

Guidance document

GMP compliance by foreign manufacturers

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List of contents

1	Introduction and objective	3
2	Scope	3
3	Duties of the responsible person (RP)	3
4	Verification of GMP compliance by the responsible person	3
5	Proof that GMP compliance has been verified	3
5.1	Manufacturers from a country whose GMP control system is considered by Switzerland to be equivalent	4
5.1.1	Manufacturers of ready-to-use medicinal products	4
5.1.2	Manufacturers of medicinal products that are not ready-to-use (active substances)	4
5.2	Manufacturers from a country whose GMP control system is not considered by Switzerland to be equivalent	4
5.2.1	Manufacturers of ready-to-use medicinal products	4
5.2.2	Manufacturers of medicinal products that are not ready-to-use (active substances)	5
5.3	Exemption for so-called "atypical active pharmaceutical ingredients"	5
5.4	Exemption for authorisation by means of the notification procedure in accordance with Art. 39 TPLO	5
5.5	Age of the documents	6
6	General requirements for audit reports	6
6.1	General conditions for the submission of audit reports	6
6.2	Information on inspection reports from a recognised authority	8
6.3	Information on risk assessment of veterinary medicinal product manufacturers	8
7	Languages used for the documents	9
8	Countries with a GMP control system that is considered by Switzerland to be equivalent.....	9
9	Inspections by Swissmedic	9

1 Introduction and objective

The objective of this guidance document is to clarify which documents should be submitted within the framework of an authorisation application (new application) or a minor type IA/IAIN variation that can be notified after the event, a minor type IB variation that must be notified in advance, or a major type II variation for a human medicinal product that has already been authorised, or for a new application or a variation with or without assessment of a veterinary medicinal product in order to demonstrate that the responsible person (RP) has verified the GMP (Good Manufacturing Practice) compliance of foreign manufacturers of active pharmaceutical ingredients and/or ready-to-use medicinal products in accordance with Art. 11, para. 1, let. i MPLO (Medicinal Products Licensing Ordinance).

2 Scope

Authorisation holders or applicants for the authorisation of ready-to-use medicines that are manufactured abroad and/or those that are manufactured in Switzerland and contain active pharmaceutical ingredients produced by foreign manufacturers.

3 Duties of the responsible person (RP)

It is the duty of the responsible person (RP) to ensure that ready-to-use medicinal products released to the market have been manufactured in compliance with the GMP rules. The RP must also ensure that the active pharmaceutical ingredients contained therein are also manufactured in compliance with the GMP rules (Art. 5, para. 1-3 and Art. 18, para. 2, let. b MPLO).

4 Verification of GMP compliance by the responsible person

Verification of the GMP compliance of foreign manufacturers must be carried out regularly under the responsibility of the RP. Documents such as GMP certificates, audit reports, inspection reports and Site Master Files that are taken into consideration for this verification may be requested by Swissmedic at any time and/or examined during inspections.

5 Proof that GMP compliance has been verified

The form *Declaration by the Responsible Person HMV4* (RP Declaration) and the documents described in section 5.1 must be submitted with applications for authorisation (new applications) or minor type IA/IAIN variations that can be notified after the event, minor type IB variations that must be notified in advance or major type II variations for authorised products. In the RP Declaration, the RP confirms the manufacturer's GMP compliance on the basis of an audit conducted by the authorisation holder or by a third party commissioned by the authorisation holder and on the basis of existing official documents and documentation from the foreign manufacturer (see point 4 above).

One form per manufacturer and per active pharmaceutical ingredient (if a product contains several active pharmaceutical ingredients) must be submitted for the finished product.

For medicinal products that are not ready-to-use (active substances), the RP Declaration and the other documents only need to be submitted for the manufacturer that carries out the last manufacturing step (including release) and guarantees the GMP-compliant manufacture of the product. The RP is responsible for ensuring that possible intermediate steps outsourced to third

parties (including QC) were also carried out in accordance with GMP. The RP must ensure that the active substance manufacturer has fulfilled its responsibilities. If a clear responsibility cascade as described above does not exist, the RP Declaration must be submitted for all individual manufacturers.

