How has the evolution of the global pharmaceutical market affected the use of WHO Certificates of Pharmaceutical Product (CPP)?

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Abstract

This article outlines the history of the Certificate of Pharmaceutical Product (CPP) scheme and the issues that are developing, particularly with regard to the growing complexity of regulations and supply chains. It also highlights the World Health Organisation (WHO) Q&A document which explains the rational use of the scheme. Also discussed are future possible developments and proposals on how CPPs can accelerate access to medicines, whereas when used incorrectly, they can become a barrier to registration of a medicinal product.

The WHO certification scheme[1] and the CPP are widely accepted and used to facilitate registration of product licences in many emerging countries (including Brazil, Russia, India, China, Mexico), and also to support variations and renewal of licences. The CPP provides assurance that a pharmaceutical product has been reviewed and approved for quality, safety and efficacy by an authority which is a member of the scheme.

The history of the scheme dates back to 1963, when it was recognised that there was a need for a means of ensuring that exported drugs complied with drug control requirements equal to those applied to domestic use products. In 1969, the World Health Assembly adopted "GMP [good manufacturing practice] as recommended by WHO", which comprised internationally recognised and respected standards. Since then the scheme has been updated several times, with the current version initiated in 1992 and adopted in 1997, when the CPP was introduced to replace Free Sales Certificates.

One of the many advantages of the scheme is standardisation of certification, as prior to its introduction there was great variation in both content and format in certificates available from issuing authorities. Another advantage is that the documents are officially produced and signed by the issuing authority and if there is any doubt about their authenticity, a recipient regulatory authority can request a copy directly. In theory, this should remove the requirement for legalisation of these documents (by Apostille or Embassy), as this adds no value and delays access to medicines by adding weeks to the process. However, legalisation is often still requested.

There are several requirements for issuing CPPs. The issuing authority must have:

- An effective licensing system for products, manufacturers and distributors
- A technically competent pharmaceutical inspectorate to assess GMP implementation and apply GMP standards similar to those recommended by WHO
- An effective post-marketing quality surveillance system
- Sufficient administrative capacity to issue the required certificates and to institute inquiries in the case of complaint.

CPPs form a critical part of the regulatory requirements in many countries, and they are needed for many types of submission. The main use is to support new product applications and line extensions, but they are also required to support lifecycle maintenance, such as renewals, shelf life extensions, prescribing information updates, manufacturing site changes, etc. They are also used to support tenders, which can form a large proportion of the business in some markets. In some countries, such as Taiwan, there are options on whether to submit a CPP to support a marketing authorisation application (MAA), but the alternative is to run a local clinical programme.

What is the purpose of the CPP?

The European Medicines Agency (EMA) gave the following definition of a Certificate of Medical Product (CMP) – which is the EMA equivalent of a CPP – in their report[2] in June 2011: "A CMP is a certificate issued for a medicinal product by the authority granting the marketing authorisation. The purpose of these certificates is to certify the marketing authorisation status of the medicinal product and that the medicinal product is produced using acceptable Good Manufacturing Practice (GMP) standards."

The FDA defines a CPP in its presentation on "Human Drug Exports Compliance" as follows: "The Certificate of Pharmaceutical Product conforms to the format established by the World Health Organisation (WHO) and is intended for use by the importing country when considering whether to license the product for sale in that country."

In essence, a CPP is a snapshot of the product licence of the issuing authority, and it includes the following product information:

- Product name
- Registration number
- Approval date
- Licence holder (name and status)
- Formulation (qualitative and quantitative)
- Manufacturing site
- GMP status
- Registered product information.

All the information contained in the CPP is confirmed by the issuing authority and refers to the product registered in that country. The CPP provides confirmation that a full review of quality, safety and efficacy has been carried out. There may be differences between the recipient and issuing country's product (eg, packing site, shelf life etc.). However there should be sufficient justification in the regulatory dossier to explain the reason for this.

In addition to the above information, the majority of CPPs also confirm whether the product is actually for sale in the issuing country. However, this is not always the case (eg, Sweden), and this can cause problems in some countries such as the Philippines and Egypt where the "on sale" statement is a requirement for CPPs. Although the WHO CPP format includes information on marketing status (if the product is actually on the market of the exporting country), the scheme also has a provision where the issuing authority can indicate why the product may not be marketed. In circumstances where the product is not actually on the market, the issuing authority can indicate that fact in the certificate. The presence on the market of the product depends on many other factors, and the main purpose of the CPP is to confirm the registration status in the issuing

country. Another factor to consider is that in Europe, the "Sunset Clause" (Article 24 (4, 5 and 6) of Directive 2001/83/EC as amended states in 24(4):[3] "Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid."

