EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Outline of a procedure for co-ordinating the verification of the GMP status of manufacturers in third countries

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Title	**Outline of a procedure for co-ordinating the verification of the GMP status of manufacturers in third countries**
Date of adoption	May 2023
Date of entry into force	1 January 2024
Supersedes	Version adopted on 21 September 2021
Reason for revision	Modifications were introduced as a result of the entry into application of Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC and Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Minor updates were done in the section Communication Between the "Supervisory Authority" and Industry
Notes	Not applicable
Last publication date:	1 August 2024
Document version	1

Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries

1. Verification of the GMP Compliance Status of Third Country Manufacturers of Medicinal and Investigational Medicinal Products.

1.1 The Supervisory Member State for the manufacturing authorisation holder who is responsible for importation of a product should verify the GMP compliance status of any third country manufacturer(s) mentioned in an application in accordance with their own policies and procedures. This evaluation is undertaken product-specifically and includes information obtained from MRA countries and may be based on the following:

1.1.1. A report of an inspection for the product or product category concerned carried out by the Supervisory Member State,

or

1.1.2. Information supplied by another EEA Competent Authority in accordance with the exchange of information procedure contained in the Compilation of Union Procedures,

or

1.1.3. A report of an inspection for the product or product category concerned carried out by another EEA competent authority,

or

1.1.4. Either an inspection report or a statement of GMP compliance obtained under an operational Mutual Recognition Agreement between the European Union and the Competent Authorities of the MRA country in which the manufacturer is located.

or

1.1.5. Either an inspection report with a clear GMP statement or a statement of GMP compliance obtained under an operational Mutual Recognition Agreement between the European Union and the Competent Authorities of an MRA country, if the scope of the operational Mutual Recognition Agreement includes those third country inspections and is not limited by territorial rules to the jurisdiction of the MRA partner. If products and production lines in question were not covered by the MRA partners inspection an EEA inspection may be considered by the EU/EEA Supervisory Authority.

If a GMP certificate has been issued by an MRA partner, the regulatory authority performing the verification of the GMP compliance status should obtain this document as a minimum. The GMP certificate should not be older than three years and may be obtained from a central repository (e.g. EudraGMDP database), the issuing MRA partner or the manufacturing site and be verified with the issuing MRA partner. If this GMP certificate obtained has a satisfactory level of detail, it can be accepted.

1.2 Triggers and risk factors for an onsite inspection

The following are examples of possible triggers or risk factors for an onsite inspection:

- There is no inspection history for the site.
- The site was not inspected by an EEA inspectorate or the MRA partner.
- The GMP certificate / available inspection report does not cover products or processes / activities that are of interest to the regulatory authority performing the assessment.
- There is evidence that another regulatory authority has not approved the manufacturing facility, or even aspects of it (e.g. sterile vs non-sterile areas).

This is not an exhaustive list and decisions on whether or not to perform an onsite inspection

should be made on a case-by-case basis taking into consideration the available information and triggers and risk factors defined within national/regional procedures. (See also the Union procedures: *A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers* and *Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers, importers and distributors of active substances and manufacturers or importers of excipients used as starting materials*)

1.3 Where the Supervisory Member State is unable to verify the GMP status of any third country manufacturer(s) on the above basis it may request another EEA Competent Authority to carry out an inspection and to provide confirmation of the manufacturer's GMP compliance status. For centralised products this arrangement should be subject to obtaining the written consent of any other Supervisory Member States involved.

1.4 The means of verification will normally be through inspection-based information as described above, however other information may be used as part of, or in exceptional cases, as the primary means for verification. For example:

1.4.1 Under the provisions of some of the existing MRAs, information from MRA partners is only accepted in connection with inspections performed in their own territories, however, the use of other information from those MRA partners, PIC/S participating authorities and/or other authorities may nevertheless provide supporting evidence in the verification of the GMP status of a manufacturing site. The Supervisory Authority should perform a risk assessment on each occasion to determine an appropriate degree of evidence that a 3rd country manufacturer operates to an equivalent level of GMP.

1.4.2 Under the provisions of some of the existing MRAs, information from MRA partners can be or is accepted in connection with inspections performed in third countries.

During national or international public health emergencies or other crises, on-site GMP/GDP inspections may not be possible for a number of reasons such as travel restrictions, risk to health, or other restrictions/guidance issued by local or national authorities. During these situations, the obligation of manufacturers, importers and distributors to comply with GMP/GDP is not waived and the ongoing verification of compliance by Supervisory Authorities is important to ensure the protection of public health.

In these circumstances, taking into account national and European legislation, distant assessments can represent a suitable means of determining compliance with the principles and guidelines of GMP/GDP. The guidance[1] (Guidance related to GMP/GDP and PMF distant assessments) should be followed by the supervisory authority.

1.5 Investigational Medicinal Products

For investigational medicinal products, inspections should be reserved for higher risk situations rather than being routinely employed. The risk assessments should take the elements described 1.2 above into account along with the following:

- the dosage form,
- type of product (e.g. placebo, marketed comparator, new technology),
- numbers of subjects involved and their clinical disposition,
- duration of treatment,
- number of clinical trials sourcing from the same site
- whether the manufacturer is in possession of the equivalent of a valid manufacturing authorisation issued by its local regulatory authority and is subject to inspections,
- whether the analytical testing performed in the third country is subject to appropriate

authorisation.

Exchange of Information on Third Country Manufacturers.

2.1 When exchanging information on third country manufacturing sites, the reporting authority should indicate whether the conclusions reached are derived from an inspection by an EEA inspectorate or MRA partner under the terms of an MRA, or whether alternative means were used such as those described in section 1.3.