Instead of an RP Declaration, only those documents mentioned in section 5.1 need to be submitted for the steps of packaging, quality control and batch release of ready-to-use medicinal products.

5.1 Manufacturers from a country whose GMP control system is considered by Switzerland to be equivalent

The following documents at least must be enclosed with the RP Declaration:

5.1.1 Manufacturers of ready-to-use medicinal products

- A GMP certificate based on an inspection within the past 3 years

or if no such certificate exists

- an official document confirming that the manufacturer satisfies the PIC/S GMP requirements and has been inspected accordingly by the authority (date of inspection within the past 3 years) (e.g. inspection report with a definitive assessment of the GMP status)

5.1.2 Manufacturers of medicinal products that are not ready-to-use (active substances)

- A GMP certificate based on an inspection within the past 3 years

or if no such certificate exists

- an official document confirming that the manufacturer satisfies the PIC/S GMP requirements and has been inspected accordingly by the authority (date of inspection within the past 3 years) (e.g. inspection report with a definitive assessment of the GMP status)

or if no such document is issued by the local authority

- a copy of an audit report, no more than 3 years old.

5.2 Manufacturers from a country whose GMP control system is not considered by Switzerland to be equivalent

The following documents at least must be enclosed with the RP Declaration:

5.2.1 Manufacturers of ready-to-use medicinal products

- A GMP certificate covering the manufacturing concerned based on an inspection within the past 3 years and issued by a foreign regulatory authority whose GMP control system is considered by Switzerland to be equivalent

Or, if no such certificate exists,

- an official document issued by a foreign regulatory authority whose GMP control system is considered by Switzerland to be equivalent and confirming that the manufacturer satisfies the PIC/S GMP requirements in respect of the manufacturing concerned and has been inspected accordingly by the authority (date of inspection within the past 3 years) (e.g. inspection report with

a definitive assessment of the GMP status). The documents demonstrating GMP compliance (i.e. audit reports, GMP certificates or other official documents) should only be submitted if they cover the relevant active substance / finished product.

If no such document exists, either:

- a copy of an audit report, no more than 3 years old

and

- a copy of a GMP certificate issued by the authority of the country in which the manufacturer is located, no more than 3 years old

5.2.2 Manufacturers of medicinal products that are not ready-to-use (active substances)

- A GMP certificate covering the active substance concerned based on an inspection within the past 3 years and issued by a foreign regulatory authority whose GMP control system is considered by Switzerland to be equivalent.

If no such certificate exists

- an official document issued by a foreign regulatory authority whose GMP control system is considered by Switzerland to be equivalent and confirming that the manufacturer satisfies the PIC/S GMP requirements and has been inspected accordingly by the authority (date of inspection within the past 3 years) (e.g. inspection report with a definitive assessment of the GMP status). The documents demonstrating GMP compliance (i.e. audit reports, GMP certificates or other official documents) should only be submitted if they cover the relevant active substance / finished product.

If no such document exists, either:

- a copy of an audit report, no more than 3 years old

and

- a copy of a GMP certificate issued by the authorities of the manufacturer's country, no older than 3 years, unless it can be demonstrated that the local authorities do not issue such certificates

5.3 Exemption for so-called "atypical active pharmaceutical ingredients"

If no proof of GMP compliance exists for an active substance because it is not manufactured as an active pharmaceutical ingredient for medicinal products but, for example, for food products or cosmetics, the RP of the authorisation holder / applicant must carry out an assessment of the manufacturing of the "atypical active pharmaceutical ingredient". The assessment must address the extent to which the GMP rules for active pharmaceutical ingredients have been taken into consideration. On the basis of this assessment, the lack of proof of GMP compliance must be justified on a risk basis. This risk-based justification must be signed and dated by the RP of the authorisation holder / applicant and enclosed with the RP Declaration.

