Certification Scheme for a Certificate of Pharmaceutical Product (CPP)

IFPMA CPP Network
Training Toolkit
Training package

- Why is training needed?
- Training modules
  - CPP overview
  - CPP scenario training
  - eCPP
  - References and glossary
- IFPMA position papers and articles
- Appendix - WHO CPP template
Under the WHO Certification Scheme, the CPP is a key document that aims to accelerate patient access to novel medicines, especially in countries that do not have the infrastructure or capabilities to complete a full dossier Quality Safety and Efficacy (QSE) review themselves.

Despite the original aim of the WHO Scheme, i.e. to provide a standard process, since the launch of the CPP in 1997 the regulatory procedures among countries have varied significantly and different approaches and interpretations apply from one country to another.

This training should be utilized in conjunction with WHO guidelines and relevant local legislative requirements.

This training aims to provide a greater understanding of the current process including highlights of the challenges and the opportunities needed to improve and modernize regulatory procedures that will ultimately accelerate patient access to novel medicines.
Training modules

1. CPP overview
2. CPP scenario training
3. eCPP
4. References and glossary
CPP overview

- What is a CPP and what is its purpose?
- Which countries require a CPP and why?
What is a CPP and what is its purpose?

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

Guidelines are located on the WHO website [www.who.int](http://www.who.int)

The CPP template (contents) are provided in the Appendix

The CPP supports the review in countries without sufficient capability to conduct a full review themselves. Ideally, a CPP should not be required in countries that have the capabilities to conduct full reviews.

The CPP should be used when a pharmaceutical product is under consideration for a product licence/marketing authorisation or when administrative action is required to renew, extend or vary such a licence.

**The CPP contains, but is not limited to the following information:**

- Confirmation of approval of QSE in the issuing country,
- A snapshot of the licence (only includes information registered in the issuing country),
- Confirms product approval, licence holder and Good Manufacturing Practices (GMP) status.

**The Scheme ensures:**

- The CPP Issuer meets a comprehensive system of quality assurance,
- Through independent inspection that all manufacturing operations are carried out in conformity with GMP.
Content of the CPP

A CPP has two DISTINCT parts:

- Evidence of QSE Review.
- Evidence of Compliance with GMP.

Refer to WHO for model certificate content (1)
Key challenges of the interpretation of the CPP scheme

- Difference in product names between certifying and requesting countries.
- The CPP confirms GMP status, additional GMP certificates should not be necessary.
- The CPP is a legal document, additional apostille and/or legalization should not be requested.
- Requirements for the ‘country of origin’ or ‘source country’ have multiple definitions and should be clarified as it could refer to the country of any one of the following: first approval or marketing, manufacture, packaging, final release, or main headquarters of the pharmaceutical company.
- The CPP provides evidence of a positive QSE review in the issuing country. A full dossier should not be requested.
- The scheme refers only to the manufacturer of the dosage form but some importing countries require additional manufacturers to be listed.
- The CPP issued is a snapshot of the Market Authorization (MA) in the issuing country and may not necessarily reflect the entire situation in the importing country.
The Scheme provides the standard format that is expected to be used.

Enables recipient CPP countries to gain assurance on the QSE of the product in the issuing country.

Obliges certifying authorities to disclose important information to the importing country.

By supporting the review and approval process it facilitates patient access to quality medicines.
Authorities issuing WHO-type certificates should satisfy the following criteria

An effective national licensing system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;

GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;

Effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country, including access to an independent quality control laboratory;

A national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples; and

Administrative capacity to issue the required certificates and to institute inquiries in the case of complaint. In addition to notify expeditiously both WHO and the competent authority in any Member State, to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.

* Refer to WHO guidelines (2)
Which countries require CPPs and why?

Countries within regions, for example:

- Latin America,
- Asia Pacific,
- Middle East/Africa,
- Eastern Europe / Commonwealth of Independent States (CIS).

The CPP may be required to support a regulatory submission. This can be submitted at the beginning of, or during the health authority review.