2.2 On the basis of a "reasoned request" from the competent authorities of another Member State or from the EMA the Supervisory Member State should provide a report of the most recent verification of the GMP status of a third country manufacturer for a particular product or product category.

2.3 Where the Member State requested to supply the information is unable to do so the requesting authorities may carry out a GMP inspection of the third country manufacturer, in which case they will provide the other authorities with shared supervisory responsibility with a copy of their inspection report or a statement of GMP compliance.

Organisation and Records of Inspections and Composition of Inspection Teams.

3.1 The EMA will maintain a plan of third country inspections connected with centralised products and will make this available on a regular basis.

3.2 Through the database on GMP certificates to be established in accordance with Article 111.6 of Directive 2004/27 (Art. 80.6 of Directive 2004/28), the EMA will maintain a record of all inspections that have been carried out by the competent authorities of the EU/EEA, which will be available to all Member States.

3.3 The competent authorities planning inspections of manufacturers in third countries may invite the participation of the other Member States who have shared "Supervisory" responsibilities for the product(s). This should take into account planned applications for marketing authorisations, problems encountered with the products from the manufacturer, their workloads, their experience in the type of inspections required, language capability for the inspection and overall economics of travel etc.

Communication Between the "Supervisory Authority" and Industry

Member States should encourage potential applicants to make early contact with the inspectorate of the supervisory authority when planning a marketing authorisation submission or variation which includes a third country manufacturing site, in order to discuss the applicant's knowledge of the GMP status of the site, its inspection history and inspection-readiness. Ideally this should be at least 3 months before submission.

The "Supervisory Authorities"

5.1 The "Supervisory Authorities" for a medicinal product and their responsibilities are defined for products for human use in Article 18 and 19 of Council Regulation (EC) No 726/2004. They are the Competent Authorities which have granted the manufacturing authorisation either for the manufacturing site if it is in the EU or for the importer if the product is manufactured in a third country. Additional information on the agreed definition of "Supervisory Authorities" for products for veterinary use can be found in the *Introduction*.

Re-assessment frequency

It is the responsibility of the MIA Holder to confirm that active substances used as starting materials have been manufactured in accordance with good manufacturing practice.

Unless otherwise required by the national competent authority, there is no obligation to apply the following requirements to manufacturers of active substances located in a third country.

6.1 In general authorities with supervisory responsibility for a third country manufacturing site should ensure that it holds a valid GMP certificate (or equivalent document(s) from MRA partners).

6.2 Where valid GMP certificates (or equivalent document(s)) are available,, it should not be necessary to withhold any application or variation pending the results of a recent inspection unless information is available suggesting that this status of GMP compliance may have changed.

6.3 GMP certificates (or equivalent document(s))based on inspections conducted more than five years ago, from whatever source, should not normally be taken into consideration.

Disagreement between Member States on acceptability of Inspection Reports

7.1 Where the Supervisory Member State and the competent authorities of another Member State are unable to agree on the acceptability of an inspection report for a manufacturer in a third country they should utilise the arrangements described for human products in Article 19 of Regulation (EC) 726/2004 or where appropriate the arbitration procedure provided by article 122 of Directive 2001/83/EC. For veterinary products in the absence of a specific legal basis in regulation 2019/6, the national competent authorities have agreed to follow the principles of the same arbitration procedure set out in article 122 of Directive 2001/83/EC for human medicinal products.

2. Annex

SCHEME FOR DISTANT ASSESSMENT OF MANUFACTURING SITES

Requirements / Rationale	Documentation to be requested
Presentation of GMP and Regulatory Enforcement system for the country	Brief presentation of changes being effected since the last inspection
Copy of the manufacturing authorisation granted by local authorities together with a certified translation	Copy of any new/modified manufacturing authorisation granted since the last inspection
SMF (site master file) documentation similar to the PIC/S guideline	SMF updated with one year from the assessment date And forecasted modifications
Plans attached to SMF **PI&D attached to SMF**	Coloured updated printouts may be acceptable in A3 or A2 format
List of all the products (medicinal or either) manufactured on site	The list may include proprietary names and INN
Copy of the last inspection report with a certified translated copy if relevant *GMP certificates coming from these inspections*	Last local authority report and last EU full report. PIC/S and WHO or FDA report(s) if aged less than 5 years

Photographic presentation of manufacturing site and utilities (outdoor/indoor)	Photographic presentation of any new room(s) of equipment not used at the time of inspection
Qualification Master Plan (premises & equipment)	List of all re-qualifications exercises carried out since the last inspection
Validation Master Plan (Manufacturing processes, cleaning, quality control)	List of all re-validations runs carried out since the last inspection
Full audit report of corporate / external audit dedicated to the product(s)	The report may be aged less than 5 years and accompanied with a recent follow-up internal report
Batch record(s) of the product(s) of interest	Last filled in batch record including the analytical part
Complaints handling	Updated list of complaints of the concerned products
Others *	Number of rejected batches for all products Number of rejected batches for the concerned product
Others (concerning the concerned product / dosage form)	Out of specification procedures On-going stability studies All 00s results and investigations* All process deviation reports (including reworked and reprocessed batches)* All quality deviation reports*
Others	Q.P certification that site has been fully audited against EU GMP in the last 2 years and all deficiencies have been rectified
Others	All Q.C results for batches imported and tested in the member state.
According to EU draft	Product Quality Review
Manufacturing Contract between manufacturing site and European applicant	Original contract and revision if applicable

*data to be provided over a period of the last 3 years