

# ***The WHO CPP Scheme in today's regulatory environment – is it time for change?***

## ***Is the fundamental purpose of providing a CPP to assist worldwide patient access to novel medicines still true today?***

### ***Background***

*The WHO Certification Scheme for Certificates of Pharmaceutical Products (CPP) is an international voluntary agreement to provide assurance for countries participating in the Scheme about the quality of pharmaceutical products moving in international commerce.*

*The Scheme was originally endorsed in 1969 as a powerful instrument to assist National Regulatory Authorities (NRAs) in sharing information and avoiding duplication. This key principle still holds true.*

*However, since 1997 the scheme has not changed despite dramatic changes in the regulatory environment within both the issuing and recipient CPP markets. In this article we examine the Scheme as it is used today and ask: is it time for change?*

*The IFPMA CPP Network has been collecting experience of how the Scheme operates and influences patient access to medicines. The key observations and recommendations of the Network are described in the following article.*

- ***Not all accredited Authorities meet the requirements or template stated in the guidelines for the Scheme when CPPs are issued***

More than 130 countries are member states of the Scheme or acknowledge and accept the Scheme. However, not all the authorities meet the requirements or adhere to the WHO template guidelines. This is problematic and often leads to confusion within the recipient countries when the requirements and template vary dependent on the issuing Health Authority (HA). This can be avoided if the template guidance is adhered to. To address this issue, we recommend that all issuing HAs use the WHO template, which will also lead to improvements in legalization requests. When the guidance is followed, many recipient HAs do not request additional certification of the CPP.

- ***The way to apply for a CPP is not harmonized with each certifying authority having its own system***

There are a variety of systems and procedures across issuing countries on how to apply for a CPP. In order to achieve more transparency of these processes and lead times, it would be helpful to work towards regional harmonization and a standard electronic submission. Harmonization of CPP applications and of payment approaches or methods should be realistic goals resulting in consistent timelines and efficient planning.

- ***Some certifying authorities have different interpretations of the CPP scheme, limiting the issuance of a CPP to products manufactured and exported from the certifying country only.***

Due to differing interpretation of the scheme across issuing HAs, when a product is not manufactured in and exported from the issuing HA country a full CPP may not be issued and sometimes no CPP will be issued at all. This can result in a substantial delay in registration and patient access within CPP dependent markets. In line with the original concept of the WHO scheme, a CPP can be issued as soon as the product is approved independent from where it is manufactured, released and exported. Adherence to this principle will then allow for products to be registered in shorter timeframes within the recipient markets, allowing patients earlier access to the medicine.

- ***The Good Manufacturing Practice (GMP) status given in the CPP is not recognized by recipient countries***

A key principle of the Scheme is to share information and avoid duplication. In this important aspect, an additional aim of the Scheme includes a statement which certifies that the respective facilities and operations conform to GMP as recommended by the WHO. The WHO clearly discourages the request of a separate GMP certificate since the GMP statement in the CPP should be acceptable.

- ***There are inconsistencies in listing the trade name of the product in the recipient country, if different from the certifying country***

Generally most of the certifying countries allow the trade name of the recipient country on the CPP. However, in some cases the trade name is not part of the formatted template application and therefore cannot be displayed within the CPP. Thus HAs can have difficulty recognizing that the CPP prepared by the issuing country is for the same product that is being registered, renewed or varied within the recipient country. The recommendation is that all issuing HAs have the option to include the trade name of the recipient country within the CPP.

- ***There is lack of understanding that the CPP reflects the approval status of the certifying country only***

For CPP dependent markets the CPP is classified as the key document for a successful submission and eventual approval of a drug product. The content of the CPP is extremely important to the recipient market – in most cases the recipient HA requires that the drug product they will receive mirrors exactly the drug product that has been approved by the certifying HA. However, complexities in modern global sourcing routes do not always allow for a direct match. When various steps of the manufacturing process differ between the recipient and issuing countries, this may result in queries and can cause unnecessary delays in approval. We recommend awareness and educational initiatives to clarify to the recipient HAs that the CPP reflects the approval status in the issuing country only with the information from which it has been approved.

