Description, harmonisation and steering of the Swiss GMP/GDP inspection system for medicinal products

Document valid from:	**19.07.2023**	
Document number:	**I-SMI.RL.02e**	**Version 4.0**
Classification:	**Public**	
Replaced document:	**I-SMI.RL.02_03**	dated: 19.02.2020
Root SMI documents:	**--**	
Referenced QMI documents:	**I-SMI.RL.01**	

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Index

1. Purpose and scope

The purpose of this document is to set a frame for the harmonization and steering of the Swiss GMP/GDP inspection system by:

- Describing the Swiss GMP/GDP inspection system for medicinal products according to the TPA and
- Defining and regulating the relevant interfaces between the Swissmedic sector Licensing, the Inspectorates of Cantons (IoC) and the Swissmedic Inspectorate (IoS).

Inspections carried out in context with the Narcotics Act (NarcA; SR 812.121) are not covered by this guideline.

2. Basics

The release of this directive follows article 63 MPLO. This directive is based on the federal legislation, especially articles 10, 34, 58, 60-63 and 64a TPA, articles 56-64 MPLO, article 23 TPLRO, article 59 TPO as well as on the relevant cantonal legislations. The PIC/S (Pharmaceutical Inspection Cooperation Scheme) document PI 002 (Recommendation on Quality System Requirements for Pharmaceutical Inspectorates) has been taken into account.

3. Definitions and abbreviations

CAPA plan	Company's response to inspection report listing the corrective and preventive actions (CAPA) or measures that will be taken to rectify and prevent the deficiencies mentioned in the report and which in each case specifies a deadline by which the measure will be implemented or whether the deficiency has already been corrected
FeeO-Swissmedic	Ordinance on Fees Levied by the Swiss Agency for Therapeutic Products (SR 812.214.5)
IBE	Swissmedic division "Inspectorates and Licences"
Inspectorate's proposal	Based on the inspection and on the company's corrective and preventive actions plan (CAPA plan) resulting from the inspection, the Inspectorate, who performs an inspection, completes a form (I-SMI.LL.05-A01) for Swissmedic. The proposal states whether the establishment licence should be issued, renewed, changed, suspended or withdrawn
IoC	Inspectorate of Cantons (regional Inspectorate): Accredited regional Inspectorate performing GMP/GDP inspections for one or more cantons according to article 60 TPA
IoS	Inspectorate of Swissmedic. It is constituted by inspectors from the Swissmedic division "Inspectorates and Licences" (IBE) who perform inspections based on article 60 TPA. The execution of these inspections is accredited according to ISO 17020
MPLO	Medicinal Product Licensing Ordinance (SR 812.212.1)
SMI	Swiss Medicines Inspectorate
Swissmedic sector „Licensing"	The Swissmedic Sector Licensing is an organisational unit that embraces among others the divisions Inspectorates and Licences, Narcotics and the Laboratories (OMCL)
TPA	Therapeutic Products Act (SR 812.21)

TPLRO	Therapeutic Products Licensing Requirements Ordinance (SR 812.212.22)
TPO	Therapeutic Products Ordinance (SR 812.212.21)

4. Responsibility

This document is binding for Inspectorates acting under article 60 TPA.

5. Description

5.1 Inspectorates

According to article 60 TPA, Swissmedic is responsible for the Swiss inspection system (see the reservation in art. 60 para. 1 TPA). The organization of the Swiss inspection system, called "Swiss GMP/GDP Inspection System" is summarized in the attached scheme (annex 5). It consists of the Inspectorate of Swissmedic (IoS), as well as of the 4 Inspectorates of Cantons (IoC). All these 5 Inspectorates are individually accredited according to ISO/IEC 17020 as Inspection body (Type A) for manufacturers and distributors of medicinal products according to GMP and GDP directives which are in the possession of an establishment licence. The IoCs are subordinate to their cantonal governments in administrative matters. Swissmedic is responsible for defining technical requirements and, where necessary, for specifying and/or supplementing them. The Inspectorates are obliged to implement these technical requirements. The IoC and IoS are responsible to fulfil their inspection duties in compliance with the SMI-documents.

According to the exchange of diplomatic notes from 11 December 2001 (SR 0.812.101.951.4) between Switzerland and Liechtenstein, the authorities of Liechtenstein are responsible for inspections within the principality. The Inspectorates must be recognised by Swissmedic. Liechtenstein has delegated the inspection of pharmaceutical companies to the Regional Medicines Inspectorate of Eastern and Central Switzerland and inspections of biologicals and transplants to Swissmedic.

