DECISION

No. 23/28.09.2007

on the approval of
Guideline on the verification of the Good Manufacturing Practice (GMP) status of manufacturers in third countries

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 28.09.2007, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as further amended, agrees on the following

DECISION

Single article. - The Guideline on the verification of the Good Manufacturing Practice (GMP) status of manufacturers in thirs countries is approved, according to the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the verification of the Good Manufacturing Practice (GMP) status of manufacturers located in third countries

CHAPTER I

Scope

Art. 1. – This Guideline is a translation into Romanian and an adaptation of the Guideline EMEA/INS/GMP/313523/2006 on the verification of the Good Manufacturing Practice (GMP) status of manufacturers of (investigational) medicinal products located in third countries, issued by the European Medicines Agency (EMEA).

CHAPTER II

Introduction

Art. 2. – The purpose of this Guideline is to provide guidance concerning the manner of verification of the Good Manufacturing Practice by a medicinal products/investigational medicinal products manufacturer in a third country, as mentioned in Art. 823 (4) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, in order to harmonise the verification procedures of third-country manufacturers, information exchange concerning those, conduct of inspections and related records, communication between authority and industry, frequency of inspections and manner of accepting inspection reports carried aut between EU Member States.

CHAPTER III

Verification of the Good Manufacturing Practice status of medicinal products/investigational medicinal products manufacturers in third countries

Art. 3. – In case of importing a medicinal product from a third country into Romania, the National Medicines Agency (NMA), as supervisory authority of a manufacturing/import authorisation holder, should verify the GMP compliance status of any manufacturer in a third country mentioned in the application; this verification may be based on the following:

a) A report edited following an inspection carried out by NMA inspectors for the respective medicinal product or category of medicinal products;

b) Information provided by another Competent Authority from the European Economic Area (EEA), in accordance with the Guideline on the exchange of information, approved through the Scientific Council Decision No. 15/15.06.2007.

or

c) A report submitted following an inspection conducted by another EEA Competent Authority, for the concerned medicinal product or class of medicinal products;

or

d) An inspection report or a declaration concerning the GMP compliance obtained via a Mutual Recognition Agreement (MRA) in force, signed between the European Community (EC) and the Competent Authorities from the third country of the manufacturer.

Art. 4. - (1) Where the NMA, as a supervisory authority, is unable to verify the GMP status of any third country manufacturer on the above basis it may request another EEA Competent Authority to carry out an inspection and to provide information on the manufacturer's GMP compliance status.

(2) For centralised medicinal products this arrangement should be subject to obtaining the written consent of any other Supervisory Member States involved.

Art. 5. – (1) The means of verification will normally be through inspection-based information as described in Art. 4 (1); however other information may be used as part of, or in exceptional cases, as the primary means for verification. Relevant examples are exposed in the following paragraphs:

(2) Under the provisions 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 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. As a supervisory authority, the NMA 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.

(3) Where an inspection has been performed by a Member State or MRA partner but does not cover the dosage form in question, compliance conclusions from inspection reports relating to a different dosage form may, with justification, be extended to other dose forms, if necessary requesting the report if it belongs to another Member State authority. In addition the elements below should be considered, together with, if considered necessary, elements of the distant assessment approach described in paragraph (4). Reports concerning non-sterile dosage forms alone do not provide sufficient evidence to extend any GMP conclusions to sterile products.

- Inspection reports of the importer: if necessary, a special inspection may be needed of the importer to assess measures undertaken by the importer to verify GMP compliance at the exporting site for the dosage form in question (such as audit reports from the Qualified Person);

- A site master file for the manufacturing site: if necessary, written questions arising from a review of this may need to be raised and the responses reviewed;

- The inspection history of the manufacturing site performed by other authorities: the existence of warning letters or other regulatory action by third country authorities should be ascertained;

- The history of reported defects for batches of all medicinal products originating at the manufacturing site.

Subject to the information reviewed, it may be concluded not to conduct a pre-authorisation inspection but verification in accordance with Art. 3 should be sought within 3 years.

