

Inspection of the Pharmacovigilance-System in GMP/GDP Inspections

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1. Purpose and scope

In order to harmonize the assessment of pharmacovigilance systems during a Routine GMP/GDP inspection, this document provides general guidance for the evaluation of such a system. It does not describe in depth GVP inspections, which are carried out by the GCP/GVP inspectorate of the Clinical Trials Division (KLV) of Swissmedic. Therefore the focus regarding pharmacovigilance in a GMP/GDP inspection lies on the system rather than on the evaluation of single cases and it covers mainly aspects that can be addressed and referenced under current GMP/GDP guidelines and the Therapeutic Products Act.

2. Basis

- Therapeutic Products Act (TPA; SR 812.21)
- Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1)
- Ordinance on Medicinal Products (OMP; SR 812.212.21)
- Clinical Trials Ordinance (ClinO; SR 810.305)
- PIC/S Guide to Good Manufacturing Practice For Medicinal Products (PE 009, part I)
- EudraLex, Volume 4, part 1

3. Definitions and abbreviations

The definition of terms in the TPA, in the MPLO and in the detailed guidelines, which are listed in the Annexes of the MPLO (throughout this document jointly referred to as Good Practices, GMP/GDP) are applicable to this document. In addition, the following definitions apply:

ADR	Adverse Drug Reaction
ClinO	Clinical Trials Ordinance (SR 810.305)
CRO	Clinical research organisation
DSUR	Development Safety Update Report
FVP	Responsible Person (according to MPLO)
GVP	Good Vigilance Practice
HQ	Headquarter
MAH	Marketing authorisation holder
MPLO	Medicinal Products Licensing Ordinance (SR 812.212.1)
OMP	Ordinance on Medicinal Product (SR 812.212.21)
PBRER	Periodic Benefit Risk Evaluation Report (replaces PSUR in the EU)
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems (WHO)
PSMF	Pharmacovigilance Systems Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
RPV	Responsible Person for Pharmacovigilance
TPA	Therapeutic Products Act (SR 812.21)

4. Responsibility

This document is binding for inspectorates acting under Art. 60 TPA.

5. Description

5.1 General considerations

The TPA states that the agency (Swissmedic) shall be responsible for monitoring the safety of therapeutic products and that to this effect, it shall in particular collect the notifications referred to in Art. 59, evaluate them and take the necessary administrative measures.

According to TPA it is a legal requirement that any person manufacturing or distributing ready-to-use therapeutic products must put in place a system of notification and has therefore to establish and operate a Pharmacovigilance system. This system must ensure that Swissmedic is notified of any adverse event or reaction that may endanger or damage the health of consumers, patients or treated animals and that appropriate measures are taken in the event that a Pharmacovigilance signal is reported.

In addition, the MAH must assure that he has an appropriately qualified person responsible for pharmacovigilance (RPV) at his disposal (MPLO) and that a system for collection, collation and evaluation and submission of all relevant safety information to Swissmedic is established (TPA).

The OMP specifies in detail the type of events to be reported and relating deadlines. The reporting period and the reporting system are also addressed in the OMP.

In order to link pharmacovigilance aspects with GMP requirements the following references can be considered:

- PIC/S 009, chapter 1.8: "GMP is that part of Quality Management, which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization, Clinical Trial Authorisation or product specification".
- EudraLex Vol. 4, principle: "The holder of a MA must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization or Clinical Trial Authorization, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy".

5.2 Frequency

As the pharmacovigilance aspects to be inspected in the scope of this Guideline are addressed in routine GMP/GDP inspections, the intervals listed in I-SMI.RL.01 "Conduct of inspections of establishments manufacturing or distributing medicinal products or collecting blood" are applicable.

5.3 Inspection

When inspecting pharmacovigilance aspects in routine GMP/GDP inspections, the focus should lie on two topics:

- Verification of the nomination of an appropriately qualified RPV
- Verification whether the manufacturer/marketing authorization holder (or research organization) has a PV-system in place, which is designed and operated fulfilling the legal requirements in order to meet their pharmacovigilance obligations.

The same legal basis applies to all companies, but GVP procedures may vary between companies.

MAHs and their subcontractors/co-marketing organizations may perform pharmacovigilance and safety evaluation activities in more than one country. It is important to ascertain (by obtaining descriptions, organizational charts, contracts/agreements and SOPs) how pharmacovigilance responsibilities are divided within the company and between marketing partners/contractors. This must be taken into account when assessing procedures.

