REGULATORY FOCUS

Quality Certificates for Small Molecule Drug Product Applications for International Regulatory Submissions

By Monika Jain, PhD

This article provides a global overview of the general requirements and issues regulatory professionals may encounter while arranging for a variety of certificates for applications for small molecule drug products to be marketed internationally in the EU, US, Canada, Australia and Japan.

Introduction

From clinical trials to marketing authorization, regulatory dossiers for small molecule drug products are incomplete without the presentation of certain regulatory certificates. Regulatory certificates are an important part of Module 1 of the electronic Common Technical Document (eCTD) submission for small molecule drug products because these certificates ensure quality and Good Manufacturing Practice (GMP) requirements are being followed.{1-5} As most drug products available in today's market are small molecule drug products manufactured using chemically manufactured active substances, regulatory certificates may include GMPs, Manufacturing and Importation Authorization (MIA) and Qualified Person (QP) declarations, among others depending on the certifying body's requirements. Accordingly, this article reviews regulatory certificates for small molecule drug products manufactured in the European Union (EU), US, Canada, Australia and Japan. Also discussed is World Health Organization (WHO) Certification.

European Union

Commonly required regulatory certificates for submission within the EU are Good Manufacturing Practices (GMPs), Manufacturing and Importation Authorization (MIA) and Qualified Person (QP) declaration.

GMP Certificate

GMP certificates are issued for manufacturing sites inside and outside the EU. Details of the GMP inspection/certificate for manufacturing sites are available via the GMP Certificate Database.

The National Competent Authority (NCA) in the EU issues a GMP certificate when the outcome of the inspection confirms good manufacturing practices have been followed in accordance with EU legislation. If inspection determines the manufacturer has not complied with GMP, a statement of non-compliance may be entered into the EudraGMDP database. For this reason, it is good practice for the regulatory department responsible for the applicant to request GMP inspection of the manufacturing sites during the early stages of drug development.

MIA Certificate

Manufacturing and Importation Authorization (MIA) certificates are issued by the National Competent Authority in the EU country in which the manufacturer operates. MIA is required by the manufacturer of medicinal products in the EU or for drugs imported from outside the EU.

MIA details the specific operations/activities permitted at the approved site, such as with aseptic preparation or sterile preparation, quality control testing or batch release. The authorization provides permission to import certain types of medicines. MIA can be obtained at the MIA Database.

QP Declaration

Qualified Person (QP) declaration is required for approval of the medicinal product. A medicinal product manufactured in the EU is released by a QP, thereby eliminating the requirement to submit a QP declaration for filling the dossier inside the EU. However, when material is imported from a third country, a QP declaration is required. The QP declaration assures the drug product meets EU requirements.

Frequently Asked Questions

EU Quality Certificates

Below are some of the frequently asked questions and issues encountered while assembling quality certificates:

Does the availability of a QP declaration mean GMP certificates are not needed?
Although QP declarations incorporate the requirement of GMP certificates, it is always advisable to submit a GMP certificate (if available) to avoid possible regulatory questions from agencies. In cases where the GMP is certified by a company or third-party audit, the QP declaration is sufficient

Can MIA and GMP certificates be substituted for each other's requirements?
MIA and GMP certificates are different kinds of documents and cannot be substituted for each other. GMP certificates guarantee good manufacturing practices have been followed in the manufacturing site, while manufacturing authorization provides the list of activities that can be performed in the manufacturing site following GMP, such as whether a manufacturing site is capable of performing sterilized operations or not. Similarly, an importation license provides the authority to import certain types of medicinal products.

Which quality certificates are required for submission of Investigational Medicinal Product Dossiers (IMPDs) in the EU?
Although the requirement of the documents varies for different drug products and clinical trials, in general, it is good practice to submit the following:

If the case product is manufactured in a country inside the EU: GMP certificate (for all the sites as mentioned in 2.1.p.3.1 section of IMPD) and MIA certificate (where activities related to manufacturing takes place).{6}

If the case product is manufactured in a country outside the EU: QP declaration is a must and if possible, supported by the GMP certificate (for all the sites as mentioned in 2.2.1.p.3.1 section of IMPD) and the MIA certificate (where activities related to manufacturing takes place).{7}

United States

The US Food and Drug Administration (FDA) conducts inspections to assess compliance with GMP requirements for manufacturing facilities engaged either in the production of medical products or facilities conducting analytical testing. Decisions regarding GMP compliance are based upon facilities inspections, sample analyses, regular updates and the compliance history of the firm. FDA can initiate various degrees of regulatory actions, impacting a manufacturer's ability to market, promote or export/import medicinal products.

FDA issues an Establishment Inspection Report (EIR) to the manufacturer with a classification. Information regarding the outcome of the inspection at the manufacturing site can be accessed at FDA GMP Inspection Reports.

Important information regarding the registered site for manufacturing can be accessed at FDA Drug Establishment Current Registration Site.

