

Relevance of a Certificate of Pharmaceutical Product for Registration and
Life Cycle Management of Imported Drugs.

How is the WHO Certification Scheme implemented by National Health
Authorities outside of the ICH?

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Anna Sahl

aus Mettmann

Bonn, 2013

Relevance of a Certificate of Pharmaceutical Product for Registration and Life Cycle Management of Imported Drugs. How is the WHO Certification Scheme implemented by National Health Authorities outside of the ICH?

Betreuer und 1. Referent: Dr. Santiago Figueroa Perez

Zweiter Referent: Dr. Birka Lehmann

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List of Abbreviations

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AMG	Arzneimittelgesetz (German Drug Law / German Medicinal Products Act)
ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología médica
ANVISA	Agência Nacional de Vigilância Sanitária
AR	Assessment Report
BfArM	<i>Bundesinstitut für Arzneimittel und Medizinprodukte</i> (Federal Institute for Drugs and Medical Devices)
CA	Competent Authority
CFDA	China Food and Drug Administration
CoO	Country of Origin
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
EEA	European Economic Area
EFGCP	European Forum for Good Clinical Practice
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMP	Essential Medicines and Health Products
EU	European Union
GMP	Good Manufacturing Practice
GRC	Guideline Review Committee
HA	Health Authority
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDL	Import Drug License
IDRAC	Thomson & Reuters; The Single-Source Global Regulatory Database
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations

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LA	Local Authority
LCM	Life Cycle Management
LRAM	Local Regulatory Affairs Manager
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MFDS	Ministry of Food and Drug Safety
MS	Member State
NDA	New Drug Application
OTC	Over the Counter (non-prescription drug)
PAR	Public Assessment Report
PEI	Paul-Ehrlich-Institut – Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel (Paul-Ehrlich-Institute – the Federal Institute for Vaccines and Biomedicines)
PIL	Patient Information Leaflet
QSE	Quality, Safety, Efficacy
RAM	Regulatory Affairs Manager
R _x	Prescription Drug
SmPC	Summary of Product Characteristics
SRA	Stringent Drug Regulatory Authority means a regulatory authority (in case of the European Union both EMEA and national competent authorities are included) which is (a) a member of the ICH (as specified on its website:); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic, Health Canada and WHO; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein.
UN	United Nations
U.S. FDA	United States Food and Drug Administration
WHO	World Health Organization

Executive Summary

The Certificate of Pharmaceutical Product (CPP) within the WHO Certification Scheme is described and its relevance for the approval of New Drug Applications (NDAs) and Life Cycle Management (LCM) of imported finished medicinal product registrations is evaluated.

In order to evaluate this some selected countries were contacted via the Local Regulatory Affairs Managers (LRAM) working in the pharmaceutical sector on NDA and maintenance activities in Regulatory Affairs. A questionnaire on the use and need of CPPs as specified for each country regulation was created and LRAMs were asked to answer the questions according their 'every day working experiences' including the country regulations in their country.

During the evaluation of the answers of the representative countries, varying from small countries with small Health Authorities (HAs) up to fast growing economies with larger HAs, it was concluded that the potential of the WHO Certification Scheme to improve the efficiency of drug evaluation is not fully exploited by HAs in countries outside the ICH, even though they decided actively to participate in the WHO Certification Scheme. The countries require certifications, such as CPPs, as mandatory supplements to NDAs or supplemental registrations in variation submissions, even though their HA also review the Quality, Safety and Efficacy completely.

Due to this kind of requirement, a delay in the approval of new innovative therapies is often the result. The WHO Certification Scheme was initially created to accelerate the availability of innovative new drugs in developing countries. The conclusion drawn by this evaluation is that the CPP as a mandatory document for filing and approval of a NDA does not really improve the review time by local HAs. The WHO, HAs and stakeholders involved to this business collaboration should work to improve acceptance and handling of the WHO Certification Scheme internationally, since the growth and development in emerging markets seem to take even less advantage of the system while the resources and knowledge is in progression.

Introduction

Within the WHO Certification Scheme the Certificate of a Pharmaceutical Product (CPP) will be the focus topic in this thesis. Not only will the requirements given by Health Authorities from countries outside of “The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)” be discussed, but also the experiences from Local Regulatory Affairs Managers (LRAMs) worldwide will be evaluated. Therefore, a short questionnaire was sent to several country affiliates requesting their personal ‘every day working experience’ on the demand and benefit of submitting a CPP to their Health Authority during the Life Cycle Management (LCM) of a finished medicinal product (MP). This could be either during new drug applications (NDA) or during maintenance activities, for prescription drugs (Rx) or over the counter (OTC) products.

The strategic use and benefits of a CPP for a Health Authority as well as for a pharmaceutical company will be addressed during the evaluation of the data.

This master thesis will analyze the value, need and importance of a CPP for countries outside of the ICH. The CPP was created within the WHO Certification Scheme on the quality of pharmaceutical products described by the World Health Organization (WHO) funded by the United Nations (UN).

Differences in the use by local HAs and the WHO recommendation will be evaluated and discussed. The need of the CPP will be analyzed regarding useful transfer reflected to the view of the HAs, patient groups and pharmaceutical companies.

Who is “WHO”? – History, origin and relevance of the World Health Organization

Since the United Nations (UN) was formed in 1945, one of their goals was to set up a global health organization. Therefore, the United Nations Organization, which currently has 193 member states (WHO, An introduction to the World Health Organization, 2013), created the World Health Organization (WHO) whose constitution came into force on 7th April 1948.

Today the WHO is the authority directing and coordinating functions around health topics within the UN system.

The responsibility of the WHO covers discussions on global health topics in general, research on health issues, providing norms and standards for research and health industry as well as the creation of guidelines available for all countries worldwide. The WHO also provides technical support to countries worldwide and further monitoring of health trends including their assessment.

The WHO coordinates the responsibility for all industrial countries to make pharmaceutical products and essential care accessible for all humans worldwide and further to provide a defense against transnational threats like epidemic diseases (WHO, An introduction to the World Health Organization, 2013). Several resources of knowledge can be utilized and accumulated using the structure of the WHO with many participating countries. Single countries or single resources could not provide so much support on the different areas of work represented by the WHO. The vision of the WHO “is that people everywhere have **access to the essential medicines and health products** they need” and further “that the medicines and health products are **safe, effective and of assured quality**; and that medicines are prescribed and used rationally...” (WHO, Medicines; About us, 2013)

WHO Guidelines

The WHO issues different guidelines and recommendations on the health sector.

The aim of the WHO is to provide guidelines and to strengthen their medicines strategy for worldwide access to medicine. One is the provision of scientific or medicinal support and ensures quality and safety of medicinal products worldwide. Guidelines created by the WHO are approved by the Guidelines Review Committee (GRC).

The GRC (including content experts, methodologists, target users, policy makers, with gender and geographical balance) reviews initial proposals for guideline development before creating final versions for publication. Guideline developments are supposed to meet the WHO requirements described in the WHO handbook for guideline development (WHO, Guideline Review Committee (GRC), 2013). The development of global guidelines, recommendations or certification schemes is relevant for the appropriate use of healthcare with suitable evidence and seen as one important function of the WHO. In general the recommendations given by the WHO with possible impact upon health policies or clinical interventions are considered guidelines for WHO purposes (WHO, World Health Organisation, 2013). Internationally recognized standards are adopted by the WHO and the methods used for guideline development ensure that guidelines are free from bias. Public health need is supposed to be addressed and recommendations are based on a wide-ranging and independent assessment of the available evidence (WHO, WHO Handbook for Guideline Development, 2012).

The WHO has different areas of defined activities. For example, “Medicine access and rational use”, “Prequalification of Medicines” or **‘Quality and Safety: Medicines’** only to mention a few within the part of the WHO strategy on Medicines. Figure 1 provides an overview on the areas of work within one sub department of the Essential Medicines and Health Products (EMP):

Quality and Safety: Medicines

- Blood Products and Related Biologicals
- Spurious/falsely-labelled/falsified/counterfeit (SFCC) medicines
- International Nonproprietary Names
- Quality Assurance
- **Regulatory Support**
- Safety and Efficacy
- The International Pharmacopoeia

Figure 1: Overview WHO Work Areas on Quality and Safety: Medicines (WHO, Areas of Work in Medicines, 2013)

Under the topic of '**Regulatory Support**' the WHO has two roles. On the one hand they provide support for the development of norms, which are internationally acknowledged, besides standards and guidelines which can be used internationally. On the other hand they provide guidance, technical assistance and training so that countries are supported in the implementation of global guidelines to meet needs and specific regulatory requirements for particular medicinal environments (WHO, World Health Organization - Medicines, 2013).

One of the guidelines created by WHO within this "area of work" is the WHO Certification Scheme on the quality of pharmaceutical products as a "voluntary and non-binding agreement between WHO and their Member States" (Rägo, 2011) in order to provide a "comprehensive system of quality assurance ... founded on a reliable system of licensing" (WHO, World Health Organisation - Model certificate of a pharmaceutical product, 2013).

Certificates of the WHO Certification Scheme

Certificates according to the WHO Certification Scheme can be stated as “certificates in conformity” according to the format suggested by the WHO.

Following the above mentioned objectives of the scheme, the content of a WHO certificate is referenced on the WHO-Homepage:

(http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index2.html).

Overall there are three different documents within the scope of the WHO Certification Scheme using a “standard format” (Rägo, 2011):

1. The statement of licensing status of pharmaceutical product(s),
2. the batch certificate of a pharmaceutical product, and
3. the Certificate of a Pharmaceutical Product (CPP), which is in focus of this master thesis.

The content of certificates according the WHO Certification Scheme can easily be transformed into national templates, as locally preferred by country specific use, in order to provide the information represented by the certification scheme. But the scope of this scheme should not be expanded by supplementing the content of the certificates.

Statement of Licensing Status

The Statement of Licensing Status confirms the information that a license has been issued for a specified finished medicinal product for use in the exporting country. This can be required for participating in tender as a condition of bidding and is meant to be used for this information, only. With respect to the specific use it is possible to include several registration licenses of one Marketing Authorization Holder (MAH) into one Statement of Licensing Status. e. g. in case of an explanation of a name change of a MAH, in order to avoid multiple documents for the same submission.

Batch Certificate

Another certificate within the WHO Certification Scheme is the Batch Certificate of a Pharmaceutical Product providing a reference on a specific batch of a finished medicinal product. Batch Certificates are often requested as a mandatory procurement documents for tender business. This certificate provides information with reference to the quality and expiry date of a specific batch including the specifications of the finished medicinal product at the time of batch release. Usually this certificate is issued by the manufacturer registered for final release of the finished product.

Certificate of a Pharmaceutical Product

The Certificate of a Pharmaceutical Product is a certificate which is presenting several details on a registered finished medicinal product. Annex I lists the content of a CPP according to the recommendation of the WHO Certification Scheme including the explanatory notes as referenced from the WHO-Homepage (WHO, World Health Organisation - Model certificate of a pharmaceutical product, 2013). The intended use of a CPP (which is usually issued by the exporting country or the so-called Country of Origin (CoO*)), in which a Health Authority of an importing country requires a CPP, can usually be separated in different typical sceneries:

1. During the review of a NDA, considering that the product which is to be registered will be imported for sale of the CoO.
2. During supplemental registration submissions, such as renewals or variations to the initial NDA and when a license is reviewed.
3. A third scenario where CPPs are often requested is for the participation and completion of tender-business with governments in countries outside of ICH. This can also be in scope of the WHO Medicines Access to Quality products and prequalification projects. Medicines should also be made available in regions where no registration process is in place, maybe due to political riots and civil wars, or when no social structure for medical care is in place. The

WHO has created a list of essential medicines where medicinal products are included to be made available via WHO programs worldwide.

[* It must be mentioned that the CoO can be defined differently in countries worldwide. In some cases this definition is used for the bulk manufacturer of the drug product or it can be applied to the manufacturer, who conducts the final release. This is difficult to differentiate in some countries since the definition of the “manufacturer” according the drug law in one country can be different to the definition of the “manufacturer” given by the WHO. On the one side the definition of the “manufacturer” can describe the responsible manufacturing site for packaging and final release but it can on the other side describe the site of bulk production. Since medicinal products can have a complex manufacturing chain with different manufacturing sites for bulk production, primary, secondary packaging and final release it can end up in mixed information in the CPP. This might be problematic on time of submission considering additionally the definition by the importing country as well and therefore the acceptance by the requesting HA.]