5.4 Exemption for authorisation by means of the notification procedure in accordance with Art. 39 TPLO

For authorisation of veterinary medicinal products by means of the notification procedure in accordance with Art. 39 TPLO or – if relevant – for variations to such products, it is sufficient to submit

a copy of the GMP certificate or manufacturing licence for each foreign manufacturer. Neither the form *Manufacturer information HMV4* nor the form *Declaration by the Responsible Person HMV4* (RP Declaration) have to be submitted.

5.5 Age of the documents

The term “No more than 3 years old” means that the inspection or audit to which the document refers must have taken place no more than 3 years ago.

6 General requirements for audit reports

6.1 General conditions for the submission of audit reports

- A GMP audit of medicinal products that are not ready-to-use (active substances) or of ready-to-use medicinal products must be carried out by qualified auditors, either internal or external. The audit report must cover all relevant GMP aspects (see for example questions 9 and 10 under Q & A [EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances](#) and [Chapter 5.29 EU GMP guide part I](#)).
- An audit carried out by the authorisation holder or the manufacturer must be carried out within the framework of their quality assurance system (i.e. in accordance with GMP rules such as SOPs and documentation). If an audit is outsourced, the requirements of Chapter 7, part I GMP must also be taken into consideration.
- The audit report must include a statement from the auditors on the proposed corrective and preventive action plan (CAPA plan) of the company audited.
- Remote audit reports are not accepted.
- An audit report may only be submitted if no relevant GMP certificate (not more than 3 years old) that has been issued by a foreign regulatory authority whose GMP control system is considered by Switzerland to be equivalent exists, or in the absence of an official document issued by a foreign regulatory authority whose GMP control system is considered by Switzerland to be equivalent confirming that the manufacturer meets the PIC/S GMP requirements and has been inspected accordingly by the authority (date of inspection within the last 3 years) (e.g. inspection report with a definitive assessment of the GMP status).
- If an audit report is submitted, a list of the inspections of the manufacturer concerned carried out by foreign authorities within the last 5 years must also be submitted, including at least the following details: name of foreign authority, date of inspection, date of completion of inspection and outcome (compliant/non-compliant).
- The approved audit report is expected to be available when the application is submitted in order to document the manufacturer's GMP compliance (see RP Declaration). Approval of the manufacturer is granted on the basis of the audit report, which is why prior authorisation of the manufacturer is not possible without the submission of a final audit report.
- Audit reports on a re-audit with a reduced, risk-based audit scope will also be accepted as audit reports. In such cases it must, however, be ensured that all information necessary for an evaluation of GMP conformity is nonetheless submitted. This can be done, for example, by submitting an assessment written by the RP or a summary based on the original, full audit which covers the missing points.

- Redacted documents (report / CAPA plan) will only be accepted if this does not impair assessment of the report. Even if the redacted comments do not directly concern the manufacture of the submitted product, they can have a considerable impact on the evaluation of the manufacturer's GMP compliance.
- The report will only be evaluated if the submitted audit report is current (not more than 3 years old) and covers the relevant active substance / finished product.

Below is a list of the topics that must be inspected during the audit, depending on the proposed manufacturing activities. This list is not exhaustive and the report should also include other important information, determined by which sections of EU-GMP and PIC/S Part II and ICH Q7 are applicable.

Topics	Points to be inspected: Information that should be available / reviewed during the audit
General information about the company	<ul style="list-style-type: none"> • Age of the company, size, address, its main activities, number of employees • Contact person at the company / contact details
Active substance / finished product manufacture	<ul style="list-style-type: none"> • Product Quality Review • Information on process validation • Information on cleaning / cleaning validation • Information on the manufacturing facility (single-purpose or multi-purpose) • Tour of the manufacturing facility • For multi-purpose facilities, state which other products are manufactured using the same equipment. The other product types (e.g. high-risk products such as highly active substances, active substances to treat cancer, ...) that are also manufactured using the same equipment must be clearly highlighted. • Description of the manufacturing processes used for the manufacturer's active substances / product that is/are under review (parts of / steps in production). • Information on potential cross-contamination in multi-purpose facilities • Review of batch documentation • Reprocessing, reworking
Quality management system (QMS)	<ul style="list-style-type: none"> • Change control • Out of specification • Deviation

Topics	Points to be inspected: Information that should be available / reviewed during the audit
	<ul style="list-style-type: none"> • Complaints • Personnel training
Quality control (only for ready-to-use medicinal products)	<ul style="list-style-type: none"> • Description of quality control • Information on the status of the methods and specifications applicable to the finished product under review • Method validation • Qualification
Auditor	<ul style="list-style-type: none"> • Contact details (e-mail / telephone) • Evidence of qualification • Statement of independence: conflicts of interest should be avoided.

