions and companies that manufacture or distribute TpP/GT/GMO are therefore subject to the mandatory reporting requirement anchored in the TPA (SR 812.21) for adverse reactions, incidents and quality defects. Section 3, Vigilance, of the Therapeutic Products Ordinance (SR 812.212.21, TPO) of 21 September 2018 describes the mandatory reporting requirement and timelines in detail. Article 60 paragraph 1 TPO specifies that holders of authorisation for a new medicinal product or active substance must periodically and spontaneously submit a report on its safety to Swissmedic for a period of 4 years.

Article 61 of the Therapeutic Products Ordinance (TPO) specifies the following reporting obligations:

The manufacturer or authorisation holder must report the following suspected drug risks where these are identified in Switzerland:
- serious adverse drug reactions;
- hitherto unknown adverse drug reactions;
- clusters of known or hitherto unknown adverse drug reactions, including serious misuse and serious cases of intoxication;
- quality defects;
- unusual restrictions on distribution.

According to Article 63 TPO, persons who use or dispense medicinal products on a commercial basis must report the following adverse drug reactions:
- suspected serious adverse drug reactions;
- suspected, hitherto unknown, adverse drug reactions, suspected quality defects.

When drug risks are identified abroad, the manufacturer or authorisation holder must report the following to Swissmedic:
- hitherto unknown adverse drug reactions, if measures to maintain drug safety or further investigations in respect of such measures are required;
- clusters of known or hitherto unknown adverse drug reactions, including serious misuse and cases of serious intoxication;
- quality defects, if these affect batches that have been placed on the market in Switzerland.

In relation to TpP/GT/GMO, events that have occurred in connection with the harvesting of cells/tissue, the manufacture/transport of the products or during administration of the products must also be reported. For products containing GMO, any release into the environment or transmission to another person or an animal should also be reported.



Swissmedic • Hallerstrasse 7 • 3012 Bern • www.swissmedic.ch • Phone +41 58 462 02 11 • Fax +41 58 462 02 12

According to EU GMP directives that apply specifically to advanced therapy medicinal products (ATMPs) or transplant products (Eudralex Volume 4, Part IV, Art. 11.5.), it is possible, under what is known as „exceptional release“, to release for administration to patients product batches that have produced an OOS result on one or more relevant tests. Exceptional release is contingent on prior consultation with the doctor responsible for treatment and notification of the body responsible for market release. Exceptional release of batches that have produced an OOS result must be notified to Swissmedic without delay or not later than 15 days after release.

This information should be collated and submitted to Swissmedic in the form of a summary evaluation report on the risk, together with the intended measures and investigations.

## 1. Timelines for mandatory reporting to Swissmedic

### 1.1 For the submission of ADR reports

The time limits are specified in Article 36 TPO on the basis of CIOMS I and ICH E2D.

ADR reports must be submitted as follows:
Manufacturers or authorisation holders must report adverse drug reactions identified in Switzerland as soon as they become aware of them:

As soon as possible, but no later than 15 days after receipt of the report in the event of:
- a fatal outcome;
- life-threatening ADR;
- unexpected clusters of known or unknown ADR (e.g. in respect of possible quality problems).

Within 15 days of receipt of the report in the event of:
- hospitalisation;
- persistent harm;
- medically important ADR;
- congenital anomalies.

Within 15 days after assessment, but at the latest 60 days after receipt in the event of:
- all other ADR (non-serious or new ADR)

Drugs risks identified abroad must be reported to Swissmedic within the following timelines after the manufacturer or authorisation holder has become aware of them in their international recording system:
- 5 days for drug risks that require immediate measures to maintain drug safety;
- for quality defects: without delay, but no later than 15 days after the problem is identified;
- 15 days for all other serious drug risks that are inadequately mentioned in the medicinal product information;
- 6 months for drug risks without a serious hazard potential.

According to Article 62 TPO, the following timelines apply to persons who use or dispense medicinal products on a commercial basis:
- Fatalities and life-threatening adverse drug reactions or suspected quality defects that represent a potential hazard must be reported without delay, but no later than 15 days after they come to light;
- a reporting timeline of 15 days applies to all other serious adverse drug reactions;
- all other compulsorily reportable events must be reported within 60 days. The mandatory reporting period extends from the time the authorisation application is submitted until the expiry date of the last batch to be delivered.



Swissmedic • Hallerstrasse 7 • 3012 Bern • www.swissmedic.ch • Phone +41 58 462 02 11 • Fax +41 58 462 02 12

### 1.2 For signals

The following mandatory reporting timelines apply:
- 5 days: Urgent safety risks that require immediate action to protect patient safety;
- 15 days: Serious risks involving a considerable risk to patient health;
- 6 months: Safety problems with little impact.

