What you can expect from the newly amended MRA between the EU and the USA – Facts and figures in the GMP Sector – Part 2

5 min. reading time

by Sabine Paris, PhD

Last week you read in part 1 of my article about the key facts of the Mutual Recognition Agreement (MRA) in the GMP sector between the EU and the USA (LOGFILE 29/2017).

It has been a long road leading to this agreement. Did you know, that the Pharmaceutical Inspection Co-operation Scheme (PIC/S) facilitated and promoted the process? The assessment of the US FDA for becoming a PIC/S participating authority provided crucial information on its organisation and processes. In addition, helpful contacts with key personnel could be established. Thus, the PIC/S assessment worked as a baseline for assessing the equivalence of US FDA with EU principles.

Today, in part two of my article, I will highlight seven questions and answers regarding the practical implementation of the MRA.

What does territorial application mean?

To ensure that the MRA conditions apply, all medicinal products imported into the EU or the USA must be industrially manufactured in the EU or the USA respectively. Chemical active ingredients and other starting material from third countries may be used. However, if the medicinal product is partially manufactured in a third country the MRA import facilitations will not apply and cannot be claimed. This means that according to Annex 16 of the EU GMP Guide the product is subject to full retesting in the EU. A GMP inspection of the MRA Partner's authority at this (partially) manufacturing site in their territory shall be recognised.

What is a third country?

A third country is a country outside the EU or the European Economic Area (EEA), with whom the EU has no Mutual Recognition Agreement.

Additionally a Party may accept official GMP documents issued by a recognised authority of the other Party for manufacturing facilities located outside the territory of the issuing authority. For instance, a German authority may accept an FDA inspection report on a manufacturing site in Brazil.

How do the authorities profit from the MRA?

The MRA helps to use inspection resources more economically and more risk-based. When the German authorities are able to recognise FDA inspections in the US, they no longer need to perform overseas inspections in the US. The inspection of a manufacturer on an MRA Partner's territory will only be an exception, whereby the other Partner's inspectors have the right to join such an inspection.

How does the pharmaceutical industry profit from the MRA?

Importers in the EU from third countries must assign a Qualified Person (QP) who is responsible to certify that each production batch meets its specifications. Medicinal products imported from third countries are required to undergo all necessary quality tests again in the EU in advance of a certification. The MRA enables the QP to rely on the third country manufacturer's batch certification (as long as the provisions set out in Annex 16 of the EU GMP Guide are fulfilled). This saves time and resources.

Another crucial advantage: The EU manufacturer no longer has to prepare himself for FDA inspections. The MRA allows for inspections by the competent local inspection authority only and the FDA will recognise these inspections. Inspections by the FDA will be an exception to the rule in future.

Who can apply for an MRA certificate (= certificate of GMP compliance) for a manufacturing facility in the EU or the USA?

A GMP certificate will be issued by a MRA Partner's competent authority in response to an application by:

- A MRA Partner's competent authority,
- An exporter located in a MRA Partner's country
- An importer located in a MRA Partner's country

The GMP compliance certificate shall be issued within 30 days. Reference can be made to the relevant information in the EU database EudraGMDP if available. If a new GMP inspection has to be carried out (in cases where the last inspection was longer than 3 years ago), this period may be extended to 60 days.

Where do you apply for an MRA certificate for a US manufacturing facility?

In general you can apply for a MRA certificate at the competent GMP authority in your EU country. In Germany you can apply for a MRA certificate at the *Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices (ZLG)*. The medicinal product department is the contact partner for the exchange of GMP information with the USA.

The relevant application form is to be found as an enclosure to the standard operating procedure 16111103 of the Federal States for the exchange of certificates in accordance to the agreements with third countries (MRA, ACAA).

In the case of applications received from importers located in a MRA Partner country or through an exporter exporting to the MRA Partner's country, the responsible German authority will inform the manufacturer in question to get his permission to issue a certificate.

Do we need to audit contract manufacturers or manufacturers of active pharmaceutical ingredients in the USA in the future?

Yes, as a medicinal product manufacturer you must continue to conduct audits of your contractors. Audits of contract manufacturers and active ingredient manufacturers are stipulated in Annex 16 and chapter 5.29 (for active ingredients) of the EU GMP Guide. These audits are stipulated in spite of the fact that the contractors have been inspected by a recognised authority and hold valid GMP certificates. Manufacturing authorisation holders should not confuse the role of inspectorates with their own obligations!

However, the results of inspections may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme.

Will the FDA also issue manufacturing authorisations and GMP certificates?

Manufacturing facilities in the USA are inspected in the course of a licensing procedure. A New Drug Application (NDA) is submitted for each new product and an Abbreviated New Drug Application (ANDA) for generics. The FDA conducts a pre-approval GMP inspection of the facilities involved before a license is issued.

The FDA neither certifies a manufacturer as "GMP-compliant" nor issues GMP certificates. A suitable transfer method of GMP information between the EU and the USA is still to be found.

Sources:

1. ANNEX to the Commission Decision on determining the Union position for a Decision of the Joint Committee set up under Article 14 of the Agreement on Mutual Recognition between the European Community and the United States of America, in order to amend the Sectoral Annex on Pharmaceutical Good Manufacturing Practices (GMPs)
2. EMA Guide to MRAs in Operation (EMEA/MRA/22/03 Final)
3. SOP 16111103 Austausch von Zertifikaten im Rahmen von Drittstaatenabkommen (MRA, ACAA)
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