Health Authorities worldwide may align to these model certificates. The content of locally issued documents is usually consistent with the provided scheme but the format and / or wording might be different.

Several health authorities provide application forms or templates for the CPPs as they can be applied for and as they are issued by their country. But the Competent Authority (CA) issuing a CPP must not necessarily be the same authority as the HA reviewing and controlling registrations of medicinal products. In some countries these functions are separated, as for example in Germany where the HA would be the BfArM or PEI but the CA is an authority of country districts (for example the district government in Cologne). Please refer to Annex II - VIII to see some examples of application forms and templates, e. g. from the MHRA/ UK, the CA in Germany or the European Medicines Agency (EMA)/ EU and U.S. FDA and further Health Authorities worldwide which include more specific information on the layout and required information for an application of a CPP.

The certification scheme of a CPP is in its function an administrative instrument involving Member States (MS) to attest to any CA of another participating MS that:

- a specific medicinal product is registered in the country with a marketing authorization in order to be placed on the country market showing the marketing status including additional requirements which might be applicable to the authorization;
- the “Good Manufacturing Practice (GMP) status for the manufacturing site of the specific medicinal product can be confirmed and that inspections as recommended by WHO take place in regular intervals, and
- the currently authorized medicinal product information, labeling and/ or Summary of Product Characteristics (SmPC) attached to the CPP is valid in the certifying country.

(WHO, World Health Organization - Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, 2013)

The following details of the finished medicinal product are usually presented in the CPP:

- i. name and dosage form of product*
- ii. name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s)),*
- iii. name and address of product license holder and/or manufacturing facility,*
- iv. formula (complete composition including all excipients; also particularly when no product license exists or when the formulation differs from that of the licensed product),*
- v. product information for health professionals and for the public (patient information leaflets) as approved in the exporting country,*

(WHO, World Health Organization - Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, 2013)

Regarding the reflection of the GMP status it should be noted that the confirmation of the GMP status can depend on the CA issuing the CPP. For example, the CA in France would only provide the evaluation on the GMP status for manufacturing sites within France. They will not confirm the GMP status for manufacturing sites in other countries.

Objectives of the WHO Certification Scheme

The objectives of the WHO Certification Scheme are described as providing information on the **Quality, Safety and Efficacy** (QSE) of imported finished medicinal products, the **appropriate use** and in a **reliable system of licensing** an **independently controlled quality control** according to **accepted norms**. A full review by HAs in emerging markets outside of ICH on QSE data submitted for registration must not be compulsory if a CPP according the WHO Certification Scheme is available and the review time could be shortened where resources are limited. According to the WHO Certification Scheme HAs in countries outside of ICH could rely on the confirmation, issued as CPP, by HAs which already completed a full review confirming the QSE of a finished medicinal product. HAs with limited resources could save on those resources by simplifying the local processes referencing to a CPP of the CoO. But the CPP should be seen as condition for approval, not for submission according the WHO (WHO, WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, 2010).

Participants of the WHO Certification Scheme

The WHO Certification Scheme is a voluntary agreement under which countries can apply for participation. WHO MSs or regional organizations can notify the Director-General of the WHO, by confirming in written notification, that they want to participate in the Scheme. With this written statement the CA must be named, which will be issuing the relevant certificate (WHO, World Health Organization - Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, 2013). MSs who are participating in the WHO Certification Scheme should be able to provide the administrative capacity for issuing requested CPPs besides having a registration system for medicinal products assuring the quality, safety and efficacy (Rägo, 2011).

Since this certification scheme is not mandatory for participation it must be seen as a possibility for countries with limited regulatory capacity in the healthcare and medicinal sector to obtain a declaration from the manufacturer of the exporting country of a medicinal finished product concerning the QSE of the pharmaceutical product confirmed by the CA of the CoO.

The WHO is providing a list of addresses of competent national regulatory authorities currently participating in the Scheme:

http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/contacts/en/index.html (WHO, Competent authorities of countries participating in the WHO certification scheme, 2013)

Issuing a certificate

As the CPP is classified as a confidential document, it can only be issued by the CA if the applicant (and MAH, if different to the applicant) apply for the certificate and give their permission to provide a CPP for a specific finished medicinal product to the requesting HA. Usually the applicant will forward the CPP, issued by the CA, to the local affiliate in the requesting country in order to send the CPP, e. g. together

with the NDA, to the relevant requesting HA.

Most competent authorities can provide a bilingual CPP. For example, in Germany a CPP could be issued in German and English (or Spanish or French) language, but only the German version will be signed with wet ink signature. A CPP issued by the EMA (usually in English) could also be issued in Spanish or French language, when requested by the applicant. But in general the responsibility to provide a translation, as it might be required by the requesting HA, must be considered by the applicant of the NDA/ supplemental registration.

Fees for issuing a CPP may be charged by the CA.

By issuing the CPP the CA is confirming the authenticity of the certified data. Whilst the CPP is issued by the CA of the participating MS of the WHO, the certificate itself does not bear a WHO emblem, but it should be noted if the content is reflected and included in the format as recommended by the WHO.

As described above according the recommended WHO format the GMP status will also be presented within the CPP, this fact implies that the CA should prove that the applicant / MAH manufactures according to GMP standards at the registered manufacturing site, where the finished medicinal product is manufactured, packed and released. It should be considered that this information is not subsequently attesting the GMP status of the manufacturer of the active substance. But the certifying authority should evaluate if it has received adequate information regarding compliance on the GMP according WHO recommendations of manufacturing, especially if the manufacturing and packaging of the finished product takes place in different production sites until the final release (WHO, World Health Organization - Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, 2013).

Usually the CPP is tacked or bound in a way that all pages bear the official stamp or

seal of the CA and every single CPP is a true original. But it may be required by some HAs that the CPP is additionally legalized by a notary, country court and / or embassy. A CPP is usually issued for the requesting country by naming the country within the CPP as importing country. Any additional information which is submitted in addition to the CPP, not being part of the content of the CPP as recommended by the WHO, must be labeled as such.

In suspected case of a falsification, an identical copy can be demanded by the importing country directly at the CA of the CoO* (*see page 10). Every CPP is marked with an individual identifier, such as a certificate number, by the issuing CA and the authenticity is therefore traceable (Rägo, 2011).

Only participating MSs (WHO, Competent authorities of countries participating in the WHO certification scheme, 2013) of the WHO are eligible to issue CPPs for registered finished medicinal products via the Competent Authorities in their countries according to their responsibility. National authorities may issue CPPs for products having a national registration. Within the European Union (EU) and the European Economic Area (EEA) it is possible to obtain registrations via the centralized procedure (CP) with the EMA as the CA. For these centrally registered finished medicinal products the CPPs can only be issued by EMA instead of the local national Competent Authorities in the member states of the EEA. But it must be clear that a CPP is never issued by the WHO directly.

The CA issuing a CPP must not mandatorily be the CoO / exporting country where the finished product is manufactured and released. This was one of the initial ideas that the CPP is issued by the CA of the exporting country/ the CoO or any other country, which performed a complete review of QSE according to ICH standards participating in the WHO Certification Scheme.

According to the WHO other countries can also issue a CPP beside the CoO when they approved the registration with review of the QES. Countries may therefore issue different types of CPPs in order to clearly identify the status of the CPP. For

example, the U.S. Food and Drug Administration (U.S. FDA) of the United States of America (USA), attach different colored Ribbons to the CPP, which mark the content details. They differentiate between three different types of CPPs for:

- Finished medicinal products that are legally marketable in the US authorized by the U.S FDA;

A **Red Ribbon** will be affixed to all (regular) CPPs issued for authorized medicinal products;

- Finished medicinal products which are not authorized by U.S. FDA but which may be legally exported;

A **Blue Ribbon** will be affixed to CPPs issued only for export of an unapproved medicinal products;

- and a CPP for Foreign Manufacturer (products manufactured outside of the U.S.).

A **Yellow Ribbon** will be affixed to CPPs with foreign manufacturing sites outside of the USA.

(Famulare & U.S. FDA, 2003)

Besides these three types of CPPs there is another specific type of U.S. FDA CPP:

- The **“Pilot-CPP”** is issued by the U.S. FDA on products which are not manufactured and not exported from the U.S. only when no other country so far has given an approval for the relevant registered finished medicinal product worldwide, in order not to delay further approvals of the respective product.

(U.S. FDA, 2012)

The U.S. FDA is confirming with the different types of CPPs slightly different contents, even though they are always reflected on a finished drug product. For example with the **Red Ribbon** CPP: They will confirm that the product described in the CPP is exactly the same drug product, which is manufactured and approved in the U.S. and which may be exported to other countries. They will provide a proof on the registered product and the approved label as well.

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This certification will reflect the intended use of the CPP according WHO Certification Scheme in order to confirm the approved quality and safety within a “comprehensive system of quality assurance... on a reliable system of licensing and independent analysis of the finished product...” including manufacturing according GMP (WHO, World Health Organization - Medicines, 2013).

Figure 2 below depicts the information, which can be presented by the different types of colored Ribbon CPPs issued by the U.S. FDA.

CPP for a finished medicinal product issued by the U.S.-FDA	Red Ribbon	Yellow Ribbon	Blue Ribbon	“Pilot-CPP”
Approved in the U.S.	✓	✓	✗	✓
Manufactured/ packaged in the U.S.	✓	✗	N/A	✗
Exported from the USA	✓	✓	N/A	✗
Ribbon Contained	✓	✓	✓	✗
Attachments (Labeling: Outer Package, SmPC/ PIL, Product Composition etc.)	✓	✓	N/A	✗
Notes	Standard CPP	CPP for Foreign Manufacturer	CPP for unapproved Human Drugs	For Product currently not approved by any other exporting country

Figure 2: Different types of CPPs issued by the U.S. FDA as described in (McRoy & U.S. FDA, 2012) and (U.S. FDA, 2012)

If a MS, which is participating in the WHO Certification Scheme, issues a CPP even though the finished medicinal product is not manufactured locally (in the MS issuing the CPP), the registration of the specific finished product might be attested including the GMP status of the product. The issuing CA can confirm that the relevant HA in the issuing country reviewed the QSE of the certified finished medicinal product. But the confirmation of the GMP status is information, which is provided within the responsibility of the CA. As in Germany the CA won't confirm the GMP status of manufacturing sites outside of Germany, other CA from other countries might act in the same way.

According to the WHO Q&A, the approach to confirm the GMP and registration status of a finished medicinal product in the range of the CPP is desirable since a delay of availability of important medicines worldwide might be reduced and the access for patients can be accelerated (World Health Organization, 2010), even if the Drug Product (DP) is not registered in the country, which is issuing the CPP. The WHO is, however, distancing itself from the need of multiple CPPs from different countries, since they "provide no additional value" (World Health Organization, 2010) considering the content and purpose of the CPP according the WHO recommendation.

Requesting a certificate

Applications are usually made by pharmaceutical companies with commercial interests. The CA of the CoO or any other country, eligible to issue a CPP according to the WHO Certification Scheme for a locally registered finished medicinal product, will issue the CPP on application of the MAH in the issuing country. The MAH or applicant will afterwards send the CPP to the requesting HA in the importing and requesting country. This is usually done via the local MAH of the importing/recipient country. This process is also depicted in Figure 3 below.

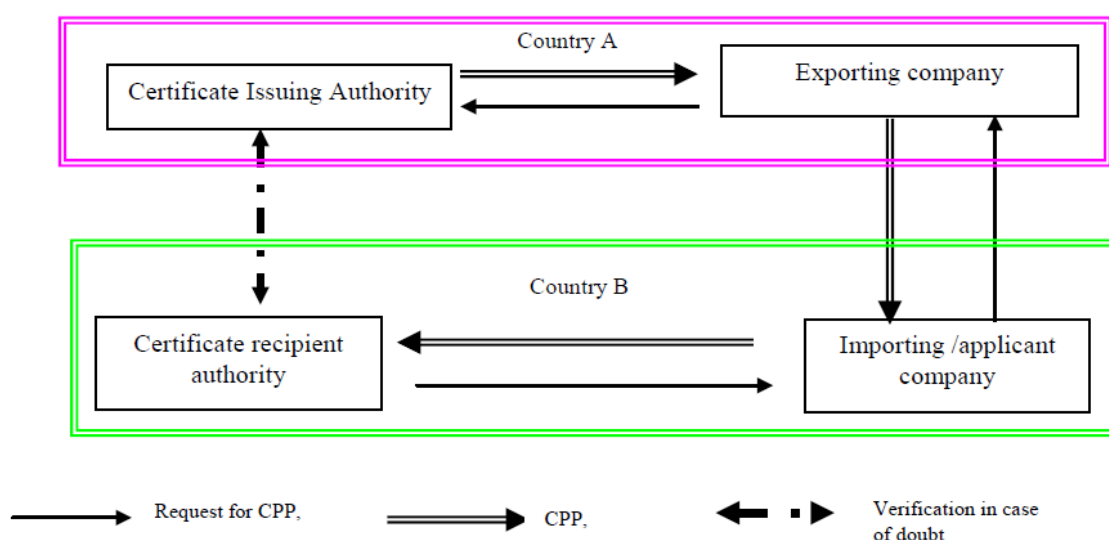


Figure 3: Process CPP Application (World Health Organization, 2010)

According to the information provided by the WHO, the certification scheme on the quality of pharmaceutical products is “applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals” (WHO, World Health Organisation - Model certificate of a pharmaceutical product, 2013).

