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Modernization of the Certificate of Pharmaceutical Product (CPP) Process: Facts and Vision

Intention and goal of this article

A number of regulatory agencies require or allow for the electronic submission of a dossier or some defined sections for the assessment of a pharmaceutical product's quality, safety and efficacy. In many cases, these are the same health authorities that issue Certificates of Pharmaceutical Product (CPP) for other countries that require or base their regulatory approval on the initial evaluation conducted by the CPP-issuing authority. Additionally, as more CPP-dependent countries start to implement electronic submissions, more dossiers and CPPs are able to be submitted electronically.

The purpose of this paper is to review the current use of CPPs and to detail some possible prerequisites for implementing an electronic version of the CPP, known as an e-CPP. The term used for eCPP is used quite loosely as it could mean that there is an electronic component to the processing of a request or for its delivery. A fully electronic CPP program should have the capability to be securely performed electronically from the request to the delivery to the requestor and the agency accessing the CPP via an electronic means (email, web link, or portal).

Current use of CPPs

The WHO Certification Scheme, implemented in 1997, regulates CPPs.[1] The CPP is a document issued by a health authority by the request of a product owner/ sponsor to support submission of a pharmaceutical product to another health authority. The CPP was introduced as a tool to facilitate the regulatory review and to essentially replace a full dossier evaluation of the quality, safety and efficacy (QSE) in the CPP-requesting country. The CPP confirms: (1) the regulatory authority approval was based on a full evaluation of the product's (QSE); (2) the product is manufactured under GMP conditions; and (3) the product is marketed in the CPP-issuing country. The well-defined quality criteria of the CPP lead to its worldwide acceptance.

In many countries, the CPP is a mandatory component of the regulatory dossier as it summarizes all relevant data regarding the pharmaceutical product. It is required for new product submissions, certain variations, renewals and tenders. Ideally, if a CPP is required, it should replace all other related documents (e.g., GMP certificates, manufacturing licenses, extracts of Chamber of Commerce, notarized copies of approval letters, etc.), full documentation and further legalization should not be required.

[1] http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/

In practice, CPP use has changed since the implementation of the WHO Certification Scheme in 1997 and several countries have enacted laws mandating additional documentation requirements. Therefore, many CPP-dependent health authorities do not rely on the approval from the CPP-issuing country alone. They require full dossiers and other documentation for their national assessment. Additionally, legalization by the Apostille or embassy is often required, which is beyond the international rules for the exchange of certificates and documents as it does not provide any enhanced evidence of authenticity. There are only a few countries that do not require legalization, usually in cases where the CPP strictly follows the WHO template or the CPP is issued in the 'country of origin', which are referred to in the sections below.

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Q&A document, provides details in responses A3 and A5 regarding how the Scheme should operate. In response A6, it states that, "It is a voluntary agreement devised to enable countries with limited medicine regulatory capacity [to] obtain partial assurance from exporting countries concerning the quality, safety and efficacy of the pharmaceutical product they plan to import."[2]

Impact on submission planning

It is well-established that CPPs are indispensable for the majority of regulatory submissions and have a direct impact on the submission planning. The availability of CPPs is dependent upon the selection of the CPP-issuing health authority along with any of the CPP-requesting country's local requirements. CPPs issued from the 'country of origin' or the 'source country' could have varying timelines dependent upon local approval. An initial approval in a Tier 1 country is generally a prerequisite for the submission of a product application in a CPP-requesting country (Tier 2-4). The processing time for CPPs can range from a few weeks to several months, depending upon the health authority. Ultimately, patients' access to new medicines is the real impact of this delay.

Product owners/sponsors should take the following aspects into consideration when planning a product submission:

1. CPP applications are unique for each country

Every country has its own application procedure for CPP requests. The application procedure may start with the submission of an application form or with the payment of fees. CPP applications may be submitted electronically via email, website or paper-based. Paper-based application procedures vary considerably and can be up to 150 pages long.

[2] http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/qas_certif_scheme_2012.pdf

2. Timelines for issuing CPPs vary

Timelines for processing CPPs depend on the resources and procedures at the CPP-issuing authority. The processing times can range from two weeks to about six months.