It is common practice for manufacturers inspected by FDA to provide a GMP statement detailing the date and outcome of the inspection. This statement should be on company letterhead and signed by the head of the regulatory department. This statement is accepted by some agencies around the globe as a GMP certificate.

Certificate of Pharmaceutical Product (CPP)–World Health Organization (WHO) Certification for Global Market

The WHO certification project for finished pharmaceutical products is an international, voluntary agreement to provide assurance to participating countries regarding the quality, safety and efficacy of pharmaceutical products in the international market.{8} Certificate of Pharmaceutical Product (CPP) is an administrative instrument and a confidential document enabling WHO certification project member states to request certain information from another WHO certification project member state by means of defined documents. Pharmaceutical products covered under the plan are:

- Finished pharmaceutical products intended for administration to human beings
- Pharmaceutical products intended for administration to food-producing animals
- Active Pharmaceutical Ingredients (API)

CPP provides a snapshot of the regulatory status of a pharmaceutical product and of the CPP applicant in the certifying country. It is applicable to a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary. WHO publishes the names and addresses of participating member states.

CPP assumes authorities issuing the CPP have the requisite knowledge and experience to assess the Quality, Safety and Efficacy (QSE) of the product they approve for marketing. Based on the intention of the project, a recipient authority could require a CPP when it does not undertake a full review of QSE data submitted for registration and subsequent evidence of approval in another country is required. The model CPP document can be accessed at CPP Format.

GMP declaration in the CPP provides GMP assurance for product approval in the certifying country at the stated manufacturing site(s). In addition, CPPs issued by the National Medicine Regulatory Authority (NMRA) associated with the Pharmaceutical Inspection Co-operation Scheme (PIC/s) and ICH regions (EU, Japan and US) provide evidence of GMP status. When a CPP is provided, it is not necessary to include additional GMP documents for finished products.

Regulatory professionals reviewing the CPP should consider the following points. First, the aforementioned certificates should not bear the WHO emblem or the acronym "WHO." The use of the emblem or acronym illegally creates the impression the certificate is issued or endorsed by WHO. Regulatory authorities around the globe receiving a CPP with a WHO emblem or acronym will reject the CPP and report the unauthorized use to WHO,

a step which may unnecessarily create regulatory hurdles for the manufacturer. The CPP should appear on the certifying regulatory authority's letter head or emblem.

Legalization of the CPP is not part of the WHO project and is not considered to be providing additional assurance of authenticity. Approval statuses in key reference countries are currently available as public information. Legalization is not necessary since an official governmental authority of the certifying country signs the CPP. However, it is still in practice and required by many countries to *apostille* the CPP by legal professionals and/or the embassy of the recipient country. An apostille is a form of authentication issued to documents for use in countries that participate in the Hague Convention of 1961.{9}

Canada

Health Canada ensures drug products manufactured in Canada or abroad meet high safety and quality standards prior to being marketed in Canada. Health Canada licenses and regularly inspects companies involved in manufacturing and marketing of the drug products, including processes related to packaging, testing, importing and distributing the drug products. Health Canada provides a searchable database that includes detailed "report cards" of their inspections, accessible at the Drug and Health Product Inspections Database.

Drug Establishment Licenses (DELs) and certificates of compliance are two important GMP certificates issued by Health Canada. DEL is a license issued to a person or company in Canada to conduct licensable activities in a building that has been inspected and assessed as being in compliance with the part C requirements of divisions two to four of the food and drug regulations.{10} A regular inspection is generally conducted within 12 months of the initial inspection. Dates of the next inspections depend on the risk-based approach.

There are several different inspection cycles depending on what process is being carried out. For example, fabricators, packagers/labellers and testing labs are inspected on a two-year cycle while

importers, wholesalers and distributors are inspected on a three-year cycle. For establishments performing multiple activities concurrently, the higher-risk activity determines the timeline of the inspection cycle.

For foreign sites needing to demonstrate the drug's GMP compliance, the requirements can be assessed by GMP Compliance of Foreign Sites.

The Certificate of Compliance (COC) is issued by a national regulatory authority under Mutual Recognition Agreement (MRA) attesting to the GMP compliance of a recognized building in their country. In Canada, the COC is issued by the inspectorate after successful completion of inspection.

Australia

Drug manufacturers in Australia are required to obtain a license, also known as GMP license/license to manufacture/GMP certificate, to manufacture therapeutic goods. The document includes important details, such as license or certificate number, full details of the manufacturing site, types of products manufactured, manufacturing steps authorized (licenses) or certified (for GMP certificates) and individuals responsible for quality assurance and production. These licenses must be displayed where they can be viewed by the public.

Product information is available from the Therapeutic Goods Administration (TGA) at Australian Register of Therapeutic Goods (ARTG).

Certificates of GMP compliance issued to Australian drug manufacturers expire after three years. Other certificates have an expiry period reflecting the intended re-inspection frequency based on the risk category of the products manufactured and the compliance rating determined at the close out of the inspection.