(4) A similar approach can be taken where inspections cannot be carried out because of an unacceptable risk to EEA inspectors. The procedure for "distant assessment" is limited to inspections in 3rd countries that present an enhanced physical threat to the inspector (for political reasons, health reasons or others) and where the enhanced level of instability is expected to be transient. The procedure should not be used where the reporting authority has reason to believe that the instability could directly affect the quality of the medicinal product(s) under consideration.

(5) A distant assessment may be performed based on a documented interview with the manufacturer that should be detailed enough to evaluate the GMP compliance of the relevant manufacturing site.

(6) This documented interview (taking place in the inspecting authority's country) should be carried out with nominated staff possessing an appropriately high level of knowledge of the process and facilities.

(7) The table in the annex provides for two levels of assessment: a full assessment where the manufacturing site which has been inspected more than 5 years ago by an EEA authority, and a reduced one for a site which has been inspected within 3 and 5 years ago by the same EEA Authority; if the last inspection was performed by another authority, a full assessment should be applied.

(8) A distant assessment should not be carried out where the manufacturing site has never been inspected, by an EEA inspectorate, nor for a sterile manufacturing process or any unusually complex non-sterile process, nor should it replace inspection more than once.

Art. 6. – 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 in Art. 3 into account along with the following:

a) the dosage form;

b) type of product (e.g. placebo, marketed comparator, new technology);

c) numbers of subjects involved and their clinical disposition;

d) duration of treatment;

e) number of clinical trials sourcing from the same site;

f) 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;

g) whether the analytical testing performed in the third country is subject to appropriate authorisation.

CHAPTER IV

Exchange of information relating to third country manufacturers

Art. 7. - (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 Art. 5 (3).

(2) On the basis of a "reasoned request" from the competent authorities of another Member State or from the EMEA, the NMA, as Supervisory Authority, should provide a report of the most recent verification of the GMP status of a third country manufacturer for a particular medicinal product or medicinal product category.

(3) Where the NMA is unable to provide the requested information, the requesting authority 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.

CHAPTER V

Organisation and Records of Inspections. Composition of Inspection Teams.

Art. 8. - (1) The EMEA will maintain a plan of third country inspections connected with centralised products and will make this available on a regular basis.

(2) Through the database on GMP certificates, the EMEA 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) The NMA planning inspections in third countries may invite other Member States who have shared "Supervisory" responsibilities for the medicinal product(s); the invitation should take into account planned applications for marketing authorisations (MAs), 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.

CHAPTER VI

Communication between the NMA and Industry

Art. 9. - The NMA 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 of the manufacturing site; ideally, this contact should be at least 3 months before submission and is particularly important for investigational medicinal products given the short timelines established to authorise trials.

CHAPTER VII

The Supervisory Authorities

Art. 10. - The "Supervisory Authorities" for a medicinal product and their responsibilities are defined in Article 18 and 19 of Council Regulation (EC) No. 726/2004 of the European Parliament and Council, 31 May 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.

CHAPTER VIII

Re-inspection Frequency

Art. 11. - (1) In general, the NMA, as a supervisory authority for a third country manufacturing site should ensure that it is inspected by an EEA authority or MRA partner authority, under the terms of an MRA, between every two to three years.

(2) Where inspection reports and information exchange based on inspections conducted more than three years ago are available, as there is evidence of acceptable GMP standards, it should not be necessary to withhold any application or variation pending the results of a new inspection unless information is available from other sources suggesting that this status may have changed; steps should nevertheless be taken to obtain an updated report.

(3) Inspection reports, and information exchange based on inspections or distant assessments conducted more than five years ago, from whatever source, should not normally be taken into consideration.

CHAPTER IX

Disagreement between Member States on acceptability of Inspection Reports

Art. 12. - Where the NMA, as a supervisory authority, 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 procedures described for medicinal products for human use in Article 19 of Regulation (EC) 726/2004 or where appropriate the arbitration procedure provided by Article 737 of Law No. 95/2006, Title XVII – The medicinal product.