According to the WHO Scheme, CPPs should not be required in countries that require full ICH CTD dossiers and have the capability to conduct full QSE reviews.
CPP scenario training

1. CPP applications and authority interpretation
2. CPPs - a snapshot of the registration in the exporting country
3. Legalization of US foreign exported CPPs
4. CPPs and the registration process in importing countries
CPP applications are not harmonized

Each certifying authority has its own system:

- Requests can be submitted as hard copy or electronically,
- Different levels of detail are required by different authorities,
- Timeline for issuing CPP is not standardized,
- Issuing authorities may not perform quality check; care should be taken as CPPs can be issued incorrectly.
There has been a change in manufacturing site of the product provided for country X. The previous site A is no longer registered, site B is now registered.

Team from country Y is requesting a country X CPP in order to file an Market Access Authorization (MAA) for a product, that will also be supplied from manufacturing site B.

In the CPP application form manufacturing site A is listed as bulk manufacturing site.

Due to lack of quality check, the CPP is issued with the incorrect manufacturing site.

The CPP cannot be submitted and a new CPP containing the correct information will need to be obtained. Ultimately, this can lead to a delay in patient’s access to novel medicines.

Recommendation: when applying for CPP, Market Authorization Holder (MAH) should perform adequate quality check of all information provided.
Key considerations

Work towards harmonization and a standard electronic submission, such as the approach with electronic Common Technical Document (eCTD). Harmonization among regulatory agencies will enable a faster, compliant and simplified issuing process. This could be achieved by the introduction of electronic CPPs (eCPP).

Applicants should take care to provide correct information when requesting CPPs.

Issuing HAs should be aware that the CPP issuing times can significantly impact registration timelines.

Issuing HAs should ensure adequate communication to industry of changes to CPP application and/or issuing processes to make sure that all involved stakeholders are aware and prepared for implementation.

Patient access to novel medicines will be enhanced by HAs willingness to accept CPPs during the review rather than at the time of submission.
Country X requires a new product to be registered rapidly due to an unmet medical need. Country X HA has a legislative requirement to provide a CPP with the initial submission.

To prepare in advance, country X sends the detailed requirements for the submission including the requirement for a CPP. The company’s regulatory team provides the CPP to Country X, based on the first approval, so that they can begin the submission procedure as quickly as possible.

Country X soon recognises that they have an issue, as the CPP issued does not reflect the information that has been provided within the dossier (e.g. different manufacturing site), and the next approval that will match is not due for additional 6 months.

How can the global regulatory submission team, HAs and country X work together to overcome this issue?
The CPP only reflects the approved manufacturing sourcing route of the certifying country

Most recipient authorities expect that the drug product they will receive mirrors that which has been approved by the authority issuing the CPP.

When developing a global submission strategy CPP requirements are considered early during the planning phase. If required HAs should be open to discussion in advance of the regulatory submission to give advice and agree on the content of the submission including the CPP to move forward as quickly possible.
Some countries require that the MAH listed within the CPP is the same as the drug product exporter.

In cases where the US is the only MAH for the drug product but the drug product is packaged and exported from a foreign country, there is a challenge getting a properly legalized CPP that will meet the importing country’s requirements.
US foreign exported CPP legalized

1. If the product is packaged, in a foreign country but is exported by the MAH, there is no issue.

2. The FDA will not currently accept Foreign Exported CPP requests.
Country X requires a CPP to be submitted as part of the initial registration dossier.

During submission preparation it is noticed that the legislative requirements for the dossier consist of submitting a full ICH CTD dossier (Modules 2, 3, 4 & 5).

It is not understood why the full ICH CTD dossier is being requested in addition to a CPP as, according to the WHO scheme, the CPP should replace the QSE review.

Upon consultation with the HA of country X, it is explained that the CPP is required as reassurance of an approval by a stringent HA rather than to replace the QSE review.
Alternatives should be considered by the HA when they move to a full ICH CTD to overcome the inappropriate use of the CPP e.g. use of an approval letter or an assessment report.

Increase flexibility in providing the CPP during the review or prior to approval, not at the time of submission, to enable earlier dossier submission and allow faster patient access to innovative treatments.