Any foreign manufacturer of medicines planning to market its products in Australia must comply with the manufacturing principles or equivalent international standards for overseas manufacturers. The process and the issuing of a document confirming compliance is known as GMP clearance. GMP clearances are required for all manufacturing steps of registered and listed medicinal products (including APIs used for the manufacture of registered products) before the products can be supplied in Australia.

Although TGA does not currently require sponsors to submit clearance applications for API(s) used in listed medicines or registered Over-the-Counter (OTC) and complementary

medicines, sponsors must ensure any manufacturing step undertaken outside of Australia is undertaken in GMP-compliant facilities. Evidence of licensing or approval of the API(s) manufacturer does not need to be submitted to TGA unless it is an intermediate product, such as premixes.

TGA has established a range of international agreements to facilitate the efficient and effective management of its regulatory compliance programs and to reduce the regulatory burden on industry, including:

- Mutual Recognition Agreements (MRAs) between Australia and other countries and enforceable under international law
- Memoranda of Understanding (MOU) arrangements between the TGA and regulatory agencies of other countries to facilitate the exchange of information
- An overseas GMP clearance can be granted by TGA to a sponsor on the basis of GMP compliance evidence by any one of the following:
  - GMP certificate issued by a country with which Australia has an MRA in relation to the relevant overseas manufacturing site
  - Compliance Verification (CV) assessment of a recent GMP inspection report of the relevant overseas manufacturing site prepared by a competent overseas regulatory agency acceptable to the TGA (e.g., MOU or PIC/s membership), together with supporting manufacturing documentation supplied by the sponsor or manufacturer
  - GMP Certificate issued by TGA following an on-site audit of the relevant overseas manufacturing site

All GMP clearances relating to overseas manufacturers are provided for a specified period and have an expiration date. The marketing authorization holder is required to periodically renew its clearances for overseas manufacturing sites as long as they continue to use that manufacturer. This permits TGA to review manufacturing and quality controls compliance with relevant international GMP standards. Any compliance-related issues recorded with TGA can be tracked at Regulatory Compliance Issues.

Japan

To comply with international standards of drug product quality, safety and efficacy, formal approval is required for individual formulations of drug products marketed in Japan. Japan's Pharmaceutical and Medical Device Agency (PMDA) inspects manufacturing sites in Japan or foreign manufacturing sites (upon request). PMDA reports inspection results to the Ministry of Health, Labour and Welfare (MHLW), using GMP compliance inspection result notification and evaluation ranking.

PMDA's evaluation ranking criteria, include:

- A (compliance) - manufacturing is performed properly.
- B (slightly defective) - there is little effect on drug quality, but improvement is necessary for complete compliance with control regulations.
- C (moderately defective) - effect on drug quality cannot be ruled out and improvement is necessary for compliance with control regulations.
- D (seriously defective) - clear violation of control regulations.

PMDA issues a copy of the GMP compliance inspection result notification to the marketing approval holder applying for the inspection. A copy of the report is sent to the foreign manufacturer located where the on-site inspection was conducted. In the case of document inspection only, a copy of the GMP compliance inspection result report is not issued.

The Japanese regulatory agency recognizes the GMP status of the foreign manufacturing sites where Japan has Mutual Recognition Agreements (MRAs), Memorandums of Understanding (MOU) or where WHO CPP certificates are in place. Japan is member of Pharmaceutical Inspection Co-operation Scheme (PIC/s) and accepts inspection results conducted by this organization. The list of accredited foreign manufacturers is available in Japanese and can be accessed at Accredited Foreign Manufacturer. GMP compliance review and license accreditation renewal are required every five years.

Conclusion

Quality certificates are an essential part of Module 1 requirements and their submissions to regulatory agencies should be planned well in advance to achieve successful regulatory submissions. Care should be taken to check the expiration date and the content of the certificates for their applicability on a case-by-case basis.

Regulatory databases are regularly updated (albeit not immediately) by the agencies to provide current information. Quality and regulatory departments of the manufacturing sites involved should be consulted before submitting certificates to the agencies in order to verify the accuracy of the certificates.

While this article aims to provide basic information for quality certificates commonly required in well-established regulatory global markets, readers are advised to carefully consider individual country requirements, regulations and various options available to fulfil the requirement of quality certificates.

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Suggested Reading

Australia
Australian Register of Therapeutic Goods (ARTG)
Australia-Regulatory Compliance Issues
Canada
Drug and Health Product Inspections Database
GMP Compliance of Foreign Sites
Europe
EU-GMP Certificate Database
EU MIA Database
GMP Frequently Asked Questions
Q&As of QP Declaration
Template of QP Declaration
Japan
Japan-Accredited Foreign Manufacturers List
United States
Drug Establishments Current Registration Site
Inspection Classification Database Search
Q&As Related to FDA cGMPs
World Health Organization
Essential Medicines and Health Products Contact List
Model Certificate of a Pharmaceutical Product

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Cite as: Jain, M. "Quality Certificates for Small Molecule Drug Product Applications for International Regulatory Submissions." *Regulatory Focus*. May 2017. Regulatory Affairs Professionals Society.

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