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European Federation of Pharmaceutical Industries and Associations

Position paper: Considerations on Good Manufacturing Practice certificates for US manufacturing sites

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Executive Summary

Some national competent authorities (NCA) in the EU/EEA and in 3rd countries may request pharmaceutical companies to provide Good Manufacturing Practice (GMP) certificates for the manufacturing sites in their supply chain. This is problematic for manufacturing sites located in the United States of America (USA), because the US Food and Drug Administration (FDA) does not issue GMP certificates following its inspections of pharmaceutical manufacturing facilities. This paper sets out proposals of the research-based industry to address this challenge:

1. It is recommended that NCAs appreciate that GMP certificates cannot be expected for manufacturing sites located in the USA;
2. We promote following the solutions available in Europe (EU/EEA) for marketed products through a Dec-2019 EMA/CMDh Q&A document and for investigational products through Qualified Person (QP) declarations;
3. EFPIA suggests NCAs outside EU/EEA to apply the EMA/CMDh approach supporting alternative documentation as demonstration of appropriate GMP compliance for marketed products;
4. EFPIA further recommends that Declarations of GMP by responsible persons acting on behalf of the sponsor for sites manufacturing investigational medicinal products are accepted by NCAs outside EU/EEA.

Situation/Challenges

The US Food and Drug Administration (FDA) does not issue Good Manufacturing Practice (GMP) certificates following its inspections of pharmaceutical manufacturing facilities.

Further, although FDA has the right to inspect any establishment in which drugs are manufactured, packed, or held, it does not have an obligation to do so and in practice FDA inspections of investigational medicinal product (IMP) manufacturing sites are very rare.

Several national competent authorities (NCA) outside the EU/EEA have relied on EU/EEA issued GMP certificates to validate applications for US based manufacturing facilities. Consequently, EFPIA member companies have been requested to provide copies of GMP certificates for US-based manufacturing facilities used to supply medicinal or investigational products to their country.

However, since the full implementation of the EU-US Mutual Recognition Agreement (MRA) in 2019, EU NCA inspections of US sites have reduced. Even prior to this, EU GMP certificates were not available for US IMP sites because the EU's risk-based approach puts the onus on an EU Qualified Person (QP) to provide a "DECLARATION OF EQUIVALENCE TO EU GMP FOR INVESTIGATIONAL MEDICINAL

PRODUCTS MANUFACTURED IN THIRD COUNTRIES"[1], so EU NCAs do not routinely inspect overseas IMP facilities and do not expect them to have a GMP certificate.

For marketed products, this issue was recognized by the European Medicines Agency (EMA) and the Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) and addressed in a December 2019 revision of "Q&A on impact of EU-USA Mutual Recognition Agreement on marketing authorisation applications and relevant variations"[2], from which part of A1 is reproduced below.

As the US FDA does not issue GMP certificates, applicants should submit all available documents as proof of GMP compliance for US manufacturing sites that have been previously inspected by US FDA, as follows:

- The 90-day facility classification decisional letter issued by FDA;
- A screenshot from the FDA Inspection Classification Database;
- The most recent relevant FDA Establishment Inspection Report;
- For products that are authorised by US FDA, a Certificate of Pharmaceutical Products (CPP) should be submitted if the manufacturing site is also registered in the US dossier. These export certificates are valid for 2 years once issued and conform to the format recommended by the World Health Organization's (WHO), Certificate of Pharmaceutical Product scheme. The applicant should ensure that the submitted CPP refers to GMP compliance of the manufacturing site(s) referenced in the EU application.

EFPIA appreciates the efforts made by EMA/CMDh to address the issue of GMP certificates not being available for all US manufacturing sites for marketed products in the December 2019 Q&A document.[2] We note that the current wording points to the submission of 'all available documents', but understand that any one of the four documents listed above is sufficient. Requests for a Certificate of Pharmaceutical Products (CPP) add to timelines and cost and only cover sites listed in the US dossier. We would value the EMA Inspectors Working Group taking opportunities to communicate in PIC/S, ICMRA, ICH and other forums the approach they have defined and to encourage equivalent approaches by non-EU/EEA NCAs.

Summary

EFPIA supports mutual reliance initiatives by NCAs globally. We propose that:

1. NCAs appreciate that GMP certificates cannot be expected for manufacturing sites located in the USA;
2. NCAs (outside EU/EEA) apply the approach allowing for alternative documentation as demonstration of appropriate GMP compliance for marketed products from US sits, as described in EMAs 2019 Q&As which has proven to facilitate the issues of the missing GMP declaration for US sites.
3. For IMPs, NCAs outside EU/EEA to accept Declarations of GMP by responsible persons acting on behalf of the sponsor for US sites manufacturing investigational medicinal products.

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[1] https://health.ec.europa.eu/system/files/2016-11/2013-12_qp_template_imp_0.pdf
[2] https://www.ema.europa.eu/en/documents/other/questions-answers-impact-european-union-united-states-mutual-recognition-agreement-marketing_en.pdf