Swissmedic adds foreign manufacturers whose GMP compliance is demonstrated by means of an audit report to a list of candidates for possible inspections carried out by Swissmedic abroad (see section 9).

6.2 Information on inspection reports from a recognised authority

Inspection reports from recognised authorities are accepted if they are less than 3 years old and the inspection was carried out on site and refers to the medicinal product that is not ready-to-use (active substance) or the ready-to-use medicinal product under review. Here are some examples:

- An inspection report can be accepted if it refers to a routine inspection and the active substance or finished product is covered in the report.
- An inspection report can be accepted if it refers to a pre-approval inspection (PAI) and the inspection refers to the active substance or finished product under review.
- An inspection report cannot be accepted, however, if it refers to a pre-approval inspection (PAI) and the inspection does not refer to the active substance or finished product under review.

6.3 Information on risk assessment of veterinary medicinal product manufacturers

If no GMP certificate or other document issued by a recognised authority is available to demonstrate the manufacturer's GMP compliance, a risk assessment by the RP can alternatively be submitted. A risk assessment does not release the authorisation holder from their obligation to carry out an audit of the manufacturer (the audit date must be shown in Part C of the form *Declaration by the Responsible Person HMV4* (RP declaration)).

It should be clear from the risk assessment that the manufacturer's GMP compliance is ensured.

The following points, among others, may be included:

- Information on the outcome of the audits performed in the last 5 years (deficiencies identified, definitive evaluation of GMP status)
- Time of the next planned audit / frequency of audits performed
- Which criteria were used to evaluate the manufacturer as qualified to perform the proposed manufacturing activities?
- If applicable, has the manufacturer already been approved for other medicinal products that are authorised for the Swiss market? For which active substances / manufacturing activities has the manufacturer already been registered?
- Have any quality deficiencies relating to this manufacturer been observed and/or reported to Swissmedic in the last 4 years?

7 Languages used for the documents

All documents listed under section 5 (with the exception of inspection and audit reports) may be written in the following languages: German, English, French or Italian. Documents in other languages must be submitted with an accompanying certified English translation.

Audit reports and inspection reports may be written in German, Italian, French or English. Reports in other languages must be submitted with an accompanying certified English translation.

8 Countries with a GMP control system that is considered by Switzerland to be equivalent

For a list of those countries whose GMP control system is considered by Switzerland to be equivalent, please refer to the *List of Countries with recognised GMP control systems (BW105_00_002e_VZ)*.

9 Inspections by Swissmedic

Swissmedic reserves the right to inspect, at the expense of the Swiss authorisation holder/applicant, manufacturers from countries whose regulatory authority does not have a GMP control system deemed by Switzerland to be equivalent to the Swiss system (Art. 60 para. 2 MPLO) and if necessary to put the relevant application on hold until the inspection has been carried out. See also section 6. Art. 14 MPLO (reanalysis) also applies.

Change history

Version	Change	sig
5.0	Section 6: In section 6.1 the general conditions were expanded; sections 6.2 and 6.3 are new.	wau
4.0	Section 6: Remote audit reports are not accepted.	sal
3.1	New layout, no content adjustments to the previous version	dei
3.0	Section 5: Insertion of a hierarchy for the documentation to be submitted Section 6: Clarification on submission of audit reports Section 9: An application can be put on hold until an inspection has been carried out.	hul
2.1	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
2.0	Implementation of MPLO/Medicrime	gme
1.0	Implementation of TPO4. Implementation of MPLO/Medicrime is still ongoing.	cfe