5.1.1 Recognition of the Inspectorates

Article 60 paragraph 3 TPA states that the Inspectorates of the cantons are to be entrusted with inspections pursuant to Articles 6, 19 and 28 of the TPA in areas not covered by article 60 paragraph 2 of the TPA. However, inspections are only entrusted to the regional Inspectorates designated by the cantons if these Inspectorates meet the requirements of national and international law applicable to Switzerland (art. 60 para. 3 TPA). These requirements are laid down in particular in articles 56 and 57 MPLO, according to which such Inspectorates must have a quality management system in accordance with internationally recognised standards and must be accredited.

Swissmedic has checked and monitors whether the Inspectorates designated by the cantons meet the requirements. Swissmedic has recognised the cantonal Inspectorates. A detailed description of the Inspectorates can be found in annex 3.

If an Inspectorate is not in a position to fulfil its inspection duties in compliance with the SMI-documents, it must inform Swissmedic without delay and indicate appropriate corrective measures to ensure continued compliance with the SMI-documents. The recognition of the Inspectorate by Swissmedic according to the provisions laid down in the TPA and the MPLO may be denied if the legal provisions are not fulfilled and the situation poses a significant risk for the Swiss GMP/GDP inspection system.

5.1.2 Designation of the inspectors

The recognition of an Inspectorate by Swissmedic pursuant to article 58 paragraph 2 MPLO also includes an examination whether the persons working in the Inspectorate meet the legal requirements. It is the responsibility of the head of the Inspectorate to determine the point in time from which the person may carry out inspections independently after completion of the training and qualification as an inspector. The head of the IoC reports personnel changes to Swissmedic. On the basis of article 58 paragraph 2 MPLO, the director of Swissmedic designates these notified persons as inspector and formally assigns them the corresponding statutory powers. If necessary, inspectors can identify themselves.

The director of Swissmedic also designates Swissmedic employees who fulfil the requirements for the function of inspector.

5.2 The competent authority issuing establishment licences and GMP/GDP certificates

Swissmedic is the competent Swiss authority for the issue or withdrawal of establishment licences and GMP/GDP certificates.

5.3 Competencies of Inspectorates

Competencies of Inspectorates are defined in article 60 of the TPA (see annex 2). Each Inspectorate or a canton may ask an Inspectorate to assist in or to take over an inspection within its competence, provided its accreditation embraces the inspection activities in question (art. 60, para. 5 TPA). Details on competences in the field of inspections are described in annexes 2 and 3.

5.4 Inspectorates' Coordinating Committee (ICC)

In order to fulfil the mandate given by article 68 paragraph 5 TPA and to effectively organize the inspections subject to article 60 TPA, Swissmedic has established the ICC. The ICC serves to harmonize inspection carried out by the IoCs and IoS by providing training and guidance on technical aspects. International standards are duly taken in account. The ICC rules are described in annex 4.

The Inspectorates Coordinating Committee (ICC) consists of:

- **Heads of Regional Inspectorates of**
  - Inspectorat de Suisse Occidentale des Produits Thérapeutiques (ISOPTh)
  - Ispettorato regionale dei medicamenti della Svizzera del Sud (IRM-S)
  - Regionale Fachstelle der Ost- und Zentralschweiz (RFS-OZ)
  - Regionales Heilmittelinspektorat der Nordwestschweiz (RHI NW)

- **Representative of Cantonal Pharmacists**
  - A cantonal pharmacist representing the association of the cantonal pharmacists

- **Swissmedic representatives**
  - Head of Division Inspectorates and Licences (ICC Chairperson)
  - Head of Section Inspectorates
  - Head of Section Certificates and Licences
  - Secretary (Inspector)

5.5 Inspectorate's documents

Article 63 MPLO states that Swissmedic ensures that the inspection procedures are uniform and that Swissmedic issues corresponding Directives after consultation with the Inspectorates designated by the Cantons. The Directives and their appendices together with Guidelines and Technical Interpretations constitute administrative regulations and are hereinafter referred to as "SMI-documents".

SMI-documents are systemized as follows:

- Directives in accordance with article 63 MPLO: basic terms of reference
- Guidelines: specific terms of reference
- Technical interpretations: instructions for inspectors for the interpretation of technical requirements (GMP/GDP)

Any Inspectorate may draft an SMI-document. The drafts are circulated for consultation to all ICC members and discussed within the ICC. The Swissmedic Director approves directives, the Chairperson of ICC approves guidelines and technical interpretations. The individual Inspectorates must incorporate the approved SMI documents in their quality management systems.

5.6 Technical working groups

Ad hoc groups, reporting to the ICC, may be formed in order to answer a specific question. One possible output of such groups may be a Technical Interpretation (see chap. 5.5).

5.7 Inspection process

The conduct of inspection is described in details in I-SMI.RL.01.

5.7.1 Inspection triggers

A trigger for the inspection process is a piece of information, an event or a request that leads (or may lead) to the conclusion that an inspection is the best and an adequate way to respond to that trigger. The Inspectorates forward a trigger that concerns a company outside their competence to the competent Inspectorate (see annex 2).
As a rule, Swissmedic issues a corresponding inspection order for inspections that are not triggered routinely.