3. Legalization adds time

Legalization is often required as an additional measure of authentication for official documents. The practice of legalization of documents falls under the rules for the international exchange of certificates and documents. All country member states of the Hague Convention Scheme receive an Apostille (a standardized stamp which substitutes the embassy legalization). Nonmembers require legalization by their embassies and can require translations of the CPP in their national language, both of which contribute to longer processing times. Some CPP-requesting countries believe that legalization protects them from receiving counterfeit documents. However, even signatures and stamps used in the legalization process may not be free from counterfeit.

4. Differing interpretations of 'country of origin'

The definition of 'country of origin' can vary by national legislations of requesting countries. It can be defined as: the country of first approval, country of manufacture, or the country of final release. Depending on the definition used, it may not be possible for a health authority to issue a CPP. For example, in cases where the 'country of manufacture' is defined as the 'country of origin', the health authority will only issue a CPP if the product is approved within the country. Additionally, in order to ensure that future product imports are not disrupted, a CPP-requesting country that requires a CPP from the Certificate of Origin (CoO)[3] should have the same authority issue both the CPP and CoO.

5. Marketing Status in the Country of Origin

A requirement for a marketing statement to be included in the CPP from the country of origin contributes to additional delays to patients' access to new medicines because this does not allow for global simultaneous dossier submissions in all intended countries. As a result, global submission strategy development includes categorizing countries to certain groups or tiers according to their CPP requirements in order to plan the most efficient sequence of submissions. An additional obstacle in registering products in CPP-dependent countries occurs when there is a requirement for the inclusion of a marketing statement from the country of origin. The issue becomes more complicated when the product has a relatively low disease burden in the importing country, and the product is not marketed in the country of origin. Other CPP-issuing countries would need to be identified, which could require waiting for regulatory approvals, contributing to delays in market entries of new pharmaceutical products, especially in developing countries. The marketing status of new

[3] Certificate of origin is an explicit confirmation of the origin of commercial goods required in international trade. Basis for the determination of the origin in the sense of international trade regulations is the customs law of the European Union. This defines that a product has its origin in a country where the complete or the biggest part of manufacture has taken place. The certificate is completed and stamped by the local Chamber of Commerce on the front page and by the Applicant of the Certificate of Origin on the back page and is mostly part of the shipment documents

products does not impact nor change the approval already granted by the authority of the CPP-issuing country, which was based on the full evaluation of the product's (QSE).

6. GMP Compliance Statement

The GMP declaration included within the CPP confirms the GMP compliance of the manufacturing site. In the event mutual GMP recognition is not available in the country of a particular manufacturing site, the product owner/sponsor must ensure the CPP-issuing authority receives confirmation of the actual GMP status through a GMP certificate. The EU has established mutual recognition with many health authorities and captures this information in the CPP application. US FDA does not issue GMP certificates confirming GMP compliance.

7. A CPP has a limited "shelf-life"

A CPP should not be requested too far in advance of the planned submission date as some requesting countries will not accept CPPs unless they were issued within the past six to twelve months. If a submission is delayed for any reason, a newer CPP may be required even if the document states it is valid for two years from the date of issuance. Additionally, depending upon local regulations, some product information changes may require that a new CPP be submitted.

Semi-electronic CPPs, a possible interim solution

Currently, the health authorities that issue electronic CPPs (e-CPP) are Brazil (ANVISA) and the EU (EMA). Though they both state their CPP is "electronic", they are not fully electronic from start to finish as the outcome of both procedures is a paper document.

In January 2012, ANVISA published a corresponding resolution offering two types of certificates, the Drug License Certificate and the Export License Certificate. Both certificates can be requested on ANVISA's website. The Export License Certificate corresponds to the CPP and confirms the GMP status.

