Guidance document
GMP compliance by foreign manufacturers

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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) which are minor type IA/IAIN variations that can be notified after the event, which are minor type IB variations that must be notified in advance and which are major type II variations 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 that has already been authorised, in order to demonstrate that the responsible person (see section “3 Duties of the responsible person (RP)” below) has verified compliance with Good Manufacturing Practice (GMP) rules on the part of foreign manufacturers of active pharmaceutical ingredients and / or ready-to-use medicinal products, in accordance with Art. 11, para. 1, part i Medicinal Products Licensing Ordinance (MPLO).

2 Scope

This information sheet is intended for authorisation holders or applicants for the authorisation of ready-to-use medicines that are manufactured abroad and / or those manufactured in Switzerland, and that 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 to be 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 (MPLO Art. 5, para. 1-3 and Art. 18, para. 2, part b).

4 Verification of GMP compliance by the responsible person

The verification of GMP compliance by 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, etc. that are taken into consideration for this verification may be requested by Swissmedic at any time and / or examined within the framework of inspections.

5 Proof that GMP compliance has been verified

Form *Declaration by the Responsible Person for foreign manufacturers HMV4* (RP Declaration) and the documents described in section 5.1 must always be submitted with applications for authorisation (new applications) for minor type IA/IAIN variations that can be notified after the event, for minor type IB variations that must be notified in advance or for major type II variations for authorised preparations. In the RP Declaration, the RP confirms the manufacturer's GMP conformity 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 preparation contains several active pharmaceutical ingredients) must be submitted for the finished preparation.

For non-ready-to-use medicinal products (active substances), the RP Declaration and the other documents only need to be submitted for the manufacturer that carries out the last manufacturing step (incl. release) and guarantees the GMP-compliant manufacture of the product. The RP is responsible for ensuring that possible intermediate steps outsourced to third parties (incl. QC) were also carried out in accordance with GMP. The FVP 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 packing, quality control or 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 pharmaceutical ingredients)

- 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

- 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 recognised by Switzerland

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)

If no such document exists

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

and

- 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 pharmaceutical ingredients)

- 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)

or, if no such document exists

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

and

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

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

If no proof of GMP compliance exists for an ingredient because the ingredient in question is not manufactured as a pharmaceutical ingredient 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 Authorisation by means of the notification procedure in accordance with Art. 39 TPLO – exceptions

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 preparations, it is sufficient to submit just one copy of the GMP certificate or manufacturing licence per foreign manufacturer. Neither the form *Manufacturer information HMV4* nor the form *Declaration by the Responsible Person for foreign manufacturers 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 three years ago.

6 Audit report

General conditions for the submission of audit reports

- A GMP audit on the product or product class must be carried out by qualified auditors, either internal or external. The audit report must cover all relevant GMP aspects (see e.g. 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.

Conditions for the submission of audit reports from countries whose GMP control system is not considered by Switzerland to be equivalent:

- 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**, where no such certificate exists, in the absence of any 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).

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).

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, Italian or Spanish. Documents in other languages must be submitted together 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 together 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 that is considered by Switzerland to be equivalent to the Swiss system, please refer to the Directory *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 of the Medicinal Products Licensing Ordinance – 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
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