Additionally, the CPP can document the GMP status of the manufacturing site, which means independent inspections are supposed to warrant the detailed examination on all manufacturing operations and that these processes are carried out in

conformity with defined norms. These inspections are carried out and licensed under the GMP which can be documented with a certificate for a specific manufacturing site of medicinal product production.

Requirements for Good Practices in the Manufacture and Quality Control of Drugs, referred to as “GMP as recommended by WHO”, are defined by the WHO initially in 1969 including 4 revisions throughout the years 1975, 1988, 1992 and 1997.

Member States are urged to adopt and to apply the internationally recognized and respected standards laid down in the guidelines (WHO, World Health Organisation - Model certificate of a pharmaceutical product, 2013).

Supplemental to the CPP the SmPC, PIL and Labeling attached to the CPP are used to provide additional information for importing countries in order to provide information on the approved product information included in the registration in the exporting country. This can be highly relevant for example during label updates in the existing registrations in the exporting and importing country. The importing country request the CPP from the MAH of the CoO not only during Quality, Safety and Efficacy (QSE) review, but also to prove any changes on the wording of the labeling in the CoO.

Review of Literature

For the current investigation available literature on the topic of the CPPs within the WHO Certification Scheme has been reviewed. Discussions such as “the value of the Certificate of Pharmaceutical Product in registration of medicinal products” by Davidson et al. (Davidson, Grace, Schwarz, & Vickers, 2002) or “How has the evolution of the global pharmaceutical market affected the use of Certificates of Pharmaceutical Product (CPP)?” by E. Whiting (Whiting, 2012) discussed the advantage of a CPP according to the WHO Certification Scheme. The conclusions of this literature review were reflected and confirmed and further extended by the findings in this master thesis. The additional information is documented by the results of a questionnaire completed by the LRAMs working in international countries outside of ICH.

The WHO conducted research in 1995 titled “Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in international commerce” (WHO, Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, 1995) evaluating the different kind of certificates used in international regions, which are not created according to or orientated with the WHO Certification Scheme, and findings on the acceptance of the CPP. Wehrli commented on this in “the WHO certification scheme on the quality of pharmaceutical products moving in international commerce” considering the scheme as helpful registration instrument with limitations such as that “there will be no WHO GMP certificate, since the WHO won’t conduct inspections as it is no “supranational organization” (Wehrli, 1997).

One question worth answering is “what has changed since the WHO’s research 18 years ago?” and “Did HAs in international Regions and Stakeholders improve the use of CPPs and take advantage on both sides (HA and pharmaceutical industry) of a CPP as recommended by the WHO Certification Scheme?”

Wileman et al. (Wileman & Mishra, 2010) considered the CPP a helpful certificate to

avoid or reduce drug lag when reflecting the intended beneficial use of the WHO Certification Scheme. But are CPPs nowadays efficiently requested and used for reducing the time to market and availability of new drug formulations and confirming the compliance of imported medicinal products in LCM?

The WHO provides some information and publications on the WHO Certification Scheme and the intended use, including Q&A's on the Scheme (WHO, WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, 2010). Furthermore, different HAs within the ICH provide guidelines on the availability of CPPs for further instructions for applications by pharmaceutical industries / MAHs. This literature was used in reference and as supporting documents within this thesis.

With regards to local medicinal product regulations Thomson & Reuters Cortellis/ IDRAC provides a collection on different RA aspects on different countries worldwide in the global module, where references to the relevant drug laws can be made. Also Fletcher et al., 2012 compared ASEAN to the Chinese drug registration requirements in more detailed discussions on dossier structures (Fletcher, Ahmed, & Pharo, 2012). Literature focused on GMP can be found as well considering the CPP as a certificate for providing evidence on the quality of pharmaceutical products according to WHO recommendations including information on the GMP status of the manufacturer and manufacturing site as, for example, in articles like "Good manufacturing practice: The role of local manufacturers and competent authorities" by Tomic et al. (Tomic, Filipovic Sucic , & Ilic Martinac , 2010).

Reflecting the situation on cost efficient manufacturing, for example, the article "Manufacturing site rationalisation - A regulatory and logistical challenge" by Motara and Fisher (Motara & Fisher, 2011) mentions the CPP as a required document for the registration of different manufacturing sites of imported finished medicinal products.

Statements or conclusions of the existing literature were collected and compared to the direct investigations via the questionnaires.

CPP relevance nowadays under examination

One idea of the creation of a CPP was that any CA issuing a CPP has the capacity and qualification to assess the QSE of the relevant finished medicinal product in order to grant a marketing authorization on positive outcome of the review. Therefore, the related Health Authority in the importing country could request a CPP supplementing the NDA with the consequence that a full review of the QSE has taken place with a positive outcome and approval of a MA by the reference HA. The following investigation will evaluate and discuss the need and value of the CPP in relation to the initial meaning of the CPP according WHO creation concept as described in the introduction above.

Methods

LRAMs in ten countries outside of ICH were asked to answer a questionnaire on details of the local use of CPPs for submissions of NDAs and variations in supplemental registrations during the LCM of finished medicinal products, imported to their countries, according their 'everyday working experiences'. The below presented questionnaire (Tab. 1), as it was sent to LRAMs, was created orientated on the tabular overview of the IDRAC (Cortellis) Global Module on CPPs (IDRAC, 2013). The questions were created in order to be compared to the data of the IDRAC Global Module on CPPs and further to give additional information for continuative examination on the use of the CPP by local HAs.

LRAMS in countries, which have a system for the registration of medicinal products in place, were selected to be contacted. Following questionnaire was sent to eleven Countries considering their local development of the medicinal sector and growing economic sector in emerging markets during the last years:

Relevance of a Certificate of Pharmaceutical Product for Registration and Life Cycle Management of Imported Drugs. How is the WHO Certification Scheme implemented by National Health Authorities outside of the ICH?

Country Region	
Name of your Health Authority (HA) responsible for granting Marketing Authorizations for finished Drug Products	
Size of your HA	
<ul style="list-style-type: none"> How many employees? 	
<ul style="list-style-type: none"> How many Employees are working on reviewing NDAs? 	
<ul style="list-style-type: none"> Budget of the HA per year? 	
<ul style="list-style-type: none"> How many applications are usually processed by your HA per year? 	
How long does a NDA usually take until approval?	
Does the local authority require CPPs (according WHO format)?	
For which processes is a CPP mandatory? (please amend as required)	
<ul style="list-style-type: none"> NDA for an imported finished product 	
<ul style="list-style-type: none"> NDA for a locally manufactured product 	
<ul style="list-style-type: none"> variation during Lifecycle management of a registered product 	
How many CPPs are required for imported products in case of:	
<ul style="list-style-type: none"> NCE 	
<ul style="list-style-type: none"> New Indication 	
<ul style="list-style-type: none"> New formulation 	
<ul style="list-style-type: none"> Generics 	
<ul style="list-style-type: none"> Variation submissions 	
From which countries are CPPs :	
<ul style="list-style-type: none"> required? 	
<ul style="list-style-type: none"> accepted? 	
Validity of the CPP :	

Relevance of a Certificate of Pharmaceutical Product for Registration and Life Cycle Management of Imported Drugs. How is the WHO Certification Scheme implemented by National Health Authorities outside of the ICH?

<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	
<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	
Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	
On which time of submission is the CPP required? e. g.	
<ul style="list-style-type: none"> at the time of submission? 	
<ul style="list-style-type: none"> before review starts? 	
<ul style="list-style-type: none"> before approval? 	
Is the CPP accepted as alternative to a GMP certificate?	
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	
For which process might a CPP be helpful but is not mandatory?	
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	
Does your Health Authority issue CPPs?	
How long does it take your HA to issue a CPP?	
Fees for a CPP issued by your HA	
Any additional comments?	

Tab. 1: Template Country Questionnaire as to be completed by LRAMs.

Seven LRAMs answered to the request to participate in this evaluation and provided the duly filled questionnaires as provided in Annex IX:

From Latin American Countries: **Argentina, Brazil and Uruguay;**

From Asia Pacific Region: **Malaysia and Korea;** and further **China and Russia.**

While the IDRAC Global Module on CPPs provides mainly data on the CA in different countries worldwide which issue CPPs providing information on fees and regulations additionally to links where to apply for the CPPs, the questionnaire created for the evaluation within this master thesis concentrates on the HAs requesting CPPs locally. The size of the local HAs and average review time in addition to the different scenarios in which a CPP might be requested were supplementary requested. An extraction of the IDRAC (Cortellis) Global Module on CPPs with focus on the countries which were asked to answer the questionnaire can be found in Annex X.

Results

The working experiences of LRAMs worldwide represent the regulations of the Health Authorities laid down in their local law. The IDRAC/ Cortellis Overview of the Global Module on CPPs (IDRAC, 2013) provides a collection of local law and regulations for several countries inside and outside of ICH.

Every country included to the questionnaire has a HA structure in place, which is working on registrations of medicinal products. The size of the HAs varies from only a small sized HA with about 14 employees (HA in Uruguay), beside mid-sized HAs with about 100 or a few hundred employees (HA in Malaysia or CFDA in China) up to larger sized HAs with up to or more than 1000 employees (ANVISA in Brazil and MFDS in Korea). The numbers of reviewed applications vary between a few hundreds in Brazil (531 in 2011) or more than 1000 at MFDS in Korea and up to several thousands in China and Russia. But the questionnaire also shows in its results that only a part of the headcount numbers is working on the review of NDAs, for example half of the employees in Uruguay, or about 50% of the employees of the CFDA, 5% of the staff in Malaysia or 2 % of the employees of ANVISA in Brazil.

Furthermore, the review time of innovative medicinal products (e. g. Brazil up to 2 years), new medicinal product registrations on known active substances, for example Argentina with 12 months, Brazil 12-19 months, Malaysia 12-18 months or Uruguay 4 months and in contrast China with up to 2 years, might be different but usually still have the same requirement of including a CPP to the NDA or supplemental registration.

Many HAs in countries outside of ICH in emerging markets require at least one CPP as a mandatory document for the filing of a NDA or supplemental registration and variation submission during LCM.

Some countries such as Brazil, Uruguay or Russia do not necessarily ask for the WHO format (even though it is preferable), but some HAs, for example in Uruguay, not that they won't accept electronic CPPs.

The HAs of the importing country usually have reference countries from which they request and accept CPPs, for example from countries defined as Annex 1 countries including USA, Japan, Germany, France, UK, Netherlands, Belgium Denmark, Spain, Sweden or Italy, Switzerland, Israel, Canada, Austria. Mostly the CoO is asked to provide a CPP preferably with a marketed status of the product. Negotiations with some HAs on other reference countries may be possible due to experiences of LRAMs in some countries.

HAs often request one CPP for every submission, for example the CFDA in China or HA in Malaysia, but in some countries HAs also accept one CPP for a specific timeframe, as the CPP is valid with expiration date. There can be the alternative for LRAMs to submit certified copies of a CPP and therefore the CPP can be used until expiration. The U.S. FDA as issuing authority for example limits the validity of a CPP to 24 months and it is not possible to re-order a CPP, but different CPPs for the same registration can be applied for/ issued within a short timeframe. A new application for any CPP must be submitted to the U.S. FDA (McRoy & U.S. FDA, 2012). In case that the CPP includes material directly connected to the change, for example labeling changes with attached SmPC and labeling to the CPP, it can also

only be used for one specific submission. CFDA in China requires a CPP for every supplemental registration, or more detailed for every variation with effect on the Import Drug License (IDL) which is submitted during maintenance of a finished medicinal product. In case of innovative new drugs it is not unusual to have several supplemental registrations per year.