A CPP request made through ANVISA's website is free of charge, but it contains some manual elements. The request must include certain documentation such as: evidence of the last license renewal, GMP certificate, copy of last CPP (MS Word version), and a copy of the previous year's tax invoice as evidence of marketing. Upon completion of the request, the certificate will be made available on ANVISA's website where the applicant may retrieve it and print it out. Authentication from ANVISA's website enables the CPP to be legalized, if needed. The process for requesting an electronic CPP from ANVISA is well-established, but it includes electronic and manual elements. Manual CPPs must be requested if the product requires additional information to be included in the CPP (e.g., a different or additional address for a packaging site), however, this procedure can take up to four months to process.

The EMA's CPP process for requesting a CPP is entirely electronic and can be performed via their website, but the CPP provided to the recipient is a paper/ hard copy. All ancillary

documents that may be required are provided electronically. The request process is flexible and relatively quick, around two weeks for the standard procedure. Accelerated requests can be much faster, but it is three times the cost of the standard procedure. The CPP may be delivered to a different mailing address other than the requester's if this information is specified within the invoice.

Some questions that need to be addressed concerning an e-CPPs interim solution include:

1. Should a CPP be considered an e-CPP when the template is submitted to the authority electronically via e-mail?
    a. Or using an electronic request form on the agency's website?
    b. Or is it an electronic request form which provides the data for the CPP and is submitted to the authority's dedicated e-mail address?
2. How will the e-CPP impact the GMP certificate, which almost always accompanies a CPP?
3. How will the e-CPP be created and saved?
4. Could a bar code solution substitute additional authentication?
5. How will the CPP be provided to the requester, a paper document or a link to download from a website?
6. Would CPP-dependent countries accept an e-CPP if they could download it from an agency's website (e.g. EUDRA GMP website)?

Implementing the use of e-CPPs tends to be a highly political topic as there are legislative and administrative changes that are required that would authorize health authorities to issue and/or accept e-CPPs.

Potential steps for implementing a complete e-CPP process may include the following:

1. Definition for an e-CPP

The definition for an e-CPP should state that a fully electronic CPP program should be securely performed electronically (no paper) from the request of the document to its delivery to the requestor and the agency accessing the CPP should be via an electronic means (e.g., email, web link, or portal).

2. Legislative Prerequisites – on the CPP requesting and issuing sides

"We ask for all these documents because it's the law!" - CPP requesting country.

Currently, a number of CPP-dependent countries require the original CPP be provided with a notarized/legalized confirmation signature by law. It is a paper-based, redundant and often a lengthy process. Before moving towards use of e-CPPs in these countries, the requirement to legalize the CPP should be removed as it is a redundant authentication. One solution would be to establish a mutual agreement between the requesting and issuing countries that indicates regulatory documents, including CPPs, would no longer be subject to the international law for documents, thereby, eliminating the legalization requirement.

Another possibility would be to substitute legalization by enabling the CPP-requesting authority to recognize the authenticity of the issuing authority's e-CPP it and of itself. As long as legalization is required, use of a true *electronic* CPP is not possible. CPP-requesting countries with legalization requirements should update and modernize their medicinal product registration regulations to eliminate outdated requirements for dossiers (e.g. legalization, free sales certificates).

A stepwise approach toward implementation of e-CPPs could be to include the acceptance of a non-legalized version or a PDF version of a CPP. The CPP technically should be accepted in its true sense according to the Certification Scheme, therefore, no additional certificates or other documentation should be needed or required.

3. Administrative prerequisites

CPP-issuing health authorities have unique procedures for processing CPPs. A few countries have conditions for issuing CPPs such as, requiring the product to be manufactured and/or exported from the issuing country, or providing documentation on the entire product life cycle. These types of restrictions are outside the scope of the WHO Certification Scheme and should not be part of the CPP requesting process.

