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GMP mutual recognition – what's the outlook for veterinary medicines?

AUTHOR

David Parry, Technical Director, Cyton Biosciences Ltd, Bristol, UK.

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ABSTRACT

The mutual recognition agreement (MRA) for good manufacturing practice (GMP) production of veterinary medicines in the EU and the US is expected soon to become fully operational. This article explores the potential for manufacturing facilities to benefit from changes to inspection regimes and looks at the steps remaining before the MRA is completed.

Just like production of human medicines, animal medicines must be manufactured in accordance with good manufacturing practice (GMP) legislation. Current GMP legislation for veterinary medicines in the EU is detailed in Commission Directive 91/412/EEC, and the full guidance used by manufacturing facilities is provided in Volume 4 of "The rules governing medicinal products in the European Union", which relates to the manufacture of medicinal products for human and veterinary use.

To manufacture a veterinary medicine for the EU market, a manufacturing site must have a GMP certificate for veterinary medicinal products (VMPs), issued following an inspection by an EU national competent authority (NCA) in accordance with Directive 2001/82/EC. Similarly, manufacturers of veterinary medicines for the US market must currently undergo an FDA inspection for current GMP (cGMP) compliance as defined in Code of Federal Regulations, Title 21 Parts 210 and 211.

Existing mutual recognition of GMP

MRAs have been in place for up to 20 years between the EU and the authorities responsible for GMP of veterinary medicines in Australia, New Zealand, Canada, Israel and Switzerland. An agreement between the EU and the US, however, has taken longer to achieve. The MRA for GMP between the US and EU has been fully operational for human medicines since July 2019, but transitory provisions remain in place for a similar agreement on veterinary medicines.

If a manufacturing site outside the EU has been inspected by a local agency that is mutually recognised by the EU, GMP inspection by an EU agency is not necessary. MRAs for GMP allow the authorities in the participating countries to avoid duplication of the inspection of facilities in each other's territories, thus increasing efficiency for both the inspecting agencies and the facilities themselves. As a result of an operational EU/US MRA, GMP inspectors from the EU and FDA will be able to focus their resources on other areas.

Under current rules, a veterinary GMP manufacturing facility in Australia has a distinct advantage over an equivalent facility in the US, because the Australian GMP certification is mutually recognised in the EU. Companies developing a veterinary product for the EU market may therefore select the Australian facility over an equivalent US facility on this basis. For a country having an MRA in place with the EU, as well as inspection of GMP by the local agency being recognised by the EU, batch testing conducted locally will also be recognised. As the name suggests, MRAs are reciprocal arrangements, and thus EU manufacturers inspected by their local agencies for veterinary GMP, are in a position to manufacture veterinary medicines for Australia, New Zealand, Canada, Israel and Switzerland without being subject to inspections by the GMP agencies of these countries.

Agencies for veterinary GMP

In the US, the FDA's Center for Veterinary Medicine (CVM) oversees facilities manufacturing animal medicines for the US market. In the EU, each country has its own agency responsible for GMP inspections within their territory. In some cases, a single agency will be responsible for inspecting facilities manufacturing both human and veterinary medicines. However, in many cases there are separate agencies to oversee manufacture of human and veterinary medicines. For example, in France, GMP inspections for human medicines are conducted by L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) whereas GMP inspections for veterinary medicines are conducted by L'Agence nationale du médicament vétérinaire (ANMV).

In order to conclude a fully operational MRA for veterinary medicines, the CVM is auditing the inspecting agencies of all the EU member states in turn. An assessment process is then completed for the member states that have been audited. On completion of the assessment to confirm that an EU agency is competent to the standards of the US CVM, the MRA is then implemented for veterinary medicines with that agency. Likewise, the EU is conducting an assessment of the FDA capability for veterinary medicines so that the MRA can be implemented in return and US standards recognised by the EU. The EU assessment will be completed once the European Commission confirms that FDA inspections are considered equivalent to EU inspections for veterinary GMP.

Differences in EU and US requirements for batch release

GMP rules for the EU and US are actually very similar, a fact which supports the implementation of an MRA between the two territories for GMP inspections and batch certification. However, differences do exist in the details of the GMP rules and inspections. For instance, EU GMP inspectors

will review a pharmaceutical quality system (PQS) in order to gain oversight of quality metrics data such as key performance indicators (KPIs) used at the manufacturing facility. In contrast the FDA inspectors' approach requires statistical analysis of quality metrics data submitted electronically to the FDA.