According to WHO Scheme, CPPs should not be required in countries that require full ICH CTD dossiers and have capabilities of conducting full QSE reviews. However, CPP requirements are often legislatively driven and it necessitates legislative changes to remove this requirement.
Electronic CPP

- The electronic CPP - considerations for the future
- Future eCPP implementation
The next step in the modernization of the CPP is expected to be the evolution to an electronic CPP (eCPP).

As more CPP-dependent countries start to implement electronic submissions, more dossiers and CPPs submitted electronically should be accepted.

Currently, several health authorities accept electronic applications but few health authorities issue eCPPs. The outcome often is still a paper document.
Considerations for a potential future eCPP implementation

The paper CPP is often the rate limiting step in patient access to novel medicines.

In keeping with the increasing number of electronic submissions the provision and acceptance of an electronic CPP should be considered by HAs.

Ongoing initiatives, such as EVMPD* and the proposed international database IDMP*, should be investigated to identify possible opportunities.

It is proposed that a harmonized process for issuing and requesting eCPPs be established.

To move this process forward a sponsor will be required to initiate further discussion and collaboration amongst concerned stakeholders, including the WHO.

* See glossary
References

1. WHO model certificate of a pharmaceutical product
2. Guidelines on the implementation of the WHO certification scheme
4. Proposal for revision of the Who Certification Scheme on the quality of pharmaceutical products moving in international commerce (draft)
Glossary

- CTD: Common Technical Document
- eCTD: electronic Common Technical Document
- EVMPD: EudraVigilance Medicinal Product Dictionary
- FDA: Food and Drug Authority
- GMP: Good Manufacturing Practices
- HA: Health Authority
- IDMP: Identification of Medicinal Products [www.idmp1.com](http://www.idmp1.com)
- IFPMA: International Federation of Pharmaceutical Manufacturers and Associations [www.ifpma.org](http://www.ifpma.org)
- QSE: Quality, Safety and Efficacy
- TOPRA: The Organisation for Professionals in Regulatory Affairs [www.topra.org](http://www.topra.org)
- MAH: Marketing Authorization Holder
- MAA: Market Access Authorization
- WHO: World Health Organization [www.who.int](http://www.who.int)
IFPMA position papers and articles

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

WHO Q&A

Electronic CPP

How has the evolution of the global pharmaceutical market affected the use of WHO CPP?

US CPP paper Q&A

View all documents
Certificate of a pharmaceutical product 1

This certificate conforms to the format recommended by the World Health Organization:

No. of certificate

Exporting (certifying country)

Importing (requesting country)

1. Name and dosage form of the product:

1.1. Active ingredient(s) and amount(s) per unit dose:

Complete composition including excipients is attached to the CPP

1.2. Is this product licensed to be placed on the market for use in the exporting country? (yes/no)

1.3. Is this product actually on the market in the exporting country?

If the answer to 1.2. is yes, continue with section 2A and omit section 2B.

If the answer to 1.2. is no, omit section 2A and continue with section 2B:
Appendix - WHO CPP template (cont.)

2.A.1. Number of product license and date of issue

2.A.2. Product license holder (name and address)

2.A.3. Status of product license holder

2.A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form is...

2.A.4. Is a summary basis for approval appended? (yes/no)

2.A.5. Is the attached, officially approved product information complete and consonant with the license?

2.A.6. Applicant for certificate, if different from license holder (name and address)
2.B.1. Applicant for certificate (name and address)

2.B.2. Status of applicant

2.B.2.1. For categories (b) and (c) the name and address of the manufacturer producing the dosage form is...

2.B.3. Why is marketing authorization lacking? (not required/not requested/under consideration/refused)

2.B.4. Remarks
3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? (yes/no/not applicable)

If not or not applicable, proceed to question 4.

3.1. Periodicity of routine inspections (years)

3.2. Has the manufacture of this type of dosage form been inspected? (yes/no)

3.3. Do the facilities and operations conform to GMP as recommended by the World Health Organization? (yes/no/not applicable)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product: (yes/no) If no, explain

- Address of certifying authority
- Telephone
- Fax
- Name of authorized person
- Signature
- Stamp and date