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Information sheet

Biovigilance (single notifications, PSURs) and quality defects relating to authorised ATMPs and other products (bacteriophages, etc.) and procedures

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1 Definitions and abbreviations

1.1 Definitions

Advanced therapy medicinal products (ATMPs)

Advanced therapy medicinal products (ATMPs) include transplant products according to the Transplantation Act (e.g. somatic cell therapy products and tissue-engineered products), gene therapy products and other nucleic acid-based products, as defined in the Therapeutic Products Act and taking into consideration the definitions in Article 5 paragraph 2 of the Gene Technology Act (GTA; SR 814.91) and Article 3 paragraph 1 letter d of the Release Ordinance (RO; SR 814.911). This also includes combinations of ATMPs with medical devices or xenogeneic cells or tissue.

ATMPs are equivalent to medicinal products and are therefore also subject to the Therapeutic Products Act (TPA).

According to Art. 3 let. b of the Release Ordinance (RO), biologically active genetic materials containing DNA and RNA are equivalent to microorganisms, but are not necessarily regarded as microorganisms. To take this legal environment into account and enable the application of a risk-based approach, the term ATMPs also refers to products with which genetic information is introduced into somatic cells, such as oligonucleotides, vectors, mRNA (including vaccines) and antisense RNA (asRNA). If ATMPs are released into the environment, the FOEN, SECB and FOPH must be notified and/or involved in accordance with Art. 81 TPO and Art. 43 RO.

This information sheet also applies to products and procedures such as autologous transplants and other therapies such as bacteriophages, blood and pathogen inactivation procedures and procedures for non-standardisable medicinal products and transplant products that do not meet the definition of an ATMP but employ similar processes.

1.2 Abbreviations

ATMPs	Advanced therapy medicinal products:
GMOs	Genetically modified organisms
GT	Gene therapy
OOS	Out of specification
PSUR/PBRER	Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report
TpP	Transplant product

2 Introduction and objective

Article 49 of the Transplantation Act states that, in addition to the requirements of this Act, the provisions specified in Article 3 (Due diligence) and Article 59 (Mandatory notification, notification system and the right to notify) of the Therapeutic Products Act (TPA) also apply by analogy to transplant products/procedures. Accordingly, the requirements pertaining to the reporting system for ATMPs have been approximated to those for medicinal products.

Institutions and companies that manufacture or distribute ATMPs are therefore subject to the mandatory notification anchored in the TPA for adverse reactions and incidents, and also for quality defects, exceptional release of out-of-specification (OOS) batches, signals and suspected illegal trading. Furthermore, this reporting requirement extends to incidents involving products, e.g. bacteriophages, procedures subject to authorisation (Art. 31–33 TPO: pathogen inactivation or elimination procedures, procedures for non-standardisable transplant products, procedures for non-standardisable medicinal products). According to Art. 34 TPO, the provisions governing the authorisation of ready-to-use medicinal products are applicable to the authorisation of such procedures or products by analogy.

Any person who professionally dispenses therapeutic products or administers them to humans or animals or who is entitled to do so as medical personnel must notify the Agency of any serious or previously unknown adverse events and reactions, observations of other serious and previously unknown circumstances or quality defects that are of significance for drug safety.

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

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. Swissmedic must be notified of exceptional releases.

Section 3 (Vigilance) of Chapter 8 (Market surveillance) of the Therapeutic Products Ordinance (TPO) describes the mandatory notification to Swissmedic and the timelines in greater detail (Articles 61–64).

Article 60 paragraph 1 TPO also specifies that holders of authorisation for a medicinal product with a new active substance must periodically and spontaneously submit a report on its safety and benefit-risk profile (Periodic Safety Update Report, PSUR) to Swissmedic for a period of 4 years.

This information sheet describes the reporting obligations of manufacturers and holders of marketing authorisation for authorised ATMPs and for individuals who use or dispense authorised ATMPs on a commercial basis and specifies conditions for timeline-compliant submissions to Swissmedic.