## 2. Classification of reports

### 2.1 Reports relating to manufacture

The manufacture of TpP/GT/GMO comprises the areas of harvesting, production, storage, testing and delivery. Incidents are:
a) Donor-related/harvesting
b) Product-related
c) Patient-related
d) Release into the environment, transmission to other persons/animals (only GT/GMO)

*a) Donor-related events/events during harvesting*
- Incidents connected with donation (blood, cells, tissue, etc.) or when preparing donation (including events connected with the administration of medicinal products given to patients in anticipation of the intended donation), that can cause temporary or lasting harm to the donor (e.g. collapse, long-term effects).

Currently, only serious donor-related side effects are subject to mandatory reporting, i.e. events that required medical treatment or hospitalisation of the donor. These are reported using the „Adverse Drug Reaction Report / Quality defect / Exceptional Release / Process TpP/GT/GMO“ form.

*b) Product-related incidents*
- Events identified during manufacture (production, storage and testing) that lead, have led, or could have led, to a deterioration in the quality/safety/efficacy of a product (e.g. contamination, interruption of cold chain, etc.).
- Serious events in the recipient that could be linked to a quality defect in the TpP/GT/GMO or its components (preservatives, media, viral vectors, etc.) or in the medical device or matrices that are components of the product.

A distinction must be made as to whether an event involves an individual error or system error (with possible infringement of GMP). Manufacturers must record product-related incidents within the framework of their QM system. This can be requested during inspections or, if required, by Swissmedic (Art. 58, Art. 59, Art. 60 TPA).

Serious incidents (e.g. contamination with a fatal outcome) must be reported within 15 days at the latest and assessed separately in each case (individual error/system error). If necessary, Swissmedic can conduct an on-the-spot inspection (for-cause inspection). If GMP regulations have been infringed, the company’s licence can be suspended (Art. 66 TPA).

*c) Patient-related incidents*
In addition to actual adverse drug reactions, under Article 35 paragraph 1 letters a to c and paragraph 4 letters a and b TPO, the following incidents must be reported for TpP/GT/GMO:
- Events in laboratories that involve errors in testing, sample handling or test results (e.g. mix-ups/transcription errors) or errors when products are delivered (e.g. delivery of perfect-quality products to the wrong person, delivery of the wrong product, delivery of a product that is not ideally suitable for patients) which occur as „near miss“ events or lead to transplantation errors (with or without consequences).



Swissmedic • Hallerstrasse 7 • 3012 Bern • www.swissmedic.ch • Phone +41 58 462 02 11 • Fax +41 58 462 02 12

*d) Incidents specifically involving GT/GMO products*
*Release into the environment, transmission to other persons/animals (only GT/GMO)*
If a GT/GMO is released into the environment or transmitted to another person or an animal, this should be reported to Swissmedic (Art. 31 and Art. 45 RO).

All reports must be submitted using the CIOMS form and/or the „Adverse Drug Reaction Report / Quality defect / Exceptional Release / Process TpP/GT/GMO“ form. Additional information should be submitted in a covering letter. All documents must be submitted as single copies, preferably by e-mail to biovigilance@swissmedic. As soon as the report is received, an acknowledgement of receipt is sent. To enable you to match up this acknowledgement of receipt with your report, please complete the subject line as follows: YYYY-MM-DD, your patient and/or case number and whether you are submitting an initial or follow-up report (e.g. 2016-07-26_PatIDxxx100020-00_inital or 2016-07-26_PatIDxxx10002000_FU1.

e) Release of „out of specification” (OOS) batches (exceptional release)
The documents must include at least the following information (see „Adverse Drug Reaction Report / Quality defect / Exceptional Release / Process TpP/GT/GMO“) form:
- Name of the TpP/GT/GMO with composition and Swissmedic authorisation number;
- Information on dosage, administration route, duration of administration; batch number, manufacturing and expiry date; manufacturing site/manufacturer (if more than one has been authorised);
- Patient's details (age, sex; diagnosis); details of centre/clinic and doctor delivering treatment;
- Description of OOS result including root cause analysis;
- Sponsor’s risk assessment;
- Proof that the responsible doctor was notified of the OOS result and doctor’s consent to providing treatment with the product batch in question.

Swissmedic reserves the right to request additional documents if necessary.