A CPP is often a mandatory requirement of high relevance and need according local regulations on medicinal product registration in countries outside of ICH; the questionnaire shows that the submission of a CPP is required and an approval is often not given when a CPP is not available. But the submission of a CPP will not accelerate the registration procedure.

While the CPP can provide information on the GMP status, some HAs accept the COPP as alternative to additionally providing a GMP certificate of the relevant manufacturing site, for example CFDA in China and HA in Russia, but they ask for the inspection date to be included to the CPP. Other HAs in countries like Argentina, Brazil, Uruguay and Malaysia will not accept the CPP as compensatory to the GMP certificate. The GMP certificate will be requested as another mandatory document for NDA.

HAs in importing countries often ask for legalization of a CPP even though the WHO Certification Scheme considered the CPP as true original, with no need of legalization. Argentina, Brazil and Russia will ask for legalization, while Malaysia will accept a CPP according to the WHO format with no need for legalization. China will ask for legalization and notarized copies if not the true original is submitted.

The results in the questionnaire give the information that no differences are made between Rx and OTC medicinal products. The requirements for the submission of CPPs for NDAs or supplemental registrations are the same. Without providing a CPP many local HAs in international regions outside ICH will not grant an approval on registrations or accept filing of variations during LCM of imported drugs.

Discussion

Emerging markets such as the countries evaluated via the questionnaire, are a widespread and diverse group of mostly growing economies. Therefore, the regulatory environment and requirements on drug registration in these countries may have increased as well.

Reviewing the questionnaire and listing of country requirements laid down in the current legislation confirms the fact that a CPP is very often a mandatory document for the application of marketing authorizations in countries with emerging markets outside of ICH. The CPP is an important certificate which is requested by the HA for the approval of NDA or even for the filing of the applications. Some importing countries may request at least two CPPs from different countries where the finished medicinal product is already authorized for marketing and also already marketed. Most HA in countries included to the questionnaire will not grant an approval when a CPP cannot be presented for imported finished medicinal products. Therefore the CPP is of very high importance for the pharmaceutical industry with local affiliates in countries outside of ICH in order to obtain and maintain registrations on imported medicinal products. Local HAs in countries outside of ICH might delay a review of a NDA because of a formal missing document, even though the local HA will carry out a complete assessment and full review of the application with all data including Module 2 to Module 5 details. But why might the HA work in this manner, knowing that a review could be delayed and therefore the availability of important drug products for patients suffering from serious diseases? One aspect for the HA could be that they don't want to waste any resources as long as there is a potential risk that a new medicinal product development might fail to be approved by any Stringent Drug Regulatory Authority (SRA).

One aspect often requested by HAs in importing countries to be available in the CPP can be that the marketing status is reflected positively in the CPP. Not all MSs issuing CPPs include this information on the certificate and it is questionable what

impact this information could give. The important evidence should be that the product is approved for marketing in the country and that a QSE review has taken place according a specific standard as defined in the objectives of the WHO Certification Scheme. This can be relevant, for example for products against tropical diseases, which are relevant for export only, when the manufacturing takes place in Germany but the disease to be treated does not occur locally.

Comparing HA from different countries huge differences in the size of the HA can be seen. For example, when comparing ANVISA from Brazil to the HA 'Ministerio de Salud Pública, Departamento de Medicamentos' in Uruguay, the HA in Uruguay has only a fraction of the amount of employees compared to the HA in Brazil. However, the normal time for reviewing a NDA is not slower. Both need about 15 months review time until approval. Both HAs require a CPP, but the advantage of relying on the CPP seems not to be taken by the HAs. It is commented for both countries that when the CPP is missing, an approval will not be granted (Brazil) or a submission can't be accepted (Uruguay). But in Uruguay an approval is also possible to be granted within 4 months of review time for novel drugs with known active substances, whereas the review in Brazil will not be faster.

A similar conclusion can be drawn for countries in the Asia-Pacific Region (Malaysia and Korea) or even countries like China and Russia, which are huge markets for the medicinal sector with high requirements and fast growing medical sector knowledge. The average review time takes usually one year or even longer with up to two years. In China and Russia a huge amount of reviews are conducted within one year, but it must also be considered that these countries are more and more confronted with rising health problems in their society due to changed lifestyles with growing and changing economic environments. The importance on relevant medical care will be growing with focus on available medication for patients in different medical fields. Due to the worldwide networking on news for example, patients in Russia can investigate that other countries may have drug products for diseases available, which are not yet available in Russia. There will be a rising

demand on the access to medicines worldwide also in diseases caused by rising standard of living and for example due to changed nutrition, like obesity and heart problems or diabetes.

Some limitations of the WHO Certification Scheme and a CPP could be that the requesting HA has to rely on the CA issuing the certificate. Dr. Rågo mentioned in a presentation on this point that “A certificate is as good as the certifying authority” (Rågo, 2011). It looks like that the WHO Certification Scheme is not fully implemented by HAs in countries outside of ICH, but still acknowledged. But how do these HAs handle and use the WHO Certification Scheme and especially the CPP? It seems that HAs, especially in growing emerging markets don’t want to depend on the review of other countries, e.g. ICH countries issuing a CPP, completely or solely. It is not only the pharmaceutical market that is growing in these emerging markets but also the medical sector including the HAs are developing quite fast, as concluded from the results of the questionnaire. For example, for Brazil’s ANVISA or Korea’s MFDS and in China the CFDA, knowledge and resources seem to be growing so that these countries are usually performing their own review on NDAs and supplemental registrations in detail. They are not demanding module 3 / Quality documents of the Common Technical Document (CTD) anymore. But HAs in countries outside of ICH use and consider WHO recommendations or regulations as shown on the example of the CPP within the WHO Certification Scheme. But they do not align to these recommendations completely; they only adjust them to their own regulations as far as they want to. They request the CPP as mandatory and ask for specific information to be included to the CPP (e.g. GMP status with inspection date, marketing status, SmPC and labeling etc.). And this can make sense for the countries themselves. They might see it more useful to require a CPP on time of submission rather than accepting it prior to approval. For the case that a CPP from the SRA of the CoO or another reference country will not become available, the requesting HA would not already waste local resources on starting a review of the NDA, which will never be approved.

But the consistency of the use and need of CPPs within the WHO Certification Scheme should be monitored closely. It is still quite clear that the recommended WHO format is not yet adopted in all issuing countries. Some HAs still tend to continue to issue Free Sales Certificates (FSC) not in line with the recommended WHO CPP format (Questionnaire Uruguay). But it must be differentiated between FSCs for medical devices which fall under different classification.

It is a known hurdle that sometimes issuing a CPP by one HA can end up in long delays. This fact does not simplify and accelerate the availability of important new medicinal products by ensuring QSE to smaller HAs in international countries worldwide.

Additionally the requirement by the requesting authority to legalize a CPP, which is usually to be seen as a true original, forces further delay. The Embassies of the requesting countries might need several weeks for confirming the authenticity of the CPP by legalization. On top of this delay it could be argued that further costs are created for example for legalizing and notary signatures, which could be avoided. In general HAs issuing and providing CPPs to requesting countries should have an effective post-marketing quality surveillance system in place and provide the administrative capacity for issuing certificates as CPPs as required in an acceptable timeframe. Furthermore, the HA should be able to answer queries in the occasion of complaints or requests given by HAs from importing countries (Rägo, 2011).

But referencing to the expected delays in issuing CPPs the importing and requesting countries should also consider to reduce an excessive demand on CPPs, e.g. for every single variation or requiring one or two CPPs for every submission. It could help to accept one CPP for a specific timeframe as the CPP is then already available at the site of submission. Changes to existing registrations at least could be simplified or accelerated. HAs accepting a CPP from the exporting country, which is qualified and eligible to issue a CPP, should therefore rely on the competence of the issuing HA, since they completed a full review of the registration dossier before.

Authorities in countries with appropriate resources for review of applications, such as ANVISA in Brazil, still conduct a full review in addition to the requirement of presenting a CPP from the Country of Origin. Even though this Health Authority might have more resources as in comparison to smaller countries, they request a CPP for the filing of a NDA. The applicant might submit the CPP later, prior to approval, but then a deficiency letter will be issued based on the missing CPP. It is to be discussed if this proceeding of the ANVISA is favorable, since they seem to have the scientific capacity and knowledge for a full review and they conduct the review completely. They would not need the CPP in addition to grant an approval for a finished product registration. The acceptance of a CPP does not accelerate the review time; worse than that the granting of a registration might be refused due to a missing CPP, even though the HA carried out a complete check of the dossier. Moreover, in addition to a CPP a GMP certificate is mandatory for submission and filing. An approval will not be given without a GMP certificate as well. This is another factor which is doubled, since the CPP from the CoO reflects the GMP status as recommended by the WHO. The EMA for example confirms that for CPPs issued for centralized registered products in the EU the CPP “is intended to confirm the status of the marketing authorization and GMP compliance in EU/EEA to support regulatory processes in importing countries” (EMA, 2012).

It might not be the situation anymore, that the *resources for conducting a review are non-existent in some emerging markets* (WHO, Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, 1995), since the requirements and knowledge are developing very fast nowadays. In the Asia-Pacific Region some countries are developing their own dossier structure in electronic format as the Asean-CTD, but the requirement of providing a CPP still exists.

Only some countries accept late filing prior to approval, but this seems to be on negotiation of the HA in agreement with the applicant of the MAA, as mentioned in the questionnaire for Malaysia. The ANMAT of Argentina e. g. can accept this

approach in order to get reviews started without delay for filing. Another alternative is for ANMAT to receive more details on clinical studies of the CTD than as mandatory with the CPP, when no CPP is available. This means a more detailed review by the HA, but according to the information of the LRAMs the overall approval time for a NDA is not changed.

It would be more efficient, not only in view of the pharmaceutical industry but this also is favorable for patients suffering from serious diseases, to request mandatory CPP prior to approval and to reduce the delay of the time to market.

The CPP as a “critical part of regulatory requirements” (Whiting , 2012) can be required not only for NDAs but for many types of submissions during the LCM of already registered finished medicinal products imported from other countries. In particular, for supplemental registrations affecting the quality of the finished medicinal product, a CPP is often required in the countries which were included to the evaluation via the questionnaires. Some local HAs accept one CPP for several submissions, even though that this means that certified copies are provided from the LRAM of the Applicant/ MAH. But further delay might be a risk if requesting new CPPs for every single submission, since issuing a CPP in the CoO might take several weeks to months (Wileman & Mishra, 2010). Considering that changes during LCM might be required due to safety aspects, it must be questioned if a delay in the review is acceptable for the patient who is already under medication of the affected registered drug product, while waiting for the CPP to be available. The Risk-Benefit must be monitored closely and it must be considered if it is legitimate, also for the HA, to wait for required changes with safety aspects only because of formal document requirements.

Whilst being mostly a mandatory requirement (possibly amended by further requirements like local clinical studies in Russia) especially for imported drugs, locally manufactured drugs are not often affected by this requirement. CPPs are usually not required for submissions of NDAs or supplemental registrations on locally manufactured finished medicinal products as it can be read out of the

questionnaire and local drug laws. But it must be considered that the resources, which could be relieved due to the acceptance of a CPP according WHO Certification Scheme for imported medicinal products, could be efficiently used for the work on local NDAs and registrations.

HAs in emerging markets must be considered to carry the burden to give neither imported drugs marketing, nor local manufactured drug marketing any advantage or disadvantage due to main differences in the approval and review process.

In the enclosed feedback given by LRAM of single countries only Brazil's ANVISA and Argentina's ANMAT consider it helpful to receive a CPP also for locally manufactured products from another country (preferably ICH or countries listed in "Annex 1" as listed in the questionnaire by several LRAMs EU, US, Canada, Australia etc.) since ANMAT and ANVISA consider it unlikely to be the first country worldwide to grant approval on a new medicinal product.

The Russian HA requests a CPP additionally to the NDA of imported finished medicinal products but it is mentioned that a WHO format is not required. But a CPP without WHO format would not necessarily reflect the standard as it is recommended by the WHO to prove the QES of the medicinal product to be reviewed and registered by another HA.