The changing face of the global pharmaceutical market

Since 1969, and in particular during the 1990s and 2000s, the economic and consequently the regulatory environments in many of the "emerging" nations have changed dramatically, influenced by global initiatives such as ICH, local regional initiatives such as ASEAN and by economic and social development. As countries' economies have developed, so have the public health expectations of governments and the publics they serve. The consequence of this is that the regulatory environments in many more advanced markets (eg, China, Korea, Taiwan, Brazil, Mexico and Saudi Arabia) have become more complex with increased data and assessment expectations. The result is an increase in data required and an expectation that a full assessment will be carried out. However, there is still a requirement from many authorities for a CPP at the time of submission, which delays product submission, product assessment and ultimately patient access to innovative medicinal products. For example, if an EMA CPP is required for submission, there can be a delay of 18 months between submission in Europe and submission in the requesting country due to the time for the EMA review. However, if the submission could take place prior to CPP availability, and then the CPP provided immediately prior to approval, the new medicine could be available more quickly to the population. If a full review is being carried out, the CPP (if required at all) should be acceptable at the end of the process to confirm that the product has also been approved by another competent authority.

In the past, the pharmaceutical market was a very different place, and manufacturing (or at least packing and release) often took place in the same country as the "exporting" company. Today, supply chains are more complex, with multiple sourcing of active pharmaceutical ingredient (API), split manufacturing, and remote release sites. This makes the "country of origin" much more difficult to define. Many authorities require the CPP to be provided from the country of origin of the drug product. The definition of the country of origin is often classed as the manufacturing site of the finished product but could also be the release site, packing site or company headquarters. Although the scheme was set up assuming that the certifying country was also the country where finished product manufacturing takes place, there is scope within the scheme for CPPs to be issued by other authorities that can provide independent assurance of the GMP compliance status.

Due to complex modern sourcing routes and other factors such as different regulatory procedures, the approval in the country where finished product manufacturing takes place may be later than in other countries. It could also be the case that a licence may not be applied for and thus no approval would be available at all for the manufacturing country. In this case, to speed patient access, it would be beneficial to accept a CPP from the earlier approving country, so long as GMP was confirmed. Implementation and compliance with GMP ensures quality of product, irrespective of source.

As manufacturing is often outsourced and the capacity of emerging countries to manufacture pharmaceuticals is increasing at great speed, there is a growing demand for CPPs to be issued by countries such as India and China. This is also complicated by the issuance of certificates by regional authorities which are not in the WHO CPP format. As described above, the WHO lists the requirements for an authority to issue a CPP, but this is self-regulated and not enforced by the WHO. This also leads to the situation when an authority that relies on a CPP for review also issues CPPs.

The scheme allows for CPPs to be issued by countries even if manufacturing occurs outside the issuing country, so long as the authority has either inspected the site or has accepted the inspection of another authority to confirm GMP. However, some issuing authorities will not confirm GMP if the product is not actually manufactured in that country. For example, the US FDA will not issue a CPP if the product is not exported directly from the US to the recipient country. The FDA offers three types of "export certificates":

- Certificate to Foreign Government – for the export of products that can be legally marketed in the US
- Certificate of Exportability – for the export of drug products that cannot be legally marketed in the US but meet the requirements of Sections 801(e) or 802 of the Act and may be legally exported
- Certificate of Pharmaceutical Product.

The FDA's interpretation of the WHO scheme is based on the historical view of the certificate as an export certificate, hence the requirement that the finished product should be directly exported to the recipient country in order for a certificate to be issued. This can cause delays in products reaching patients, particularly in emerging countries. If the FDA is the first authority to approve a product, there is a "pilot scheme" which allows for a CPP to be issued even if the product is not manufactured in, or exported from, the US. However, as soon as the product is approved in another country, the pilot scheme CPP can no longer be obtained.

As the requirements from the recipient authorities and the restrictions from the issuing authorities increase, it is more difficult to provide a CPP which is suitable for use. This leads to market access issues, either due to delays in approvals or inability to renew a licence. For example, if the recipient authority demands country-of-origin CPP and the product is manufactured in the US but packed in another country, it may not possible to obtain a CPP. This could result in loss of a licence.

IFPMA CPP Network

The IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) CPP Network is a group of representatives from member companies that work with the WHO and issuing and recipient authorities where possible to encourage rational use of CPPs for the benefit of patients, regulatory authorities and industry. Some of the main challenges are as follows:

- Resource constraints in issuing authorities leading to extended timelines
- Requirement of a CPP from country of origin
- Non-confirmation of GMP on CPPs by some authorities
- CPPs issued by authorities not complying with the WHO scheme
- Counterfeit certificates
- Requirement for legalisation of CPPs
- Requirement for a CPP at the time of submission rather than just prior to approval
- Interpretation of CPP as an "export certificate".