SCHEME FOR DISTANT ASSESSMENT OF MANUFACTURING SITES

REQUIREMENTS/NATIONALE	**Last EEA inspection more than 5 years ago**	**Last EEA inspection carried out between 3 and 5 years ago**
Presentation of GMP and Regulatory Enforcement system for the country	Complete presentation of the regulatory system and full copy of the local GMP guideline	Brief presentation of changes being effected since the last inspection
Copy of the manufacturing authorisation granted by local authorities together with a certified translation	Complete set of copies of all original/modified manufacturing authorisations	Copy of any new/modified manufacturing authorisation granted since the last inspection
SMF (site master file) documentation similar to the PIC/S guideline	SMF completed/updated within 6 month from the assessment date and forecasted modifications	SMF updated with one year from the assessment date and forecasted modifications
Plans attached to SMF **PI&D attached to SMF**	Coloured printouts of Water treatment, Air Handling PI & Ds in A3 or A2 format	Coloured updated printouts may be acceptable in A3 or A2 format
List of all the products (medicinal or other) manufactured on site	The list should include proprietary names and INN	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 have been granted***	Local authority report aged less than two years and, if available, copy of PIC/S or WHO or FDA report(s)	Last local authority report and last EU full report. PIC/S and WHO or FDA reports if aged less than 5 years
Photographic presentation of manufacturing site and utilities (outdoor/indoor)	External general view (aerial) Detailed rooms views of any step carried out (sample, weighing etc.)	Photographic presentation of any new room of equipment not used at the time of inspection
Qualification Master Plan (premises & equipment)	List of premises, equipment and utilities used in the manufacturing with their qualification status	List of all re-qualifications exercises carried out since the last inspection
Validation Master Plan (Manufacturing processes, cleaning, quality control)	List of processes used for the manufacturing/control of products and their validation status	List of all re-validations runs carried out since the last inspection
Full audit report of corporate/external audit dedicated to the medicinal product(s)	The report should include the product flow chart and should be one year old as a maximum	The report may be aged less than 5 years and accompanied with a recent follow-up internal report
Batch record(s) of the medicinal product(s) of interest	Last filled in batch record together with the master batch record including the analytical part	Last filled in batch record including the analytical part
Complaints handling	Updated list of complaints for all products manufactured on site	Updated list of complaints of the concerned products
Others *	**Number of rejected batches for all products** Number of rejected batches for the concerned product	**Number of rejected batches for all products** **Number of rejected batches for the concerned product**
Others (relating to the concerned product/dosage form)	Out of specification procedures concerning the results analysis Ongoing stability studies	Out of specification procedures Ongoing stability studies All out of specification results and

	All out of specification results and related investigations* All process deviation reports (including reworked and reprocessed batches)* All quality deviation reports*	related investigations* All process deviation reports (including reworked and reprocessed batches)* All quality deviation reports*
Others (relating to the concerned product/dosage form)	Out of specification procedures concerning the results analysis Ongoing stability studies All out of specification results and related investigations* All process deviation reports (including reworked and reprocessed batches)* All quality deviation reports*	Out of specification procedures Ongoing stability studies All out of specification results and related investigations* All process deviation reports (including reworked and reprocessed batches)* All quality deviation reports*
Others	Qualified Person certification that the manufacturing site has been fully audited in compliance with the EU GMP in the last 2 years and that all deficiencies have been rectified	Qualified Person certification that the manufacturing site has been fully audited in compliance with the EU GMP in the last 2 years and that all deficiencies have been rectified
Others	All Quality Control results for batches imported and tested in Romania.	All Quality Control results for batches imported and tested in Romania.
GMP Guideline-chapter I	Annual Product Quality Review	Annual Product Quality Review
Manufacturing Contract between manufacturing site and European applicant	European contract and revision if applicable	European contract and revision if applicable

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