CPP issuing authorities should come to a uniform and more pragmatic request process. For example:

- a CPP's issuance should not be dependent upon where the product is manufactured or exported, only that the product is approved.
- If the CPP can be requested directly from the health authority's website, additional documentation on the product life cycle should not be required.
- GMP information should be more accessible within the health authority's systems so, it should not be required to be included with the CPP application request. GMP information is already available at the authority, but often this information is not easily available to the group responsible for issuing CPPs. Additionally, the health authority should ensure this information is available by promptly updating the database after the initial and variation approvals. Many health authorities do not update their internal systems in a timely manner, which delays the verification and issuance of a correct CPP.
- Health authorities should perform updates to the information technology infrastructure to enable automated CPP request processing, which would reduce the typical long lead times for obtaining a CPP. The system should be similar to or compatible with systems used at other health authorities for consistency and potential cost-savings. This effort would require investment of time and resources, both of which are lacking at health authorities. There are ways to simplify and potentially reduce the cost of technical updates. For example, the EU achieved cost savings by building their CPP database on top of an existing pharmacovigilance system.

- Fee schedules and processing should be more flexible in order to prevent delay in processing CPP requests. Advance payment or confirmation of payment should not be required prior to submitting the CPP request to the health authority unless the CPP requesting process is completely electronic. The requester can gain considerable time by requesting CPPs via an online system without being held up by financial or documentation issues.

Major improvements to the overall CPP process and the health authority's technology infrastructure to enable a fully functional electronic CPP procedure would require changes to the corresponding national legislation. The fully electronic CPP procedure would replace the original signed application forms as this would be all performed online. An electronic procedure could save time for registering products that would ultimately contribute to increasing patients' access to medicines.

However, the concept of electronic CPPs is very political and CPP-issuing health authorities tend to push any potential responsibility for changes to the WHO. Any negotiations or developments in relation to the current CPP process should also include WHO representation. Many CPP-issuing countries will not be able to support both paper and electronic CPP systems. Although there are advantages to implementing the use of eCPPs, there are several political challenges and legal hurdles to overcome.

4. Technical Prerequisites

Most technical prerequisites and basic infrastructure are already available. A new CPP-processing system could potentially be set up based on the EVMPD or EUDRA GMP databases. This system could cover all EU countries, which provide many of the CPPs worldwide. Another method for authentication and ensuring security in global supply chains is the use of barcodes (or a Quick Response code), which would be a good model for authenticating CPPs. The barcodes would potentially provide an extra level of authenticity that would protect from counterfeit CPPs without the need for legalization.

5. Adaptation of the CPP template for an electronic format solution

The current WHO CPP format would require adaptation in the text and in the related explanatory notes to enable changes to make an electronic version from the paper version. A potential solution would be to have open access to one part of the CPP and a closed section which would be confidential to the public. This approach is similar to what is used for the Drug Master File system. The product owner/sponsor grants access or authorization for the requesting authority to download confidential information such as the full quantitative composition.

The wording in the CPP for the term 'export' should be updated and modernized to enable consistent interpretation and use. CPPs should be issued whenever a product is approved, not only where it is manufactured or sourced. An appropriate harmonized definition would enable the proper use of CPPs according to the original intent of the Certification Scheme

where full QSE assessment in requesting countries is not required but replaced by the evidence provided in the CPP.

6. Clarification of responsibilities

Responsibilities of the product owner/sponsor and CPP-issuing authorities should be clear to ensure an efficient CPP request and procurement process is in place. As the overall CPP process evolves, inevitably there will be three essential parties involved that include: the product owner/sponsor (industry), the health authority assessing/procuring country, and the health authority of the requesting country.

In an ideal future state, a global CPP database would exist that would enable the countries that perform full QSE reviews (i.e. CPP issuing countries) to upload the CPP information in the global CPP database once the product was approved. The CPP requesting countries could then retrieve this information from the database electronically in a secure and reliable way. Even if CPP-issuing countries could agree on participating and maintaining a global CPP database, coordination of CPP-issuing countries are needed to ensure issuance from the country of origin, if required.