Due to the concept of the WHO Certification Scheme to provide some proof of completely reviewed QSE and the requirements which the WHO ask for from issuing HAs and CAs, these reviews are mainly done by SRAs which are mainly the countries within ICH, their observers and associated countries to ICH members. These HAs are supposed to have more resources to complete assessments; the CPP should be an alternative to complete local reviews and therefore reducing the delay of the availability of important drug developments.

But it is also possible that CPPs are issued by local HA which are mandatorily requesting CPPs. It might be needed that HAs in countries like Argentina, Brazil or countries with even smaller HAs have to issue CPPs for export of finished medicinal products. These medicinal products must not be manufactured locally but some

countries are often attached to strategic logistical chains in order to supply important products to sub-regions.

Another fact which could be evaluated by the questionnaire is to determine whether the local HA accepts the CPP as evidence for GMP even though the CPP as recommended by the WHO Certification Scheme includes the information on GMP status. Most HA such as ANVISA from Brazil or from Uruguay and Korea require a GMP certificate in addition to the CPP. But some HAs from countries like China or Russia will waive on the requested GMP certificate, if the inspection date is included in the CPP presenting the GMP status. But this information on the inspection date is not necessarily reflected in the CPP, for example in the German CPP from the 'Bezirksregierung Köln' it is not listed, which is only presenting the inspection status and timeframe (please refer to Annex III below) as recommended by the WHO content of the CPP (WHO, World Health Organisation - Model certificate of a pharmaceutical product, 2013).

For pharmaceutical companies it will be mandatory to follow up on the changed requirements in order to ensure that new medicinal products can be available in countries all around the world and also emerging markets, which will be important for sales. But the working experiences of LRAMs can be different or at least amending to the regulations written down by the local HAs. It will be challenging for the pharmaceutical companies since it can be shown that growing emerging markets with growing demands and requirements are distancing themselves from reduced reviews with trusting CPPs from ICH countries only. The CPP still remains to have a positive value. But it can't be denied that the full potential remains to be utilized inefficiently due to extended requirements of HAs especially in growing emerging markets. And for the MAH or Applicant during NDAs or supplemental registration the hurdle to provide a CPP is of very high relevance since the availability of new medicinal products on the market is not only very important for the health sector, but also for the pharmaceutical industry on a business aspect.

Regulatory planning to provide CPPs for countries where the finished medicinal product is meant to be registered and marketed is very important since the competitiveness of a product on a market is also determined by the time it is first available. One strategy could be for pharmaceutical companies to create a sub-department which is focusing on and dealing with all mandatory and requested certificates such as CPPs and GMP certificates, since it can be of very high workload to take care of this request, e.g. when a company is operating internationally in many countries.

Since many countries would refuse an approval on a NDA for imported finished medicinal products, the relevance of the CPP must be seen as very important and can't be neglected.

Some pharmaceutical companies might want to follow the concept to submit NDAs/MAAs on the same day for the same product worldwide, creating a good benchmark performance. But this concept can't be used if CPPs are required for filing of NDAs in several countries. Regulatory submission planning could follow a wave concept; countries needing a CPP for filing have to follow in a second wave, when CPPs are available due to first approvals by SRAs.

There are already associations by stakeholders working in detail on the use of a CPP. Formerly the European Federation of Pharmaceutical Industries and Associations (EFPIA) including "33 European national pharmaceutical industry associations as well as 40 leading companies undertaking research, development and the manufacture in Europe of medicinal products for human use" (EFPIA, 2013) worked together in the CPP Network. They are also conducting reviews and collecting industry experience of certification (e. g CPP, GMP certificates) requests and Regulatory Authority issuance. One of this networks is now allocated by the IFPMA (International Federation of Pharmaceutical Manufacturers & Associations), a "global, non-profit, nongovernmental organization" (IFPMA, 2013) and includes members of the pharmaceutical industry. They follow up new and changing requirements on CPPs since, being a highly important part for obtaining regulatory

approvals on drug registrations outside of ICH, this business is very important and it can't be disregarded by the industry. These associations are evaluating and discussing changed requirements and handling of the different requests by international HA. By this approach a delay in the application processes of NDAs or during variation submission is supposed to be minimized by the pharmaceutical industry as far as possible. Good regulatory planning is absolutely essential during LCM, beginning with NDAs. The stakeholders should try to seek consultations with HAs, in case the acceptance or the need for CPPs is not supportive regarding timesaving proceedings.

Outlook

Additionally there is an outlook developing by different HAs inside and outside of ICH to create electronic CPPs. Brazil's ANVISA already creates electronic documents, whereas EMA started discussions about this option. This could be favorable if the time for issuance can be reduced and if other MSs within the Certification Scheme are willing to accept the approach of electronic allocation. There would not be the need to provide new CPPs for every submission, but the CA could confirm that the electronic version is still valid. A similar approach is already in place for GMP certificates issued by the Spanish CA. They won't issue a paper-version of the GMP certificate for a specific manufacturing site anymore, but they present a certificate number and the electronic document can be downloaded and verified from the internet platform (<https://localizador.aemps.es/localizador/localizador.do>) of the HA Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).

To pick up the idea of electronic CPPs which could be made available faster, if HAs in emerging markets outside of ICH are willing to accept this documents electronically. But some HAs still insist on documents with wet ink signatures. Maybe a dialog with these HAs could improve the value of an electronic document which is available faster replacing a wet ink signature which is not providing any additional significance to the content of the certificate. Another additional approach to be assessed may be that SARs could also provide their Assessment Reports (AR) to other HAs during

review, as well when issuing a CPP. The EMA already grants access to the Public Assessment Report (PAR) after completion of a registration of medicinal products, but this PAR does not contain all details of their assessment due to confidential data. But maybe it could be approached in a way that the ARs could be transferred confidentially between HAs to accelerate the review process in other countries and make important new drug developments available to patients worldwide without delay and drug lag.

As already described by Whiting (Whiting , 2012), Răgo (Răgo, 2011) or Davidson et. al (Davidson, Grace, Schwarz, & Vickers, 2002), a need to amend the WHO Certification Scheme and encourage the HAs worldwide to adjust their regulations in order not to delay the availability of new innovative finished medicinal products for local markets can be discussed. But it must be considered how a new scheme would change the practice in the countries “as it is lived”? The HAs would not automatically adhere to recommendations only because they are set up new.

Anyway the HAs requesting a CPP, especially when mandatory for filing, could take advantage if they visualize their processes to the pharmaceutical industry explaining their approach not to accept any NDA for filing when a CPP is missing. Review times could be made more transparent, also explaining why resources are protected and used more efficiently by this planning.

Conclusion

The evaluation of this theses revealed that the CPP is a mandatory document needed for filing and approval of NDAs and different kinds of supplemental registrations during LCM of imported finished medicinal product registrations. But the requirement of presenting a CPP often creates a delay on the availability of these products in countries outside of ICH, although the WHO Certification Scheme was meant to accelerate the access to innovative new drug developments worldwide. Therapeutic feasibilities are not available as fast as it might be possible when considering the WHO recommendations more strictly. Countries outside of ICH could gain more advantage out of the WHO recommendations or regulations in order to save resources for other aspects in their authorities. But there is also room for the WHO recommendations to be adapted to the rapidly changing environment of Regulatory Affairs, which should be processed in collaboration with the WHO, Health Authorities and Stakeholders involved in this business. Current developments seem to worsen than to getting better.

While having a closer look at the sizes of HAs compared to their average review time needed to grant approvals on registrations the conclusion can be drawn that even a full review by smaller HAs in countries like Uruguay do not need more time or even less time than HAs with more resources due to size and headcount working on NDAs (e.g. in Brazil Korea or China). The potential of the WHO Certification Scheme to improve the efficiency of drug evaluation is not fully exploited by HAs in countries outside the ICH.

References

- Davidson, A., Grace, A. J., Schwarz, E. W., & Vickers, C. (2002). The Value of the certificate of Pharmaceutical Product in Registration of Medicinal Products. *Drug Information Journal*, 36, 163-167.
- EFPIA. (2013, 07 04). <http://www.efpia.eu/about-us>. Retrieved from <http://www.efpia.eu/about-us>
- EMA. (2012, October 25). *Information package for certificates of medicinal products issued by the European Medicines Agency (EMA) EMA/13878/2012*. London: EMA.
- Famulare, J. C., & U.S. FDA. (2003). *U.s. Food and Drug Administration*. Retrieved 05 2013, from Cetificate of Pharmaceutical Products Application Instruction: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm095808.pdf>
- Fletcher, J., Ahmed, M., & Pharo, C. (2012, July/ August). A comparison of ASEAN and Chinese drug registration requirements. *Regulatory Rapporteur*, 9(7/8), pp. 12-18.
- IDRAC, G. M. (2013, 06 03). *IDRAC Global Module Certificate of Pharmaceutical Product*. Retrieved 06 03, 2013, from <http://www.idrac.com/GlobalModule/ReportMatrix.aspx?Id=157&CountryCode=>
- IFPMA. (2013, 07 04). <http://www.ifpma.org/about-ifpma/welcome.html>. Retrieved from <http://www.ifpma.org/about-ifpma/welcome.html>
- McRoy, B., & U.S. FDA. (2012, 08 08). CDER Small Business Webinar on CDER Export Compliance and the Certificate of a Pharmaceutical Product (CPP) Application Process. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM314784.pdf>: U. S. Food and Drug Administration. Retrieved 05 2013, from Certificate of a Pharmaceutical Product* (CPP) Application Process: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM314784.pdf>
- Motara, A., & Fisher, I. (2011). Manufacturing site rationalisation - A regulatory and logistical challenge. *Regulatory Rapporteur*, 8(2), pp. 8-10.
- Rägo, L. (2011, 04). *APEC Harmonisation Center (AHC)*. Retrieved 06 2013, from Efficient Use of CPPs: http://www.apec-ahc.org/files/tp201105/Lembit_Rago_CPP_Asia_Regulatory_April2011.pdf
- Tomic, S., Filipovic Sucic , A., & Ilic Martinac , A. (2010). Good Manufacturing Practice: The role of local manufactureres and competent authorities. *ARH. HIG. RADA TOKSIKOL*, 61 (4), pp. 425-436.
- U.S. FDA. (2012, 06 01). *CDER Export Certificate Program Frequently Asked Questions (FAQs)*. Retrieved from

Relevance of a Certificate of Pharmaceutical Product for Registration and Life Cycle Management of Imported Drugs. How is the WHO Certification Scheme implemented by National Health Authorities outside of the ICH?

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/UCM318409.pdf>

- Wehrli, A. (1997). The WHO Certification Scheme on the Quality of Pharmaceutical Products moving in international commerce. *Drug Information Journal*, 31(3), pp. 899-902.
- Whiting, E. (2012, April). How has the evolution of the global pharmaceutical market affected the use of Certificates of Pharmaceutical Product (CPP)? *Regulatory Rapporteur*, Vol 9(No 4), 8-10.
- WHO. (1995). Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Geneva: World Health Organization.
- WHO. (2010). *WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce*. World Health Organization.
- WHO. (2012). *WHO Handbook for Guideline Development*. Geneva: WHO.
- WHO. (2013, 06). *An introduction to the World Health Organization*. Retrieved 06 2013, from http://www.who.int/about/brochure_en.pdf
- WHO. (2013, 04). *Areas of Work in Medicines*. Retrieved 04 2013, from <http://www.who.int/medicines/areas/en/>
- WHO. (2013, 05). *Competent authorities of countries participating in the WHO certification scheme*. Retrieved 05 2013, from http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/contacts/en/index.html
- WHO. (2013, 08 20). *Guideline Review Committee (GRC)*. Retrieved from WHO: http://www.who.int/kms/guidelines_review_committee/en/index.html
- WHO. (2013, 07 25). *Medicines; About us*. Retrieved from <http://www.who.int/medicines/about/en/>
- WHO. (2013, 05). *World Health Organisation*. Retrieved 05 2013, from <http://www.who.int/publications/guidelines/en/index.html>
- WHO. (2013, 05). *World Health Organisation - Model certificate of a pharmaceutical product*. Retrieved 05 2013, from http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html
- WHO. (2013, 04). *World Health Organization - Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce*. Retrieved 04 2013, from Guidelines on the implementation

Relevance of a Certificate of Pharmaceutical Product for Registration and Life Cycle Management of Imported Drugs. How is the WHO Certification Scheme implemented by National Health Authorities outside of the ICH?

of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce:

http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index2.html

WHO. (2013, 04). *World Health Organization - Medicines*. Retrieved 04 2013, from http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate/en/index.html

Wileman, H., & Mishra, A. (2010, April-June). Drug Lag and Key Regulatory Barriers in the Emerging Markets. *PICR*, 1(2), 51-56.