5.3.1 Organisation

Organisation chart(s) providing an overview of the global and Swiss PV units, illustrating the relationship between them, with affiliate/parent companies, licensing partners and contractors should be available. The chart(s) should show the reporting relationships with management and clearly show the position of the Swiss RPV and other key PV personnel within the organisation.

Links with other departments involved in PV activities should be indicated; e.g. regulatory affairs, medical information, sales and marketing, complaint handling, quality assurance (internal audits) and with IT supporting PV database(s).

5.3.2 Responsible person for PV

The following aspects regarding the RPV may be addressed and verified in GMP/GDP Inspections:

- Name, address, contact details of the RPV (also for out of hour contacts)
- Experience (curriculum vitae) of the RPV
- Arrangements regarding the deputy of the RPV
- Job descriptions (including responsibilities) of the RPV and the deputy
- Qualification of the RPV in correlation with the organizational structure of the company
 - if the collected safety data are evaluated by a medically qualified person (physician) somewhere else in the company (e.g. at the headquarter abroad), the RPV does not need to be medically qualified. A sound knowledge of regulatory requirements is sufficient
 - if the safety evaluation is done on site, the RPV either has to be medically qualified (physician) or has to report to a medically qualified person. This person can be either “in house” or an external consultant. In the last case, contractual details must be available

5.3.3 Procedures/Pharmacovigilance system

The company should be able to provide a list of the written policies and procedures (SOPs), which describe the pharmacovigilance system and regulate the related activities. These documents should describe in detail processes, workflows, timelines as well as responsibilities and should address the following aspects:

- Generation and maintenance of risk management plans
- Reception of reports and signals
- Ways of signal detection, e.g. by periodic monitoring of the worldwide scientific literature
- Performance of a causality assessment
- Preparation/assessment of domestic ADR reports
- Assessment of ADR reports from abroad
- Assessment of reports from clinical studies (DSURs)
- Reporting of single cases (ad hoc reporting of relevant safety signals)
- Compilation of Periodic Safety Update Reports/Periodic Benefit Risk Evaluation reports (PBRERs)
- Reporting period (until the expiry of the last distributed batch)

- Notification of Swissmedic and related timelines
- Link between complaint handling procedures and the pharmacovigilance system
- Measures to avoid duplicate reporting
- Management of urgent safety restrictions
- Integration of pharmacovigilance aspects in the internal audit programs
- Archiving

5.3.4 Data management

- Data must be collected, collated and evaluated in a comprehensive way that allows a systematic evaluation within a reasonable timeframe
- For very small companies that receive only a very limited number of reports per year, a simple system can be sufficient, provided the original reports are retrievable within a reasonable time, data are protected from alteration and there is an “audit trail”
- A short description of the database (or databases) used for PV activities should be available. This applies to commercial as well as in-house developments. A validation status statement should be available
- Whatever system is in use, it should allow data access out of hours
- If data are collected at HQ outside Switzerland, the company is required to document how and within which timelines database extracts (incl. single case reports) can be retrieved and forwarded on request to the Swiss regulatory authority
- An audit trail for single case reports should be implemented

5.3.5 Contractual agreements

If PV activities are outsourced either to another company or CRO or to private consultants, contractual documentation must be provided (including reporting responsibilities and arrangements for literature searches). This applies also for co-marketing agreements.

In case the RPV is an external person, it should be verified that appropriate data access is guaranteed and the availability of the RPV for fulfilling his/her duties is assured.

5.3.6 Training

The personnel involved in pharmacovigilance should be trained adequately to perform PV activities. This applies particularly to all persons in direct contact with customers or patients, e.g. sales representatives and persons doing complaint handling. Depending on the function of a person, the training should include:

- Company internal SOPs
- Company global SOPs and guidelines
- National Swiss requirements according to legal requirements
- Information and notification forms of Swissmedic

A description of the training system and training records should be available.

5.4 Inspection report

The inspection report (as a part of the GMP/GDP-report) is issued and deficiencies are referenced and classified according I-SMI.RL.01 “Conduct of inspections of establishments manufacturing or distributing medicinal products or collecting blood”. It is possible to create a new chapter in the inspection report in order to summarize the results regarding the pharmacovigilance aspects of the inspection.

5.5 Corrective measures

After having received the corrective action plan and if needed, the inspector might check with the GCP/GVP inspectorate of the Clinical Trials Division of Swissmedic for the final assessment.

6. Changes to the previous version

- Whole document: Simplification and update of the reference to laws and guidelines.