Triggers coming from the inspection process:
- The annual inspection plans of the Inspectorates based on the inspection frequency as defined in document I-SMI.RL.01. This trigger leads to a general GMP/GDP inspection [1]
- An inspection outcome that requires an additional inspection. This trigger leads to a re-inspection [1]

Triggers coming from the establishment licence process:
- An application for a new establishment licence. This trigger leads to an initial general GMP/GDP inspection [1]
- An application for the extension or modification of the establishment licence, e.g. a new site or additional activity. This trigger leads to a general GMP/GDP inspection [1] (or to a partial inspection focusing on the GMP/GDP compliance of the new site or activity)

[1] The terminology strictly corresponds to the one in document I-SMI.RL.01

- Notification of major changes to facilities, equipment or procedures (art. 41 para. 2 MPLO). This notification may lead to a general GMP/GDP inspection[1] (or to a partial inspection focusing on the GMP/GDP compliance of the notified major change)[1].

Triggers coming from the registration process:
- A new manufacturing process submitted with a registration application. This trigger may lead to a product- or process-related inspection [1] before approval of the marketing authorisation
- The adherence to the manufacturing process submitted with a registration application needs to be assessed, especially with new and/or innovative products. This trigger may lead to a product- or process-related inspection [1]

Examples of other triggers, usually leading to a product- or process-related inspection:
- A request for an inspection by a company to inspect the requesting company itself (technical meeting). There is no obligation to meet such a request; it is within the Inspectorate's discretion to proceed to an inspection
- A request for an inspection by a foreign authority. There is no obligation to meet such a request; Swissmedic decides based on the necessity whether to proceed to an inspection taking into consideration international agreements on cooperation with partner authorities
- Information on quality defects
- Rapid Alerts
- Information gathered though an inspection in a third company
- Denunciations of non-compliance

5.7.2 Inspectorate's proposal

The inspector issues an Inspectorate's proposal to Swissmedic (see definitions and abbreviations). No copy is sent to the inspected company. Should Swissmedic disagree with a proposal, the case will be treated as follows:

- The case will be discussed between Swissmedic and the competent Inspectorate (IoC)
- If no agreement is reached, the ICC may be consulted as a mediator in finding a consensus
- Swissmedic is entitled to take a final decision in any case, taking the result of the ICC mediation in consideration. Swissmedic will communicate that decision in an appropriate manner.

Invoicing inspections:
All inspections are invoiced according to internal rules of each Inspectorate.

5.7.3 Coordination of inspections between Inspectorates

As described in chapter 5.3. Inspectorates may delegate inspections to each other. If inspections are delegated or a co-inspection is performed, the involved Inspectorates agree in advance on the Quality Managements System (incl. reporting to cantonal authorities, invoicing, etc.) to be applied.

5.8 Types of inspections

The types of inspections (Chap. 5.8.1-5.8.3) are described in detail in document I-SMI.RL.01. The ones quoted in chapter 5.8.7 and 5.8.8 serve training purposes and the harmonization of the Swiss inspection system, respectively.

5.8.1 General GMP/GDP inspections (basic, routine or first inspections)

These serve to assess the GMP/GDP conformity of companies.

5.8.2 Re-inspections

Re-inspections (follow up inspections) serve to check the implementation of corrective and preventive actions.

5.8.3 Product-, process-related or problem oriented inspections

These serve to address specific questions. So called “for cause” inspections, “pre”- and “post-approval” inspections fall in this category, too.

5.8.4 Technical meeting

A technical meeting takes place at the request of the company. This request will be taken into account within the framework of the available capacities, if concrete plans are available. This means that the project to be assessed, e.g. a new building or a new plant, must have passed the design qualification phase (according to annex 15 of the GMP Guidelines) or be about to be completed. Care should be taken that no consultation is given.

5.8.5 Inspections abroad

These inspections may be product-, process-, or problem-related, or general (routine). In a purely Swiss inspection according to article 60 paragraph 2 MPLO, the inspection team is led by an IoS inspector and may consist of IoS and/or IoC inspectors. Swiss inspectors of the IoS or IoC may participate in inspections of partner authorities or international organisations, e.g. WHO or EDQM.

5.8.6 Escort of foreign inspections

In accordance with article 64a of TPA, inspections carried out in Switzerland by foreign inspectors may be fully or partially accompanied by a representative of an Inspectorate (either IoS or the IoC) in whose area of competence the inspection takes place. These inspections have to be notified in advance to Swissmedic by the foreign authorities according to a written procedure.

5.8.7 Training inspections

Any type of inspection which is observed by a trainee or wherein a trainee actively participates contributes to the initial or continuous training of inspectors.