The term "export certificate" is misleading, as the use of a CPP as a regulatory document is not to support exports but to facilitate review of regulatory dossiers and approval of new medicines. While the scheme has not been amended since its introduction in 1997, the global pharmaceutical market has changed dramatically. This (and other issues with CPPs) has been recognised by the WHO, and the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO certification scheme on the "Quality of Pharmaceutical Products Moving in International Commerce" should be reviewed in line with changing practices and rapid globalisation of the pharmaceutical

manufacturing sector, regulatory environment and procurement systems. However, this is a long-term goal and will need to be approved by the World Health Assembly. As an interim measure, a question and answer document[4] was prepared on the rational use of the scheme. This document gives details on the issuance and use of CPPs and is available on the WHO website (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/qas_certif_scheme_2011.pdf).

One recommendation of the document relates to the issues with country-of-origin CPPs and explains why this is not relevant to the issuance of the CPP. In addition it explains that it is not necessary for a product to be exported from the certifying country and that the GMP declaration on the CPP refers to assurance of GMP for the product approved in the certifying country at all addresses listed on the CPP, even if the manufacturing site is in a different country than the issuing authority.

A further recommendation is the acceptance of a regulatory submission without a CPP with the option of a CPP to be provided prior to the approval. This would enable the review process to begin sooner to accelerate access to medicines. There are other alternative options which can verify approval of a product, such as:

- Approval information on authority websites (eg, US FDA, Japan PMDA, Australia TGA, etc)
- EU CHMP Positive Scientific Opinion
- European Public Assessment Report (EPAR)
- European Commission (EC) Decision
- Approved product information on competent authority websites
- Copy of National Marketing Authorisation
- Copies of corresponding pages in national compendia.

For products developed for disease areas that are not prevalent in Europe but are widespread in some emerging markets, a process exists whereby a product can be reviewed by the EMA up to the point of positive scientific opinion without proceeding to EC decision. Article 58[5] was introduced for these products, which allows for a CPP to be issued after the positive scientific opinion, which is earlier than CPPs are usually available.

Looking to the future – electronic solutions

As technology advances and websites improve, it is envisaged that CPPs may become available electronically directly from an authority website (eg, as GMP certificates are beginning to be available via EudraGMP – see below for more information). This would benefit the environment by reducing the use of paper and transport, and would reduce the opportunity for CPPs to be counterfeited or adulterated.

The EMA already utilises an electronic database containing information on GMP inspections which is available for health authorities within the EU. Access may be extended to more worldwide health authorities in the future. EudraGMP is the name for the Community database on manufacturing and import authorisations and GMP certificates. The EMA launched the first release in April 2007 and future releases will include planning of inspections in countries outside the EU and alerts for quality defects, and it is expected to also include information on wholesale distributors as a result of new Community legislation on anti-falsification.

Limited public access to EudraGMP, with information from only some EU national competent authorities (NCAs), has been available since July 2009 for manufacturing and importation authorisations and GMP certificates, with the exception of information of a commercially and/or personally confidential nature. The current version of EudraGMP provides access to the general public for all EU NCAs (as of February 2011).

EudraGMP greatly improves the sharing of information and coordination of action in the area of authorisations and GMP certificates between national competent authorities by eliminating duplication of work and the administrative paper exchange between NCAs. It also provides a future platform for facilitating collaboration with international regulatory partners.

Authorisation and certificate formats, together with relevant procedures, are harmonised and published in the "Compilation of Community Procedures".[6]

Information in the EudraGMP database is continually updated and in time will include information on an estimated 10,000 manufacturers and importers in the EEA. Each year, more than 3,000 new GMP certificates will need to be entered into the database.

The European legislation does not require mandatory routine GMP inspections for active substance manufacturers (see "Questions and Answers"[7] section "EU GMP Guide Part II: Basic requirements for active substances used as starting materials"). Therefore, the absence of a GMP certificate for a manufacturer of active substances in EudraGMP does not automatically mean that the manufacturer does not comply with GMP. The long-term aim of EudraGMP is collaboration between the EU and other countries to avoid duplication of inspections.

Conclusion

The CPP is a critical document which forms part of the regulatory requirements laid down in the legislation of many countries. It is a highly regarded document and is essential in the approval of medicines and the maintenance of product licences. The development of the global pharmaceutical market and increasing complexity of requirements are contributing to challenges in providing the CPP as required and in a timely manner. It is hoped that the WHO Question and Answer document[2] enables clarification on some of these issues, and will lead to more rational use of the document.

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