Conclusion

The implementation of a globally harmonized e-CPP process will require close interactions between issuing and requesting countries, industry members, and the WHO, as the developer of the CPP certification scheme and role in promoting international harmonization. Changes to administrative processes, national legalization and the creation of a secure international database would all be required to set up a proper electronic CPP process. There are great challenges to be addressed, including reaching consensus among stakeholders, achieving a high level of security, and obtaining commitment to implement the complex changes to the overall process for CPPs. Ultimately, the outcome of the improvements to the process would ensure secure documentation is shared amongst all stakeholders, which will improve product approval timelines and expedite patients access to safe and effective medicines worldwide. As more issuing agencies are looking to improve, streamline and simplify their CPP- issuing procedures and implement electronic capabilities, it is expected that further collaborative discussions on improving the system for will occur in the near future.

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Annex 1: Illustration of possible solution for the request and procurement procedure for CPPs.

Step 1: The Product license owner/sponsor submits the license application to the assessing authority.

The application contains:

- The template for future eCPPs
- The authorization for the assessing authority to procure eCPPs in future
- Submission fees cover this future service

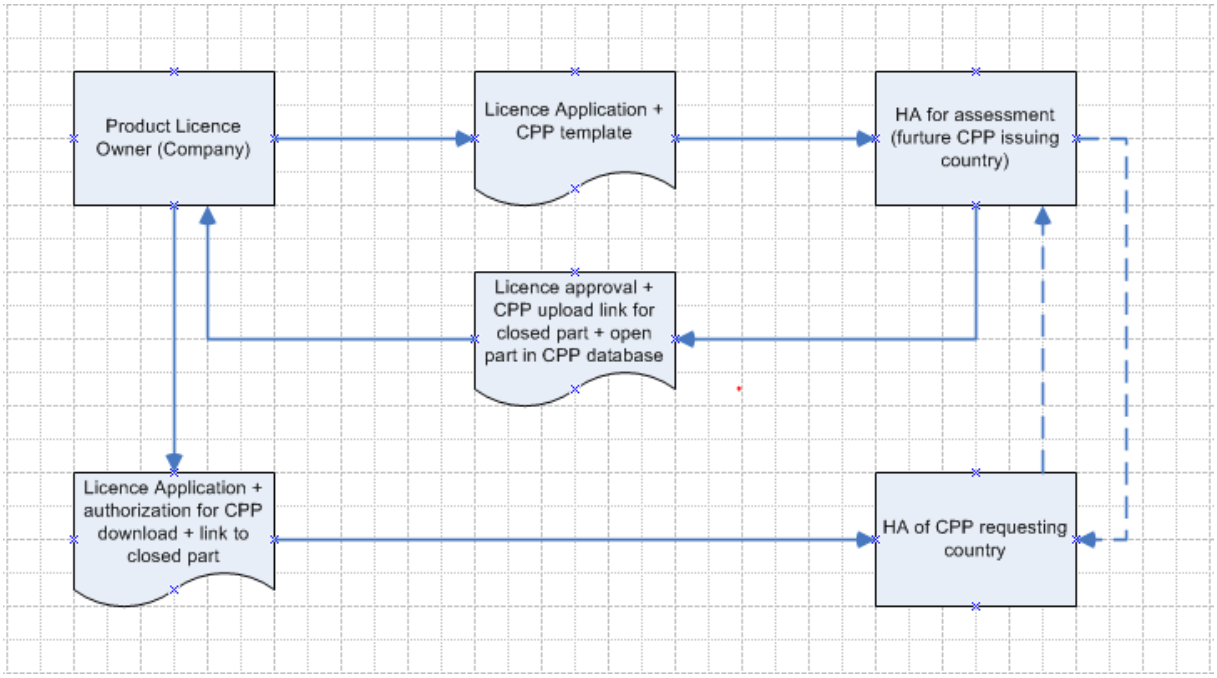
Step 2: With product approval, the assessing authority assumes the role the future eCPP procuring authority and uploads the eCPP into a secure database, split into open and closed eCPP part, as per new WHO template.

Step 3: The product license owner/sponsor prepares and submits the product license application to a CPP dependent country/authority (requesting authority)

The application contains:

- Authorization for requesting authority to download the CPP from the secure database (if the CPP is not needed with the license application), or
- Link to the CPP, which is equivalent to the CPP submission when a CPP is required for the license application

Diagram 1: Illustration of CPP request and procurement process



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