3 Legal basis

Switzerland

- Clinical Trials Ordinance (ClinO; SR 810.305)
- Gene Technology Act (GTA; SR 814.91)
- Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1)
- Release Ordinance (RO; SR 814.911)
- Therapeutic Products Ordinance (TPO; SR 812.212.21)
- Therapeutic Products Act (TPA; SR 812.21)
- Transplantation Act (SR 810.21)
- Transplantation Ordinance (SR 810.211)

International

- EU Regulation 1394/2007 on Advanced Therapy Medicinal Products
- Eudralex Volume 4, Part IV, GMP requirements for ATMP of 22 November 2017
- ICH Guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)
- ICH Guideline E2D post-approval safety data management: definitions and standards for expedited reporting
- ICH Guideline E2F on development safety update report Good Case Management Practice (CIOMS V)

4 Reporting to Swissmedic

4.1 Adverse drug reactions

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.

Article 61 TPO specifies the following reporting obligations for a manufacturer or authorisation holder:

- Serious adverse reactions and hitherto unknown reactions that are suspected to be related to a medicinal product and that are identified in Switzerland.
- Clusters of the aforementioned adverse drug reactions should also be reported.
- Adverse reactions that are suspected to be related to a medicinal product and that are identified in Switzerland or abroad, if
  - these involve hitherto unknown risks or new aspects of known risks that require further clarification in respect of risk-reducing measures, that require risk-reducing measures or that have led to risk-reducing measures abroad, or
  - such adverse drug reactions are observed in clusters.

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;
- Observations of serious or hitherto unknown circumstances that jeopardise drug safety.

Notification timelines

The time limits are specified in Article 62 TPO on the basis of CIOMS I and ICH E2D.
The manufacturer or marketing authorisation holder should report the following adverse drug reactions after they come to light within

- 15 days: serious adverse drug reactions and clusters of known or hitherto unknown adverse drug reactions.
- 60 days: hitherto unknown, non-serious adverse drug reactions.

According to Article 63 TPO, the following timelines apply to persons who use or dispense medicinal products on a commercial basis:

- Serious adverse drug reactions or observations of serious circumstances must be reported within 15 days.
- All other events must be reported within 60 days.

Notification route

Reports should be submitted as follows:

- For all products and procedures (excluding blood and pathogen inactivation procedures):
  - via the ElViS portal or a Gateway connection.

  Registration is required for both options. Follow the links below for more information:
  Vigilance System (swissmedic.ch)
  ElViS – Electronic Vigilance System (swissmedic.ch)
  Reporting/submitting suspected adverse drug reactions by pharmaceutical companies (swissmedic.ch)

- For blood and pathogen inactivation procedures:
  - Haemovigilance (www.swissmedic.ch/haemovigilance)

4.1.1 Donor-related incidents/incidents during harvesting for manufacture

Incidents may occur during donation (blood, cells, tissue, etc.) or when preparing donations 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 notification, i.e. events that required medical treatment or hospitalisation of the donor.

These should be reported as described in section 4.1. Adverse drug reactions

4.1.2 Patient-related incidents during manufacture

In addition to actual adverse drug reactions according to Article 61 paragraph 1, paragraph 2 and paragraph 4 letters a and b TPO, the following incidents must also be reported for ATMPs:

- 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).

These should be reported as described in section 4.1. Adverse drug reactions

4.2 Quality defects

Article 61 TPO specifies the following reporting obligations for a manufacturer or authorisation holder:

- Quality defects identified in Switzerland.
- Quality defects identified abroad and involving batches that have been placed on the market in Switzerland.

According to Article 63 TPO, persons who use or dispense medicinal products on a commercial basis must report suspected quality defects:

Notification timelines

In accordance with Article 61 paragraph 6, quality defects identified by the manufacturer or marketing authorisation holder in Switzerland or another country must be reported without delay, but at the latest 15 days after they come to light (Article 62 paragraph 3 TPO).

Persons who use or dispense medicinal products on a commercial basis must report suspected quality defects without delay, but at the latest 15 days after becoming aware of them (Article 63 TPO).

Notification route

Reports must be submitted via the Swissmedic Market Monitoring of Medicines Division (see Information sheet MU102_10_001e_MB Notification of quality defects) using either form MU102_10_001e_MB Notification of quality defects or the online form.

These forms and the information sheet can be downloaded using the following link: Reporting quality defects (swissmedic.ch)

On the form, it must be stated under point 3.2 “Details of defect or problem” whether this is the initial or a follow-up report, and the patient number must be stated where available.