World Health Organization. (2010). *WHO CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE*. http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/qas_certif_scheme_2012.pdf: Working document QAS/10.374.

Annex

Annex I – Model certificate of a pharmaceutical product

http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate/en/index.html

Annex II – MHRA CPP Application Form UK

<http://www.mhra.gov.uk/Howweregulate/Medicines/Importingandexportingmedicines/Exportingmedicines/index.htm#l2>

Annex III – ZLG CPP Template DE + Bezirksregierung Köln

<https://www.zlg.de/nc/arzneimittel/service/dokumente.html>

Annex IV – EMA CPP Application Form

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000249.jsp&mid=WC0b01ac058005bee5

Annex V – FDA CPP Application Form

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM052388.pdf>

Annex VI – Malaysia CPP Application Form

<http://portal.bpfk.gov.my/index.cfm?&menuid=114>

Annex VII – Argentina CPP Application Form

http://federal.anmat.gov.ar/federal.anmat/principal_en.php

Annex VIII – Brazil CPP Application Form

<http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Medicamentos/Assunto+de+Interesse/Certificados+e+Certidoes+de+Exportacao/Modelos+de+Certificados+de+Produtos+Farmaceuticos>

Annex IX – Country Questionnaires

Supported by LRAMs in Argentina, Brazil, Uruguay, Malaysia, Korea, China and Russia

Annex X – IDRAC Global Module on CPP (extract)

<http://www.idrac.com/GlobalModule/ReportMatrix.aspx?Id=157&CountryCode=>

Annex I – Model Certificate of a Pharmaceutical Product

*Model certificate of a pharmaceutical product
according WHO recommendation*

Certificate of a Pharmaceutical Product¹

No. of certificate

Exporting (certifying country):

Importing (requesting country):

1. Name and dosage form of the product:

1.1. Active ingredient(s)² and amount(s) per unit dose³:

For complete composition including excipients, see attached⁴:

1.2. Is this product licensed to be placed on the market for use in the exporting country?⁵ (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 2B⁶:

2.A.1. Number of product licence⁷ and date of issue:

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

2.A.3. Status of product license holder⁸: (Key in appropriate category as defined in note 8)

2.A.3.1. For categories b and c the name and address of the manufacturer producing the dosage form is⁹:

2.A.4. Is a summary basis for approval appended?¹⁰ (yes/no)

2.A.5. Is the attached, officially approved product information complete and consonant with the licence?¹¹ (yes/no/not provided)

2.A.6. Applicant for certificate, if different from license holder (name and address)¹²:

2.B.1. Applicant for certificate (name and address):

2.B.2. Status of applicant: (Key in appropriate category as defined in footnote ⁸)

2.B.2.1. For categories (b) and (c) the name and address of the manufacturer producing the dosage form is:⁹

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

consideration/refused)

2.B.4. Remarks¹³:

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? (yes/no/not applicable)¹⁴

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?¹⁵ (yes/no/not applicable)¹⁴

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product¹⁶: (yes/no)

If no, explain:

Address of certifying authority:

Telephone:

Fax:

Name of authorized person:

Signature

Stamp and date

(WHO, World Health Organization - Medicines, 2013)

Explanatory notes

- 1. This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.*
- 2. Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.*
- 3. The formula (complete composition) of the dosage form should be given on the certificate or be appended.*

4. *Details of quantitative composition are preferred but their provision is subject to the agreement of the product-license holder.*
5. *When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product license.*
6. *Sections 2A and 2B are mutually exclusive.*
7. *Indicate, when applicable, if the license is provisional, or the product has not yet been approved.*
8. *Specify whether the person responsible for placing the product on the market:*
 - a. *manufactures the dosage form;*
 - b. *packages and/or labels a dosage form manufactured by an independent company; or*
 - c. *is involved in none of the above.*
9. *This information can only be provided with the consent of the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product license. If the production site is changed, the license has to be updated or it is no longer valid.*
10. *This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.*
11. *This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC)*
12. *In this circumstance, permission for issuing the certificate is required from the product-license holder. This permission has to be provided to the authority by the applicant.*
13. *Please indicate the reason that the applicant has provided for not requesting registration.*

- a. *the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;*
- b. *the product has been reformulated with a view to improving its stability under tropical conditions;*
- c. *the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;*
- d. *the product has been reformulated to meet a different maximum dosage limit for an active ingredient;*
- e. *any other reason, please specify.*

14. *Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.*

15. *The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).*

16. *This section is to be completed when the product-license holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.*

Annex II – MHRA CPP Application Form UK

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

UNLICENSED PRODUCTS MANUFACTURED IN THE UK

APPLICATION FORM

PLEASE COMPLETE ALL RELEVANT SECTIONS IN THIS FORM
LEGIBLY USING BLACK INK. OMISSIONS MAY LEAD TO DELAY.

To be completed only by MHRA staff - Application Number:	
--	--

<u>SECTION 1</u>	
1.1. Date of application:	
1.2. Applicants own reference number :	
1.3. Name and dosage form of the product:	
1.4. Applicant details:	
Name:	
Company Name:	
Address:	
Postcode:	
1.5. Invoice details (if different from above):	
Name:	
Company Name:	
Address:	
Postcode:	

MHRA Licensed CPP Unlicensed app form (November 2010)

SECTION 1 continued

1.6. Importing country for which the certificate is required:

1.7. Name of the product in the importing country (if different from 1.3.):

1.8. Language required:- Please tick the appropriate box. If no box is ticked English will be used.

English ☐ French ☐ German ☐ Italian ☐ Portuguese ☐ Spanish ☐

1.9. Service required:- Please tick the appropriate box. If no box is ticked the standard service will be provided.

Standard ☐

Urgent ☐

1.10. Number of copies of the certificate required:

Up to three copies of the certificate will be supplied at no additional cost to the fee for the selected service. Further copies are available at a cost of £28.00 per additional copy. Please enter in the box(es) below the number of copies of the certificate required. If no entry is made in either box one copy will be supplied.

Number of certificates required (up to three at no additional cost)

Number of additional copies at £28.00 per copy

When complete please return the form to : exports@mhra.gsi.gov.uk

or

**The Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road
London
SW1W 9SZ**

FAO: Export Certificate Group, 5th Floor

MHRA Licensed CPP Unlicensed app form (November 2010)

SECTION 2

2.1. Please list active ingredient(s) and amount(s) per unit dose.

Active Ingredient

Amount per unit dose

Please list excipients giving the formulation in full.

Excipient

Amount per unit dose

TICK IF YOU WANT EXCIPIENTS TO BE EXPRESSED QUALITATIVELY ONLY

☐

Please write in the box below the number of supplementary pages attached (if any).

SECTION 2 continued

2.2. Is this product actually on the market in the UK ? (Please tick the appropriate box)

Yes ☐ (a)

No ☐ (b)

If (b) is ticked go to 2.3. If (a) is ticked go to Section 3.

2.3. Indicate the reason the product is not on the market in the UK by ticking the appropriate box

- the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the UK ☐ (a)
- the product has been reformulated with a view to improving its stability under tropical conditions ☐ (b)
- the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import ☐ (c)
- the product has been reformulated to meet a different maximum dosage limit for an active ingredient ☐ (d)
- for commercial reasons this product is not marketed in the UK ☐ (e)
- the product is licensed but awaiting launch ☐ (f)
- the product Marketing Authorisation is under assessment by the MHRA ☐ (g)
- any other reason ☐ (h)

If box (h) is ticked explanatory text (not exceeding 180 characters including spaces) for inclusion on the certificate may be entered below.

SECTION 3

3.1. Company name to appear on the certificate (the exporter) :

Name:

Address:

Postcode:

3.2. Status of the exporter (Please tick the appropriate box)

manufactures the dosage form and is responsible for the quality assurance and release of the product ☐ (a)

packages and/or labels a dosage form manufactured by another company but is responsible for the quality assurance and release of the product ☐ (b)

is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product ☐ (c)

is involved in none of the above ☐ (d)

3.3. Do you want details of:

(a) Manufacturing Site

Yes

No

☐☐

(b) Manufacturing Licence Holder

☐☐

to be stated on the Certificate? Please tick the appropriate box.

If Yes is ticked complete 3.4 and 3.5. If No is ticked complete 3.4, omit 3.5 then go to 3.6.
(See Appendix 1 of Guidelines)

SECTION 3 continued

- 3.4. For categories a, b, c and d in question 3.2. the name and address of the manufacturing site where the dosage form is produced are:

Name:
Address:

--

If required, please use the section below to provide further names and addresses.

Name:
Address:

--

Manufacturer ☐ Assembler/
Packager ☐

Name:
Address:

--

Manufacturer ☐ Assembler/
Packager ☐

Name:
Address:

--

Manufacturer ☐ Assembler/
Packager ☐

Name:
Address:

--

Manufacturer ☐ Batch-Release ☐

Name:
Address:

--

Assembler/
Packager ☐ Batch-
Release ☐

Name:
Address:

--

Assembler/
Packager ☐ Batch-Release ☐

SECTION 3 continued

3.5. For categories b, c and d in question 4.2. the name and address of the manufacturing licence holder are:

Name:

Address:

Please enter the manufacturer's licence number here:

3.6. Why is the Marketing Authorisation lacking ? (Please tick the appropriate box)

Under assessment by the MHRA ☐ (a)

Not requested ☐ (b)

Refused ☐ (c)

If (a) is ticked go to 3.7. If (b) is ticked go to 3.8. If (c) is ticked go to [Section 4](#).

3.7. If (a) was ticked at 3.6. enter the provisional Marketing Authorisation number (if known) in the box below and go to [Section 4](#).

Provisional Marketing Authorisation number :

3.8. Indicate the reason for not requesting Marketing Authorisation by ticking the appropriate box

- the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the UK ☐ (a)

- the product has been reformulated with a view to improving its stability under tropical conditions ☐ (b)

- the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the UK ☐ (c)

- the product has been reformulated to meet a different maximum dosage limit for an active ingredient ☐ (d)

- this type of product does not require a Marketing Authorisation in the UK ☐ (e)

- any other reason ☐ (f)

If box (f) is ticked explanatory text (not exceeding 180 characters including spaces) for inclusion on the certificate may be entered below.

SECTION 4

4.1. Does the Medicines and Healthcare products Regulatory Agency arrange for periodic inspection of the manufacturing plant in which the dosage form is produced ? (Please tick the appropriate box)

Yes ☐

No ☐

If the answer to question 4.1 is Yes, proceed to question 4.2.

If the answer to question 4.1 is No, proceed to Section 5.

4.2. Has the manufacture of this type of dosage form been inspected ? (Please tick the appropriate box)

Yes ☐

No ☐

4.3. Do the facilities and operations conform to GMP as recommended by the World Health Organisation ? (Please tick the appropriate box)

Yes ☐

No ☐

Not Applicable ☐

SECTION 5

5.1. Do you require a copy of the "Letter to the Recipient Health Authority" ? (Please tick the appropriate box)

Yes ☐

No ☐

Please use this page to list further excipients and further active ingredient(s) if required

DO NOT ATTACH TO APPLICATION FORM UNLESS REQUIRED

If required, please list excipients.	
<u>Excipient</u>	<u>Amount per unit dose</u>

If required, please list active ingredient(s) and amount(s) per unit dose.	
<u>Active Ingredient</u>	<u>Amount per unit dose</u>

Please attach further pages as required

MHRA Licensed CPP Unlicensed app form (November 2010)

Annex III – ZLG CPP Template DE + Bezirksregierung Köln

Zertifikat eines pharmazeutischen Produkts¹

Dieses Zertifikat entspricht der von der Weltgesundheitsorganisation empfohlenen Form (Allgemeine Hinweise und Erläuterungen beigelegt).