The role of the EU qualified person (QP) is a key area of difference between EU and US GMP for veterinary medicines. A QP certifies GMP compliance for each batch of a veterinary medicine. When a veterinary medicine is manufactured or packaged in the US and imported into the EU, in the absence of an MRA, every batch is subject to additional testing before it can be released onto the EU market. Drug substance suppliers for EU veterinary medicines must also be qualified by compliance audits, performed by the QP or on behalf of the QP. It should be noted that such QP audits cannot be replaced by agency inspections, therefore US veterinary drug substance suppliers will continue to be subject to QP audits, even after full implementation of the MRA.

In the US, the certification of GMP compliance and batch release is handled differently. The quality control department of a GMP facility is responsible for review of production records, to certify batch release, in place of QP certification.

Changes to the inspection and testing regimen

As stated previously, under the current rules, a VMP manufactured in the US is subject to full batch testing once imported into the EU. The EU QP is responsible for certifying this EU batch testing as part of the batch release process. Therefore, not only does a US facility currently require a duplicate inspection by an EU agency (in addition to domestic inspections by the FDA's CVM), the veterinary medicine must also undergo EU testing once imported, duplicating the quality control that was carried out prior to export. With a fully operational MRA in place, inspection and testing steps by the EU will no longer be necessary for US manufacturers, bringing significant benefits to companies selling US-manufactured veterinary medicines in the EU. The MRA stipulates that this will apply if the required batch testing has been conducted in a US GMP facility and not elsewhere.

An EU manufacturer making veterinary medicines for the US is currently subject to GMP on-site inspections by the FDA. This can entail a significant cost to the manufacturer both financially and in regard to the time required – for accommodating the audit itself, and implementing resulting actions for the quality management system (QMS). Following the completion of the fully operational MRA for veterinary products, EU GMP manufacturers will no longer require an FDA inspection for production of US veterinary medicines. A single inspection by the local EU agency will allow a manufacturing facility to produce VMPs for both the US and EU markets. The elimination of inspections by the FDA is a significant step forward for EU manufacturers and represents a competitive advantage for EU facilities compared with those in other territories.

Current status of the MRA for veterinary medicines

At the time of writing, the European Medicines Agency (EMA) considers the MRA for veterinary medicines to be in a transition phase. The transition phase implies that assessment of the GMP inspectorates for veterinary medicines is still ongoing. The decision from the EMA on expansion of the EU-US MRA's operational scope to include veterinary medicines was scheduled for 15 July 2019 and then deferred to December 2019. No update on this schedule is currently available.

In the US, the decision to include veterinary medicines in the MRA has been confirmed by the CVM in a statement published on 13 March 2020. The statement confirms that the CVM continues to audit the GMP inspection agencies of the EU countries, and the assessment process for EU member states that have been audited so far is also ongoing. The CVM has indicated that the MRA may be implemented for a particular country after confirmation of the capability of the GMP inspection agency in that country.

The most recent high-level discussion of the veterinary MRA took place during the bilateral regulatory dialogue meeting on 18–19 June 2020 – a meeting of senior officials from the European Commission's health directorate (EC-DG SANTE), the EMA and the FDA.

Conclusion

The inclusion of veterinary medicines in the MRA between the US and EU will bring significant benefits to both regulators and manufacturers in both territories. This change will lead to greater efficiencies and recognise the similarities and strengths of the inspection agencies. EU and US manufacturing facilities for VMPs will be able to reduce the resource demands resulting from GMP inspections, since duplication of inspections at a facility should be avoided by relying on a single inspecting authority to cover both of these major markets for veterinary products. Following the recent CVM statement on progress made and continuing, the veterinary medicines industry is anticipating a rapid conclusion of the assessment process, leading finally to a fully operational MRA. ■

FURTHER READING

Information from the FDA and EMA, including a Q&A document from the EMA, are available using the following links:

- FDA: www.fda.gov/animal-veterinary/cvm-updates/fda-include-animal-drugs-eu-mutual-recognition-agreement-pharmaceutical-good-manufacturing-practice?utm_campaign=3-13-2020-EU&utm_medium=email&utm_source=Eloqua
- EMA: www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra#united-states-section
- EMA Q&A: www.ema.europa.eu/en/documents/other/questions-answers-impact-mutual-recognition-agreement-between-european-union-united-states-11-july_en.pdf