- ***The CPP is no longer provided to substitute the full dossier Quality, Safety and Efficacy (QSE) review***

Today many countries require provision of the CPP in addition to carrying out their own QES review thus increasing the time for approval and patient access to novel medicines. In recent years we have seen rapid changes to the global regulatory landscape, however, in many countries the WHO Certification Scheme has remained largely unchanged for the last 20 years. More countries than ever before receive full dossiers including country specific Module 1's containing all details in the CPP from GMP certificates to worldwide Marketing Authorisation (MA) status. In order to reaffirm the original intention of the CPP i.e. to support countries with 'limited Drug Regulatory capacity', countries capable of carrying out a full QSE evaluation should be advised to review their regulatory requirements and cease to require a CPP as a mandatory element for approval, unless it is to be used for a priority review thus accelerating patient access to novel medicines.

- ***CPPs are required in the majority of reference country approval markets as a prerequisite for a regulatory submission rather than being provided just prior to approval***

CPPs are mostly required as a prerequisite for applications in the full life cycle of the drug product (from MA approval to subsequent renewals and variations), thereby directly impacting the availability of novel drugs for patients in those markets. Furthermore, authorities in these markets are moving from requesting an abbreviated dossier (by relying on approval in a reference market) to a more complex regulatory framework which includes a full dossier (e.g. ICH CTD) *plus* the CPP. This situation leads to excessively lengthy submission and approval timelines.

It is recommended that HAs accept abbreviated dossiers when they are requesting CPPs and that CPPs are not a requirement for the initial review cycle but can be provided at a later time.

- ***Required consulate/embassy legalizations lead to delays in CPP availability***

The CPP is a legal document that adheres to the principles of the WHO which are endorsed by the majority of countries. Consulate legalization is sometimes required, which is beyond the international rules for the exchange of certificates and documents as it does not provide any enhanced evidence of authenticity and does not provide value to the safety of the patients. In addition, required legalizations lead to delays in CPP availability, impacting registration timelines and the availability of new medicines to patients. Where a country requires a CPP prior to the approval of a product, consulate/embassy legalization should not be required since the CPP was issued by the HA in accordance with the adopted WHO requirements.

- ***Lead times of the certifying authorities can be very long, sometimes several months***

Experience shows there are differences in the timelines for issuing of CPPs across national authorities, ranging from days to several months. Lengthy issuing times from certifying authorities, especially those from source countries of new medicines, increase registration timelines and delay availability of those medicines in CPP dependent markets. It is recommended that HAs that have successfully shorter issuing timelines share best practices with others where issuing timelines are longer.

In addition, there are no specific review timelines for CPP requests. If there is an issue with the application, the applicant is not informed until many weeks after the initial application. Opportunities for the applicant to discuss the submission with the issuing HA during the process would benefit both the HA and applicant and allow for any corrections or updates to be managed efficiently.

- ***The Marketing Authorisation Holder (MAH) holder stated within the CPP can be registered as the MAH within the recipient country license***

There has been a growing trend within markets that requiring reference country approval to register the MAH listed within the CPP as the MAH within the recipient market. This leads to issues as the MAH can differ depending on the issuing HA's legislative requirements. In addition there is often a requirement within the recipient HA, that the MAH must be from where the product is formulated and/or released. This makes it impossible to provide a CPP that fits the legislative requirements in the recipient country. Is it correct to use the CPP content in this way? This is not aligned with the scheme's original purpose to ensure QSE of the drug product moving in international commerce, regardless of whether the MAH listed in the CPP formulates and/or releases the drug product. The original purpose of the scheme should be reflected within the recipient HA legislative requirements, allowing CPPs to be provided to support regulatory submissions with proof of the QSE of the drug product only.

As a conclusion, in answer to the question, 'Is the fundamental purpose of providing a CPP to assist worldwide patient access to novel medicines still true today?' we have the following opinion:

The CPP is still valid, but not in its current state and only when used to support countries that do not have the infrastructure to complete a full dossier quality, safety and efficacy review themselves.

For the Scheme to be successful now and in the future, both recipient and issuing HAs need to work together with the WHO and pharmaceutical industry to harmonize CPP templates, align legislative requirements of recipient countries, reduce timelines and accept the CPP at a later time within the review cycle.

Whilst doing this we also need to remain focused on the initial fundamental purpose of the Scheme, ensuring its continuous improvement and adaptation as we move forward with advancements within the regulatory environment.

Only once this has been achieved, will the Scheme work again to its full potential, positively impacting patients worldwide independent of their agency resource and capability.

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