5.8.8 Accompaniment of inspections

As a measure to improve harmonisation and to ensure uniform approaches in inspections carried out by an IoC or by IoS, an inspector may accompany an inspection carried out by another Inspectorate. It should be clarified in advance between the Inspectorates / inspectors whether the accompanying inspector will either participate actively in the inspection or only as an observer.

5.9 Exchange of information between Swissmedic and Inspectorate of cantons (IoC)

5.9.1 Annual reports on inspections

By the start of the year, the IoC/IoS provide Swissmedic with a report on their inspection activities of the previous year. It includes a standardized table listing the number of inspections carried out during the reporting year as well the number of overdue inspections (backlog). Swissmedic compiles a survey of all the inspection activities for an annual publication.

5.9.2 Copies of establishment licences

When issued, Swissmedic sends copies of the establishment licence (EL) to the relevant IoC(s) and cantonal pharmacist(s), and if applicable to the cantonal veterinary(ies).

5.9.3 Updated list of relevant documents for inspections

Documents of the Inspectorate (see chap. 5.5) are managed by the administrator of the quality management system Inspectorate (VS-QMI) of Swissmedic. The administrator (VS-QMI) forwards to the concerned Inspectorates the current version of the documents. Most of the documents for inspections are also available on the Swissmedic Website for information.

5.9.4 Access to product information

Based on article 61-63 TPA the IoC have access to product information (e.g. extracts from the marketing authorisation file) by sending requests to Swissmedic.

5.10 Training

Swissmedic organizes at least one training seminar yearly. This seminar of generally two to three days, is open to all inspectors of the IoS and the IoC, all cantonal pharmacists as well to some other Swissmedic collaborators such as Quality Reviewers and also to inspectors from foreign authorities.

With the exception of costs for travel, hotel and administration, the participation to these seminars is free of charge for IoC-inspectors and Swissmedic employees. Swissmedic may refrain from charging fees from inspectors from foreign authorities. Further training events may additionally be organised by Swissmedic or by Inspectorates of the cantons.

5.11 Complaints against inspection activities relevant for all Inspectorates

5.11.1 Inspection process related complaints

Each Inspectorate deals with inspection process related complaints according to its internal quality management system. If an inspection process related complaint is also relevant for the other Swiss GMP/GDP Inspectorates (i.e. complaints related to the document I-SMI.RL.01, e.g. inspection frequency) the complaint should be presented in the ICC.

5.11.2 Complaints about the interpretation of legal requirements

The involved Inspectorate will resolve the contentious point related to interpretation of legal requirements with the company and take the appropriate measures to enforce its compliance in the frame of the ongoing inspection process. All queries to Swissmedic from the involved company related to this specific interpretation issue are forwarded to the involved Inspectorate for

proceeding: Swissmedic does not interfere with the company on inspection related issues during the inspection process of the involved Inspectorate. Swissmedic may support the involved Inspectorate if requested. The involved Inspectorate should in any case first close its inspection process, having the option of highlighting an open question that could not concluded finally during the inspection, in the Inspectorates' proposal. Any supporting documents from the Inspectorate and the company should be sent to Swissmedic by the Inspectorate. The contentious point can have a potential impact on the establishment licence of the company (potential GMP/GDP non-compliance).

Swissmedic will assess the issue and decide how to proceed. Among others, one of the following course of action may be taken:

a) Swissmedic takes a decision
b) Swissmedic submits the case to ICC
c) Swissmedic consults one or both parties / organizes a hearing (general by email, letter but could exceptionally be a face-to-face meeting) with the company and the involved Inspectorate

After that (cases b and c), Swissmedic takes a decision.

The Swissmedic decision is usually communicated to the involved Inspectorate which in turn will inform the company and enforce the decision in the frame of its inspection program. If the company does not accept the decision, it may appeal to Swissmedic which will then take the appropriate measures based on article 66 paragraph 1 and 2 TPA by an administrative ruling. The ruling can be challenged in court.

5.12 Relationship with other authorities or organisations (national or international)

Swissmedic maintains the official contact with national or international authorities, whose competence lies with inspections. This normally also applies to contacts with organisations. However, a regional Inspectorate may have direct contacts with an organisation, e.g. in a collaboration for international inspections for the WHO. In such cases, the Inspectorate informs Swissmedic.

6. Changes to the previous version

Chapter 5.7.1: Supplement with article 41 paragraph 2 MPLO

7. Annexes

- Annex 2: Table – Types of inspections: Competencies of Inspectorates
- Annex 3: Table – Description of the Inspectorates
- Annex 4: Guidance document – Rules of the ICC
- Annex 5: Information sheet – Swiss GMP/GDP Inspection System

- Annex 1: Flowchart – Inspection process *(cancelled)*