If the report involves a Class I defect, the contact point must be informed in advance by telephone (see section 7 of the above information sheet for contact details) to ensure that the report is processed within the short timeline available for serious quality defects of this type.

4.2.1 Product-related incidents during manufacture

Product-related incidents include:

- Events identified during manufacture (production, storage, transport 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 ATMP as well as to the other products and procedures, their components (preservatives, media, viral vectors, etc.) or to 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 to Swissmedic within 15 days at the latest and assessed separately in each case (individual error/system error).

They should be reported as described in section 4.2 Quality defects.

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).

4.3 Exceptional release – release of OOS batches

Information on the exceptional release of an out-of-specification (OOS) batch 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.

The documents should include at least the following information:

- Name of the ATMP 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;
- Marketing authorisation holder'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.

Notification timelines

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.

Notification route

As described in section 4.2 Quality defects.

4.4 Incidents specifically involving GT/GMO products – Release into the environment, transmission to other persons/animals (only GT/GMOs)

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).

Notification timelines

The release or transmission of GT/GMOs must be reported to Swissmedic without delay, but at the latest within 5 days.

Notification route

Incidents should be reported as described in section 4.1. Adverse drug reactions.

Additionally, incidents should be reported to biovigilance@swissmedic.ch using form "BW314_00_991e_FO Form Notification release/transmission of authorized GT/GMO".

4.5 Signals

Safety signals and signals relating to efficacy (national and international) which affect the benefit-risk assessment of an ATMP 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). Further information can be found in the Guidance document "MU101_20_001e_WL Guidance document Drug safety signals HMP".

Notification timelines

Safety signals should be reported after they are identified:

- Without delay, but at the latest within 5 days if the safety signals require prompt measures to maintain drug safety
- Within 15 days for other safety signals with a serious hazard potential

Notification route

Reports should be submitted using form "MU101_10_025e_FO Signal Notification Form", via portal ("Safety communication") or by post (CD) to Swissmedic, Operational Support Services, Hallerstrasse 7, CH-3012 Bern, (see "Guidance document Drug safety signals HMP" above).

4.6 Suspected illegal trading

Article 62a TPO requires anyone who manufactures or places on the market medicinal products to report any suspicion of illegal trading in medicinal products connected with their activities, one of their products or its constituents.

More information can be found in the Information sheet "MU104_20_001e_MB Mandatory notification regarding suspected illegal trading in medicinal products".

Notification timelines

Any suspicion according to Article 62a TPO should be reported without delay, but at the latest within 5 days.

Notification route

Reports must be submitted via Market Surveillance/Illegal drug imports/Report regarding suspected illegal trading in medicinal products using the online form (see Information sheet "Mandatory notification regarding suspected illegal trading in medicinal products" above).

4.7 PSURs according to Art. 60 TPO

According to Article 60 TPO, holders of authorisation for a medicinal product with a new active substance must periodically and spontaneously submit a report on the safety of this medicinal product to Swissmedic for 4 years after authorisation. 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 60 TPO.

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. Observation period:
   - 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 4th anniversary of the official decision.

2. The 4-year obligation restarts if important amendments are made:
   - 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.
4. Format of reports:
   - According to Guideline ICH E2C (R2)
   - 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:
   - Completed form "MU103_10_002e_FO Form PSUR/PBRER for human medicines",
   - CCDS (Company Core Data Sheet) (if appropriate), EU SmPC (EU Summary of Product Characteristics),
   - Tabular comparison of the current Swiss Information for healthcare professionals with the EU SmPC sections 4.1–4.9 (only if national authorisations exist in the EU: F, D or GB);
   - RMP update if applicable (see guidance document below. This applies mutatis mutandis to ATMPs).

Notification timelines

- PSURs: As in guidance document "MU103_10_002e_WL Guidance document Information of PSUR PBRER submission HMP"
- RMP updates: As in guidance document "MU103_10_001e_WL Guidance document RMP ICH E2E information submission HMP".

Notification route

PSURs/RMPs must be submitted via Swissmedic Submissions/Portal (see Submissions (swissmedic.ch)).

Queries

Please send preferably written queries to: biovigilance@swissmedic.ch

Change history

Version	Description	sig
4.0	Content updated, new reporting routes	pad
3.0	ATMP processes transferred to the Licensing Sector New ident number assigned Formal amendments, new layout	dei