What you can expect from the newly amended MRA between the EU and the USA – Facts and figures in the GMP Sector – Part 1

5 min. reading time

by Sabine Paris, PhD

All good things come to those who wait and now everyone is pinning their hopes on the newly amended Mutual Recognition Agreement (MRA) in the GMP sector signed by the EU and the USA in February 2017.

Back in 1998 the EU and the USA already set up an MRA. So far it has not been operational for all the originally intended areas but only for medical devices, electromagnetic compatibility and telecommunication devices. The agreement contains an annex on Good Manufacturing Practice (GMP) for medicinal products, that has not yet been able to be applied. In the past the European GMP surveillance systems and regulations were said to differ greatly from their counterparts in the USA, ruling out any possibility of mutual recognition. In the meantime these reservations have been dispelled since both parties have come to a better understanding and have established a good cooperation.

The MRA will come into effect in November 2017 and will be applicable in the GMP sector. How will this affect your daily life? What are the advantages? How can you apply for a MRA certificate?

Let's take a look at the facts and figures of the MRA with the USA and you will find the answers to all these questions.

In this first part of the article you will read an overview of the key facts. Next week in part two, I will highlight seven questions and answers regarding the practical implementation.

Why do we need agreements on mutual recognition in relation to conformity assessments? (MRAs)?

The purpose of the MRAs is to:

- Reduce technical trading obstacles by facilitating market access whilst still protecting the consumer's health interests
- Mutually recognise reports, certificates, authorisations and conformity marks and the manufacturers' declarations of conformity
- Exchange information
- Encourage greater international harmonisation
- Optimise inspection resources i.e. by avoiding double inspections

Good to know: Important facts on the MRA between the EU and the USA in the GMP sector

The MRA in the GMP sector applies to:

- Medicinal products which have undergone one or a series of manufacturing processes either in the EU or USA. This includes manufacturing, labelling, testing and wholesale activities.
  The term "medicinal products" includes: Bulk, intermediates (for the EU), in process materials (for the USA) and marketed finished pharmaceuticals as well as biological products for human use.
- Active pharmaceutical ingredients

The MRA does not currently apply to:

- Vaccines for human use and plasma derived pharmaceuticals
  A decision on the inclusion of these products is expected by July 22, 2022.
- Human blood, human plasma, human tissues and organs
- Veterinary products
  A decision on the inclusion of veterinary products is expected by July 15, 2019.
- Veterinary immunologicals
- Investigational medicinal products
  The FDA does not routinely conduct GMP inspections for investigational medicinal products. Inspection information on these products will be provided if available and as far as resources allow.

According to the GMP annex both Parties can mutually recognise:

- GMP inspections of manufacturing facilities
- Official GMP documents i.e. manufacturing authorisations, GMP certificates

Batch certificate issued by the manufacturer on batch conformity without retesting requirements after the drug has been imported (see: Article 9 of the GMP Annex to MRA between EU and USA, page 3)

When will the MRA alleviations take effect?

The mutual recognition of manufacturing authorisations and GMP inspections come into effect on **November 1, 2017** on the condition that the FDA has assessed at least 8 EU authorities by then. Otherwise the enforcement will be delayed until the assessment has been finalised. The EU is obliged to finalise the assessment of the FDA by July 1, 2017 at the latest.

Note: The mutual recognition of **batch testing** will not take effect until all the relevant EU authorities have been recognised by the FDA and that will **not be before July 15, 2019.** The FDA has time to complete the assessment of the EU authorities until then. This means that even after November 1, 2017 all medicinal products manufactured in the USA will still require full retesting in the EU prior to marketing.

Batch testing in the GMP regulations:

Annex 16 of the EU GMP Guide:

1.5.4 The QP certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the marketing authori-

zation (MA). Unless an MRA or similar agreement is in place between the EU and the exporting country, the QP is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the MA.

Article 9 of the GMP Annex to MRA between EU and USA:

Batch testing

In the EU, as provided in Article 51 paragraph 2 of Directive 2001/83/EC and in Article 55 paragraph 2 of Directive 2001/82/EC, the qualified person will be relieved of responsibility for carrying out the controls laid down in Article 51 paragraph 1 of Directive 2001/83/EC and in Article 55 paragraph 1 of Directive 2001/82/EC provided that these controls have been carried out in the United States, the product was manufactured in the United States and that each batch/lot is accompanied by a batch certificate (in alignment with the WHO certification scheme on the quality of medicinal products) issued by the manufacturer certifying that the product complies with requirements of the marketing authorization and signed by the person responsible for releasing the batch/lot.

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)
4. EMA: Questions and answers: Good manufacturing practice

Author:

Sabine Paris, PhD
Maas & Peither AG – GMP Publishing
Schopfheim, Germany
E-Mail: sabine.paris@gmp-publishing.com

Next week in Part 2 of the article you will get the answers to the following questions:

- What does territorial application mean?
- How do the authorities profit from the MRA?
- How does the pharmaceutical industry profit from the MRA?
- Who can apply for an MRA certificate (= certificate of GMP compliance) for a manufacturing facility in the EU or the USA?
- Where do you apply for an MRA certificate for a US manufacturing facility?
- Do we need to audit contract manufacturers or manufacturers of active pharmaceutical ingredients in the USA in the future?
- Will the FDA also issue manufacturing authorisations and GMP certificates?

