Mutual Recognition Agreements in the EU, Canada and Other Countries

By Salma Michor, PhD, RAC and Sue Diaz
Human and veterinary drugs are heavily regulated to ensure that they meet minimum requirements regarding quality and safety before being placed on the market. Historically, drug regulations were based on the same fundamental obligations of quality, safety and efficacy; however, regional differences in technical requirements have arisen over time. These differences often require time-consuming and expensive duplicate testing and inspections for international registrations.1

Mutual recognition agreements (MRAs) improve the pace of global trade by promoting acceptance of one country’s inspections and quality systems by another. MRAs have been established to:
- reduce technical barriers to trade by facilitating market access while ensuring consumer protection against poor-quality products
- grant mutual acceptance of reports, certificates, authorizations and conformity marks issued by the regulatory authorities
- exchange information concerning procedures used by the conformity assessment bodies to ensure that they comply with agreed-upon requirements
- encourage international harmonization

The MRA system requires each country or region to evaluate the other’s pharmaceutical legislation, guidance documents and regulatory systems during a transitional phase. Evaluation encompasses individual and/or joint inspections by Competent Authorities (CAs), and compliance visits. If equivalence is established during the transitional period, an MRA can be set up and the operational phase initiated.

MRAs may cover GMPs; labeling; testing; manufacturing authorizations, batch certification and release; and inspection reports. For example, if an MRA exists between the EU and a non-EEA country, imported batches manufactured in that country are no longer required to be retested by a Qualified Person in the EU before release.3

**Benefits for CAs and Industry**

The importance of MRAs to both authorities and manufacturers is manifold.

According to Article 20 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use and Article 24 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for veterinary use, CAs must ensure that any products manufactured in other countries and imported into the EU comply with EU requirements regarding manufacture, controls and GMP. Mutual recognition of GMP certificates eliminates redundant inspections by CAs. Similarly, MRAs benefit manufacturers by allowing them to rely on batch records and release carried out in other countries without having to repeat quality control testing and batch release in the EU.

**Status of MRAs Between the EU and Other Countries**

**Australia**

The MRA between Australia and the EU is fully operational and took effect 1 January 1999 for human medicinal products and 1 June 2001 for veterinary medicinal products.4 This agreement covers the exchange of certificates of GMP compliance for manufacturers and batch certificates. In addition, a two-way alert system based on the European system is in operation.

**Canada**

The EU MRA with Canada is operational, except for preapproval inspections and medicinal products derived from blood or blood plasma.

The MRA covers both human and veterinary medicinal products (excluding immunological products) and is based on the exchange of certificates of GMP compliance for manufacturers and batch certificates.5 Further, a two-way alert system is in operation. Preapproval inspections are not covered by the agreement and neither are stable medicinal products derived from human blood or human plasma.

More information about the scope of this MRA is set out below.

**Japan**

The MRA with Japan became operational on 29 May 2004, with limited scope.

The MRA with Japan applies to human medicinal products only.6 After some preparatory work and inspections, the GMP Annex became operational on 29 May 2004, and includes:

- chemical pharmaceuticals
- homeopathic medicinal products, as long as they are treated as drugs and subject to GMP requirements in Japan
- vitamins, minerals and herbal medicines considered medicinal products by both parties

**Not Covered by the GMP Annex**

- medicinal gases, in vitro diagnostics, blood, plasma and any unstable medicinal products derived from human blood or plasma, as these are neither treated as medicinal products nor subject to GMP requirements by the two parties
- biological pharmaceuticals, including immunologicals and stable medicinal products derived from human blood or plasma, and sterile medicinal products; these may be added at a later date when GMP equivalence has been confirmed
medicinal products for clinical trials and active pharmaceutical ingredients; these may be covered in the future when GMP equivalence has been confirmed

November 2001 but no decision on a formal extension was taken.9

The two-way alert system remains in operation.

**Status of MRAs Between Canada and Other Countries**

Canada is a participant in several MRAs covering medicinal products, GMPs and compliance programs.10 These MRAs do not include harmonization of standards and drug regulations, but do provide opportunities to develop closer and stronger relationships with other regulatory authorities. The MRAs apply to products regulated under the Food and Drugs Act and Food and Drug Regulations, including biologicals, pharmaceuticals and radiopharmaceuticals, and cover drugs and medicinal products manufactured in both countries to which GMP requirements apply.

Canada has MRAs with the EU/EEA, Australia and Switzerland (see Table 1). In addition, a trilateral cooperation between Canada, the US and Mexico covers regulatory issues pertaining to drugs, biologics, medical devices, food safety and nutrition.11
Table 1 illustrates the products to which the MRAs with Canada apply.

Although natural health products are considered drugs in Canada, due to regulatory issues, at this time they are treated as a separate category in MRAs.

To smooth over the differences in the regulation of these products, regulatory amendments are being prepared in Canada to allow natural health product companies to hold an establishment license in addition to the site license required under the Canadian natural health products regulations.

Other Countries

Australia has MRAs with the EU, the US, Canada, Switzerland and Singapore. In 2004, Australia and Canada signed an MRA on conformity assessment regarding medicines and GMP inspection and certification. Australia also has an MRA on standards and conformity assessment with the European Community (EC) covering medicinal products, GMP inspection and batch certification and medical devices conformity assessment that took effect January 1999. In addition, Australia has agreements in place with Singapore (as of 2001) and Switzerland (as of 2006) covering GMP issues. There is a cooperative agreement (effective November 2007) and a free trade agreement (effective August 2006) with the US.

In the US, international collaborations are coordinated by FDA’s Harmonization and Multilateral Relations Office. This office works with various international organizations such as the World Health Organization (WHO), International Conference on Harmonisation (ICH) and International Cooperation on Harmonisation for Veterinary Products (VICH), International Cooperation on Cosmetic Regulation (ICCR) and Global Harmonization Task Force (GHTF).

Pharmaceutical Inspection Convention

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities that provide active and constructive cooperation in the field of GMP. PIC/S promotes harmonized GMP standards and quality systems in the field of medicinal products via:

- mutual recognition of inspections
- uniform inspection systems
- training of inspectors
- exchange of information
- mutual confidence

There are currently 37 participating authorities under PIC/S.

Conclusion

The MRA approach is an effective way to enhance international regulatory cooperation and maintain high standards of product safety and quality while reducing the regulatory burden for the pharmaceutical industry. MRAs are not the only forms of collaboration among regulatory agencies; most are also involved in partnerships with GHTF (medical devices), ICH (drugs), PIC/S and WHO. All these efforts help improve safety by establishing harmonized criteria while reducing waste and cost for agencies and companies alike by eliminating redundant inspections and analytical testing.

References

2. EMEA/MRA/22/03, Mutual Recognition Agreements, May 2003.
3. Ibid 1.
13. Ibid 1.

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