Nr. des Zertifikats:

Ausführendes (zertifizierendes) Land: Deutschland

Einführendes (anforderndes) Land:

1. Name und Darreichungsform des Produkts:

1.1 Wirkstoff(e)² und Menge(n) pro Dosierungseinheit³:

Komplette qualitative Zusammensetzung inklusive Hilfsstoffe siehe Anlage.⁴

1.2 Ist dieses Produkt für ein Inverkehrbringen im Ausfuhrland zugelassen?⁵

☐ ja ☐ nein

(bitte Zutreffendes ankreuzen)

1.3 Ist dieses Produkt gegenwärtig im Ausfuhrland im Handel?

☐ ja ☐ nein ☐ unbekannt

(bitte Zutreffendes ankreuzen)

Wenn die Antwort von 1.2 „ja“ ist, mit Abschnitt 2A weitermachen und Abschnitt 2B überspringen.

Wenn die Antwort von 1.2 „nein“ ist, Abschnitt 2A überspringen und mit Abschnitt 2B weitermachen.⁶

2A.1 Zulassungsnummer des Produktes⁷ und Ausstellungsdatum:

2A.2 Zulassungsinhaber (Name und Adresse):

2A.3 Status des Zulassungsinhabers:⁸
☐ a ☐ b ☐ c
(bitte zutr. Kategorie eintragen wie in Anm. 8 angg.)

2A.3.1 Für die Kategorien b und c Name und Adresse des Herstellers der Darreichungsform angeben:⁹

2A.4 Ist eine Zusammenfassung der Zulassungsgrundlagen beigelegt?¹⁰
☐ ja ☐ nein
(bitte Zutreffendes ankreuzen)

Certificate of a Pharmaceutical Product¹

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

No. of Certificate:

Exporting (certifying) country: Germany

Importing (requesting) country:

1. Name and dosage form of product:

1.1 Active ingredient(s)² and amount(s) per unit dose:³

For complete qualitative composition including excipients, see attached.⁴

1.2 Is this product licensed to be placed on the market for use in the exporting country?⁵

☐ yes ☐ no

(key in as appropriate)

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

☐ yes ☐ no ☐ unknown

(key in as appropriate)

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.⁶

2A.1 Number of product licence⁷ and date of issue:

2A.2 Product-licence holder (name and address):

2A.3 Status of product-licence holder:⁸
☐ a ☐ b ☐ c
(key in appropriate category as defined in note 8)

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are:⁹

2A.4 Is Summary Basis of Approval appended?¹⁰
☐ yes ☐ no
(key in as appropriate)



2A.5	Ist die beigefügte, offiziell anerkannte Produktinformation vollständig und in Übereinstimmung mit der Zulassung? ¹¹ <input type="checkbox"/> ja <input type="checkbox"/> nein <input type="checkbox"/> nicht beigefügt (bitte Zutreffendes ankreuzen)	2A.5	Is the attached, officially approved product information complete and consonant with the licence? ¹¹ <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> not provided (key in as appropriate)
2A.6	Antragsteller des Zertifikats, wenn nicht identisch mit dem Zulassungsinhaber (Name und Adresse): ¹² ,	2A.6	Applicant for certificate, if different from licence holder (name and address): ¹² ,
2B.1	Antragsteller des Zertifikats (Name und Adresse): ,	2B.1	Applicant for certificate (name and address): ,
2B.2	Status des Antragstellers: <input type="checkbox"/> a <input type="checkbox"/> b <input type="checkbox"/> c (bitte zutreffende Kategorie eintragen wie in Anmerkung 8 angegeben)	2B.2	Status of applicant: <input type="checkbox"/> a <input type="checkbox"/> b <input type="checkbox"/> c (key in appropriate category as defined in note 8)
2B.2.1	Für die Kategorien b und c Name und Adresse des Herstellers der Darreichungsform angeben: ⁹ ,	2B.2.1	For categories b and c the name and address of the manufacturer producing the dosage form are: ⁹ ,
2B.3	Warum fehlt die Genehmigung für das Inverkehrbringen? <input type="checkbox"/> nicht verlangt <input type="checkbox"/> nicht erbeten <input type="checkbox"/> in Bearbeitung <input type="checkbox"/> abgelehnt (bitte Zutreffendes ankreuzen)	2B.3	Why is marketing authorization lacking? <input type="checkbox"/> not required <input type="checkbox"/> not requested <input type="checkbox"/> under consideration <input type="checkbox"/> refused (key in as appropriate)
2B.4	Bemerkungen: ¹³	2B.4	Remarks: ¹³
3.	Führt die zertifizierende Behörde regelmäßige Inspektionen des Herstellungsbetriebs durch, in dem die Darreichungsform produziert wird? <input type="checkbox"/> ja <input type="checkbox"/> nein <input type="checkbox"/> nicht zutreffend ¹⁴ (bitte Zutreffendes ankreuzen) Wenn „nein“ oder „nicht zutreffend“ mit Frage 4 weitermachen.	3.	Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> not applicable ¹⁴ (key in as appropriate) If no or not applicable proceed to question 4.
3.1	Zeiträume der regelmäßigen Inspektionen (Jahre):	3.1	Periodicity of routine inspections (years):
3.2	Wurde die Herstellung dieses Darreichungsform-Typs inspiziert? <input type="checkbox"/> ja <input type="checkbox"/> nein (bitte Zutreffendes ankreuzen)	3.2	Has the manufacture of this type of dosage form been inspected? <input type="checkbox"/> yes <input type="checkbox"/> no (key in as appropriate)
3.3	Entsprechen die Einrichtungen und Abläufe den GMP, wie von der Weltgesundheitsorganisation empfohlen? ¹⁵ <input type="checkbox"/> ja <input type="checkbox"/> nein <input type="checkbox"/> nicht zutreffend ¹⁴ (bitte Zutreffendes ankreuzen)	3.3	Do the facilities and operations conform to GMP as recommended by the World Health Organization? ¹⁵ <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> not applicable ¹⁴ (key in as appropriate)
4.	Genügt der zertifizierenden Behörde die vom Antragsteller eingereichte Information - die Herstellung des Produkts betreffend - in allen Punkten? ¹⁶ <input type="checkbox"/> ja <input type="checkbox"/> nein (bitte Zutreffendes ankreuzen)	4.	Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? ¹⁶ <input type="checkbox"/> yes <input type="checkbox"/> no (key in as appropriate)

Wenn nein, bitte erklären:

If no, explain:

Adresse der zertifizierenden Behörde:

Address of certifying authority:

Telefonnummer:
Faxnummer:

Telephone number:
Fax number:

Name der befugten Person:

Name of authorized person:

Unterschrift:

Signature:

Stempel und Datum:

Stamp and date:

Allgemeine Hinweise

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Zusätzliche Blätter zur Unterbringung von Erläuterungen und Erklärungen sollten, wenn nötig, beigelegt werden.

Erläuterungen

- 1 Dieses Zertifikat in der von der WHO empfohlenen Form weist den Status des pharmazeutischen Produkts und des Antragstellers für dieses Zertifikat im Ausfuhrland nach. Es ist nur für ein Produkt vorgesehen, da sich Herstellungsvoraussetzungen und zugelassene Informationen für verschiedene Darreichungsformen und Dosierungsstärken unterscheiden können.
- 2 Benutzen Sie, wenn möglich, internationale (INNs, International Nonproprietary Names) oder nationale Nicht-Markennamen.
- 3 Die Zusammensetzung (komplette Zusammensetzung) der Darreichungsform sollte auf dem Zertifikat angegeben oder beigelegt werden.
- 4 Details der mengenmäßigen Zusammensetzung werden bevorzugt, aber ihre Bekanntgabe ist abhängig von der Zustimmung des Zulassungsinhabers.
- 5 Wenn zutreffend, fügen Sie alle Einzelheiten einer Einschränkung den Verkauf, Vertrieb oder die Verabreichung des Produkts betreffend, wie in der Produktzu-

General instructions

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Explanatory notes

- 1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
- 2 Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
- 3 The formula (complete composition) of the dosage form should be given on the certificate or be appended.
- 4 Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-licence holder.
- 5 When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.

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lassung spezifiziert, bei.

- | | |
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| <p>6 Die Abschnitte 2A und 2B schließen sich gegenseitig aus.</p> <p>7 Geben Sie an, wenn zutreffend, ob die Zulassung vorläufig ist, oder ob das Produkt noch nicht zugelassen ist.</p> <p>8 Erläutern Sie, ob die für das Inverkehrbringen des Produktes verantwortliche Person
a) die Darreichungsform herstellt;
b) eine von einer unabhängigen Firma hergestellte Darreichungsform verpackt und/oder etikettiert oder
c) mit keinem der o.a. befasst ist.</p> <p>9 Diese Angaben können nur nach Absprache mit dem Zulassungsinhaber oder im Falle eines nicht zugelassenen Produkts mit dem Antragsteller erteilt werden. Ein Nichtausfüllen dieses Abschnittes zeigt, dass die betroffene Partei nicht der Einfügung dieser Informationen zugestimmt hat.</p> <p>Es soll angemerkt werden, dass Informationen über den Produktionsort Bestandteil der Produktzulassung sind. Wenn der Produktionsort gewechselt wird, muß die Zulassung auf den neuen Stand gebracht werden oder sie verliert ihre Gültigkeit.</p> <p>10 Dieses bezieht sich auf das Dokument, wie ausgestellt von einigen nationalen Zulassungsbehörden, das die technischen Grundlagen zusammenfasst, auf denen die Zulassung basiert.</p> <p>11 Dieses bezieht sich auf die Produktinformation, genehmigt durch die zuständige nationale Aufsichtsbehörde, wie z.B. eine "Zusammenfassung der Produkteigenschaften" (SPC).</p> <p>12 Unter diesen Umständen wird vom Zulassungsinhaber die Erlaubnis zum Ausstellen des Zertifikats benötigt. Diese Erlaubnis muß der Behörde vom Antragsteller vorgelegt werden.</p> <p>13 Bitte erläutern Sie Begründung des Antragstellers, warum keine Registrierung angefordert wurde:
(a) das Produkt wurde ausschließlich für die Behandlung von Erkrankungen - insbesondere Tropenkrankheiten - entwickelt, die im Ausfuhrland nicht endemisch sind;
(b) das Produkt wurde neu formuliert im Hinblick auf eine Verbesserung der Stabilität unter Tropenbedingungen;
(c) das Produkt wurde neu formuliert, um Hilfsstoffe, die im Einfuhrland nicht zum Gebrauch in pharmazeutischen Produkten zugelassen sind, zu entfernen;
(d) das Produkt wurde neu formuliert, um für einen Wirkstoff eine andere Dosierungsobergrenze zu erreichen;
(e) aus irgendwelchen anderen Gründen, bitte erläutern.</p> <p>14 Nicht zutreffend bedeutet, dass die Herstellung in einem anderen als dem das Produktzertifikat ausstellenden Land stattfindet und die Inspektion im Auftrag des Herstellungslandes durchgeführt wird.</p> <p>15 Die Anforderungen an Gute Praktiken bei der Herstellung und Qualitätskontrolle von Arzneimitteln, auf die im Zertifikat Bezug genommen wird, sind im 32. Bericht des Expertenausschusses für Spezifikationen für phar-</p> | <p>6 Sections 2A and 2B are mutually exclusive.</p> <p>7 Indicate, when applicable if the licence is provisional, or the product has not yet been approved.</p> <p>8 Specify whether the person responsible for placing the product on the market:
a) manufactures the dosage form;
b) packages and/or labels a dosage form manufactured by an independent company;
or
c) is involved in none of the above.</p> <p>9 This information can be provided only with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.</p> <p>It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence must be updated or it will cease to be valid.</p> <p>10 This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.</p> <p>11 This refers to product information approved by the competent national regulatory authority, such as a Summary of Product Characteristics (SPC).</p> <p>12 In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission must be provided to the authority by the applicant.</p> <p>13 Please indicate the reason that the applicant has provided for not requesting registration:
(a) the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the country of export;
(b) the product has been reformulated with a view to improving its stability under tropical conditions
(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
(e) any other reason, please specify.</p> <p>14 Not applicable means that the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.</p> <p>15 The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Prepara-</p> |
|---|--|



mazeutische Zubereitungen (WHO-Fachschriftenreihe Nr. 823, 1992, Anlage 1¹⁾) enthalten. Speziell für biologische Produkte zutreffende Empfehlungen wurden durch den WHO Expertenausschuss für biologische Standardisierung (WHO-Fachschriftenreihe, Nr. 822, 1992, Anlage 1¹⁾) formuliert.