**Address to which the report should be sent:**
Preferably by e-mail to biovigilance@swissmedic.ch

or, if reporting by e-mail is not possible, to:
Swissmedic
Swiss Agency for Therapeutic Products
Inspectorates and Licences Division (IBE)
Case Manager, Transplants Unit
Hallerstrasse 7
3012 Bern
Switzerland

## B. Submission of the report on the safety of a medicinal product (Periodic Safety Update Report, PSUR, according to Art. 34 TPO)

According to Article 34 TPO, holders of authorisation for a medicinal product with a new active substance or a medicinal product must periodically and spontaneously submit a report on the safety of this medicinal product to Swissmedic for 5 years after authorisation. According to Article 17.2, the obligation to submit PSUR also applies to a new indication. This obligation can be prolonged at any time, in the form of a requirement (legal basis: Art. 16 para. 1 TPA), beyond the timelines specified

in Article 34 TPO (in which case enter a cross in the „PSUR/PBRER TpP/GT/GMO“ form when making your submission).
As a matter of principle, Swissmedic generously adapts this requirement to the international rhythm, only requiring the preparation of a periodic report specifically for Switzerland in justified exceptional cases.

Explanations:
1. The observation period covered by the PSUR/PBRER must include the date of the official decision and continue without any gaps at least up to the 5th anniversary of the official decision
2. The 5-year obligation restarts if important amendments are made (in accord. with Art. 17 TPO)
   - Determined by Swissmedic on a case-by-case basis – no automatic procedure
   - Mandatory notification of the current end date of the reporting obligation by Swissmedic in the official decision on periodic reports
   - In the event of an important amendment after the obligation has elapsed, mandatory notification by Swissmedic in the official decision on the amendment (requirement)
3. Submission
   - Once a year. Swissmedic can require a shorter period for innovative treatments
   - The period between submissions can be modified in response to a justified request. If this is incompatible with the international report period, a request can be sent to Swissmedic asking for a modification
   - No Bridging Reports
   - Submission timeline according to ICH E2C (R2):
     - *“PBRERs covering intervals of 6 or 12 months: within 70 calendar days*
     - *PBRERs covering intervals in excess of 12 months: within 90 calendar days*
     - *ad hoc PBRERs: 90 calendar days, unless otherwise specified in the ad hoc request*
     - *where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority”*
4. Format of reports
   - according to Guideline ICH E2C (R2)
   - old PSUR format is still being accepted at present

   For legislative reasons, the term „PSUR“ is retained despite the new ICH Guideline in the new EU legislation (GVP Module VII). The new format for periodic reports in accordance with ICH envisages the tabular listing of adverse reactions. This should include summary tables for the principal case categories (cases with fatal outcome, serious cases, serious unlisted cases, medically confirmed cases total). These summary tables are an important element in the assessment of a periodic report. They should therefore be submitted separately if they are not listed in the report.
5. Accompanying documents, including RMP updates and timelines
   - Completed PSUR / PBRER TpP/GT/GMO form, CCDS (if appropriate), EU SmPC, tabular comparison of the current Swiss Information for healthcare professionals with the EU SmPC sections 4.1–4.9 (if only national authorisations exist in the EU: F, D or GB)
   - new version of the RMP since the last submission: enclose with the submission together with a note in the „PSUR/PBRER TpP/GT/GMO“ form

**Queries:**
Please send written queries if possible to: biovigilance@swissmedic.ch



Swissmedic • Hallerstrasse 7 • 3012 Bern • www.swissmedic.ch • Phone +41 58 462 02 11 • Fax +41 58 462 02 12

**Address to which the report should be sent:**
Swissmedic
Swiss Agency for Therapeutic Products
Inspectorates and Licences Division (IBE)
Case Manager, Transplants Unit
Hallerstrasse 7
3012 Bern
Switzerland

Other:
New national or international safety signals must be reported to Swissmedic on an ad hoc basis without delay (see Art. 59 TPA: findings and assessments with a potential impact on the basis for assessment / Art. 35 and 36 TPO).

**Legal basis**

- Transplantation Act (SR 810.21)
- Therapeutic Products Act (TPA; SR 812.212.21)
- Therapeutic Products Ordinance (TPO; SR 812.212.21)
- Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1)
- Release Ordinance (RO; SR 814.911)
- Containment Ordinance (ContainO; SR 814.912)
- EU Regulation 1394/2007 on Advanced Therapy Medicinal Products
- Ordinance on the Fees charged by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic; SR 812.214.5)
- ICH Guideline E2D post-approval safety data management: definitions and standards for expedited reporting
- ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)
- ICH guideline E2F on development safety update report Good Case Management Practice (CIOMS V)
- Eudralex Volume 4, Part IV, GMP requirements for ATMP of 22 November 2017



Swissmedic • Hallerstrasse 7 • 3012 Bern • www.swissmedic.ch • Phone +41 58 462 02 11 • Fax +41 58 462 02 12