- 16 Dieser Abschnitt sollte vervollständigt werden, wenn der Zulassungsinhaber oder Antragsteller dem Status (b) oder (c), wie unter Nr. 8 oben beschrieben, entspricht. Dies ist besonders wichtig, wenn ausländische Vertragspartner in die Herstellung des Arzneimittels eingebunden sind. Unter diesen Umständen sollte der Antragsteller die zertifizierende Behörde entsprechend unterrichten, um die Vertragsparteien, die für die einzelnen Herstellungsstufen des Fertigarzneimittels verantwortlich sind und den Umfang und die Art der Kontrollen, die bei jeder dieser Parteien durchgeführt werden, zu ermitteln.

tions (WHO Technical Report Series, No. 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No.822, 1992, Annex 1).

- 16 The section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.



Zertifikat eines pharmazeutischen Produkts¹

Dieses Zertifikat entspricht der von der Weltgesundheitsorganisation empfohlenen Form (Allgemeine Hinweise und Erläuterungen beigelegt).

Nr. des Zertifikats:

Ausführendes (zertifizierendes) Land: Deutschland

Einführendes (anforderndes) Land:

1. Name und Darreichungsform des Produkts:

1.1 Wirkstoff(e)² und Menge(n) pro Dosierungseinheit³:

Komplette qualitative Zusammensetzung inklusive Hilfsstoffe siehe Anlage.⁴

1.2 Ist dieses Produkt für ein Inverkehrbringen im Ausfuhrland zugelassen?⁵
☐ ja ☐ nein
(bitte Zutreffendes ankreuzen)

1.3 Ist dieses Produkt gegenwärtig im Ausfuhrland im Handel?
☐ ja ☐ nein ☐ unbekannt
(bitte Zutreffendes ankreuzen)

Wenn die Antwort von 1.2 „ja“ ist, mit Abschnitt 2A weitermachen und Abschnitt 2B überspringen.

Wenn die Antwort von 1.2 „nein“ ist, Abschnitt 2A überspringen und mit Abschnitt 2B weitermachen.⁶

2A.1 Zulassungsnummer des Produktes⁷ und Ausstellungsdatum:

2A.2 Zulassungsinhaber (Name und Adresse):

2A.3 Status des Zulassungsinhabers:⁸
☐ a ☐ b ☐ c
(bitte zutr. Kategorie eintragen wie in Anm. 8 angg.)

2A.3.1 Für die Kategorien b und c Name und Adresse des Herstellers der Darreichungsform angeben:⁹

Hersteller der Darreichungsform:

Verpackung:

Endfreigabe:

2A.4 Ist eine Zusammenfassung der Zulassungsgrundlagen beigelegt?¹⁰
☐ ja ☐ nein
(bitte Zutreffendes ankreuzen)

2A.5 Ist die beigelegte, offiziell anerkannte Produktinformation vollständig und in Übereinstimmung mit der Zulassung?¹¹
☐ ja ☐ nein ☐ nicht beigelegt
(bitte Zutreffendes ankreuzen)

Certificate of a Pharmaceutical Product¹

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

No. of Certificate:

Exporting (certifying) country: Germany

Importing (requesting) country:

1. Name and dosage form of product:

1.1 Active ingredient(s)² and amount(s) per unit dose³:

For complete qualitative composition including excipients, see attached.⁴

1.2 Is this product licensed to be placed on the market for use in the exporting country?⁵
☐ yes ☐ no
(key in as appropriate)

1.3 Is this product actually on the market in this exporting country?
☐ yes ☐ no ☐ unknown
(key in as appropriate)

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.⁶

2A.1 Number of product licence⁷ and date of issue:

2A.2 Product-licence holder (name and address):

2A.3 Status of product-licence holder:⁸
☐ a ☐ b ☐ c
(key in appropriate category as defined in note 8)

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are:⁹
Bulk Manufacturer:

Packaging:

Final Release:

2A.4 Is Summary Basis of Approval appended?¹⁰
☐ yes ☐ no
(key in as appropriate)

2A.5 Is the attached, officially approved product information complete and consonant with the licence?¹¹
☐ yes ☐ no ☐ not provided
(key in as appropriate)

<p>2A.6 Antragsteller des Zertifikats, wenn nicht identisch mit dem Zulassungsinhaber (Name und Adresse):¹²</p> <p>2B.1 Antragsteller des Zertifikats (Name und Adresse):</p> <p>2B.2 Status des Antragstellers: <input type="checkbox"/>a <input type="checkbox"/>b <input type="checkbox"/>c <i>(bitte zutreffende Kategorie eintragen wie in Anmerkung 8 angegeben)</i></p> <p>2B.2.1 Für die Kategorien b und c Name und Adresse des Herstellers der Darreichungsform angeben:⁹</p> <p>2B.3 Warum fehlt die Genehmigung für das Inverkehrbringen? <input type="checkbox"/>nicht verlangt <input type="checkbox"/>nicht erbeten <input type="checkbox"/>in Bearbeitung <input type="checkbox"/>abgelehnt <i>(bitte Zutreffendes ankreuzen)</i></p> <p>2B.4 Bemerkungen:¹³</p> <p>3. Führt die zertifizierende Behörde regelmäßige Inspektionen des Herstellungsbetriebs durch, in dem die Darreichungsform produziert wird? <input type="checkbox"/>ja <input type="checkbox"/>nein <input type="checkbox"/>nicht zutreffend¹⁴ <i>(bitte Zutreffendes ankreuzen)</i> Wenn „nein“ oder „nicht zutreffend“ mit Frage 4 weitermachen.</p> <p>3.1 Zeiträume der regelmäßigen Inspektionen (Jahre):</p> <p>3.2 Wurde die Herstellung dieses Darreichungsform-Typs inspiziert? <input type="checkbox"/>ja <input type="checkbox"/>nein <i>(bitte Zutreffendes ankreuzen)</i></p> <p>3.3 Entsprechen die Einrichtungen und Abläufe den GMP, wie von der Weltgesundheitsorganisation empfohlen?¹⁵ <input type="checkbox"/>ja <input type="checkbox"/>nein <input type="checkbox"/>nicht zutreffend¹⁴ <i>(bitte Zutreffendes ankreuzen)</i></p> <p>4. Genügt der zertifizierenden Behörde die vom Antragsteller eingereichte Information - die Herstellung des Produkts betreffend - in allen Punkten?¹⁶ <input type="checkbox"/>ja <input type="checkbox"/>nein <i>(bitte Zutreffendes ankreuzen)</i></p> <p>Wenn nein, bitte erklären:</p> <p>Adresse der zertifizierenden Behörde: Bezirksregierung Köln, Zeughausstr. 2-10, 50667 Köln, Deutschland</p> <p>Telefonnummer: +49-221-147-2534</p> <p>Faxnummer: +49-221-147-3424</p> <p>Name der befugten Person:</p> <p>Unterschrift:</p>	<p>2A.6 Applicant for certificate, if different from licence holder (name and address):¹²</p> <p>2B.1 Applicant for certificate (name and address):</p> <p>2B.2 Status of applicant: <input type="checkbox"/>a <input type="checkbox"/>b <input type="checkbox"/>c <i>(key in appropriate category as defined in note 8)</i></p> <p>2B.2.1 For categories b and c the name and address of the manufacturer producing the dosage form are:⁹</p> <p>2B.3 Why is marketing authorization lacking? <input type="checkbox"/>not required <input type="checkbox"/>not requested <input type="checkbox"/>under consideration <input type="checkbox"/>refused <i>(key in as appropriate)</i></p> <p>2B.4 Remarks:¹³</p> <p>3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? <input type="checkbox"/>yes <input type="checkbox"/>no <input type="checkbox"/>not applicable¹⁴ <i>(key in as appropriate)</i> If no or not applicable proceed to question 4.</p> <p>3.1 Periodicity of routine inspections (years):</p> <p>3.2 Has the manufacture of this type of dosage form been inspected? <input type="checkbox"/>yes <input type="checkbox"/>no <i>(key in as appropriate)</i></p> <p>3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization?¹⁵ <input type="checkbox"/>yes <input type="checkbox"/>no <input type="checkbox"/>not applicable¹⁴ <i>(key in as appropriate)</i></p> <p>4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product?¹⁶: <input type="checkbox"/>yes <input type="checkbox"/>no <i>(key in as appropriate)</i></p> <p>If no, explain:</p> <p>Address of certifying authority: Bezirksregierung Köln, Zeughausstr. 2-10, 50667 Köln, Germany</p> <p>Telephone number: +49-221-147-2534</p> <p>Fax number: +49-221-147-3424</p> <p>Name of authorized person:</p> <p>Signature:</p>
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Stempel und Datum:

Stamp and date:

Allgemein Hinweise

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Erläuterungen

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- 2 Benutzen Sie, wenn möglich, internationale (INNs, International Nonproprietary Names) oder nationale Nicht-Markennamen.
- 3 Die Zusammensetzung (komplette Zusammensetzung) der Darreichungsform sollte auf dem Zertifikat angegeben oder beigelegt werden.
- 4 Details der mengenmäßigen Zusammensetzung werden bevorzugt, aber ihre Bekanntgabe ist abhängig von der Zustimmung des Zulassungsinhabers.
- 5 Wenn zutreffend, fügen Sie alle Einzelheiten einer Einschränkung den Verkauf, Vertrieb oder die Verabreichung des Produkts betreffend, wie in der Produktzulassung spezifiziert, bei.
- 6 Die Abschnitte 2A und 2B schließen sich gegenseitig aus.
- 7 Geben Sie an, wenn zutreffend, ob die Zulassung vorläufig ist, oder ob das Produkt noch nicht zugelassen ist.
- 8 Erläutern Sie, ob die für das Inverkehrbringen des Produktes verantwortliche Person
 - a) die Darreichungsform herstellt;
 - b) eine von einer unabhängigen Firma hergestellte Darreichungsform verpackt und/oder etikettiert oder
 - c) mit keinem der o.a. befasst ist.
- 9 Diese Angaben können nur nach Absprache mit dem Zulassungsinhaber oder im Falle eines nicht zugelassenen Produkts mit dem Antragsteller erteilt werden. Ein Nichtausfüllen dieses Abschnittes zeigt, dass die betroffene Partei nicht der Einfügung dieser Informationen zugestimmt hat.
Es soll angemerkt werden, dass Informationen über den Produktionsort Bestandteil der Produktzulassung sind. Wenn der Produktionsort gewechselt wird, muss die Zulassung auf den neuen Stand gebracht werden oder sie verliert ihre Gültigkeit.
- 10 Dieses bezieht sich auf das Dokument, wie ausgestellt von einigen nationalen Zulassungsbehörden, das die technischen Grundlagen zusammenfasst, auf denen die Zulassung basiert.

General instructions

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Explanatory notes

- 1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
- 2 Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
- 3 The formula (complete composition) of the dosage form should be given on the certificate or be appended.
- 4 Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-licence holder.
- 5 When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.
- 6 Sections 2A and 2B are mutually exclusive.
- 7 Indicate, when applicable if the licence is provisional, or the product has not yet been approved.
- 8 Specify whether the person responsible for placing the product on the market:
 - a) manufactures the dosage form;
 - b) packages and/or labels a dosage form manufactured by an independent company;
 - or
 - c) is involved in none of the above.
- 9 This information can be provided only with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence must be updated or it will cease to be valid.
- 10 This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

- | | |
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| <p>11 Dieses bezieht sich auf die Produktinformation, genehmigt durch die zuständige nationale Aufsichtsbehörde, wie z.B. eine "Zusammenfassung der Produkteigenschaften" (SPC).</p> <p>12 Unter diesen Umständen wird vom Zulassungsinhaber die Erlaubnis zum Ausstellen des Zertifikats benötigt. Diese Erlaubnis muss der Behörde vom Antragsteller vorgelegt werden.</p> <p>13 Bitte erläutern Sie Begründung des Antragstellers, warum keine Registrierung angefordert wurde:
 (a) das Produkt wurde ausschließlich für die Behandlung von Erkrankungen - insbesondere Tropenkrankheiten - entwickelt, die im Ausfuhrland nicht endemisch sind;
 (b) das Produkt wurde neu formuliert im Hinblick auf eine Verbesserung der Stabilität unter Tropenbedingungen;
 (c) das Produkt wurde neu formuliert, um Hilfsstoffe, die im Einfuhrland nicht zum Gebrauch in pharmazeutischen Produkten zugelassen sind, zu entfernen;
 (d) das Produkt wurde neu formuliert, um für einen Wirkstoff eine andere Dosierungsobergrenze zu erreichen;
 (e) aus irgendwelchen anderen Gründen, bitte erläutern.</p> <p>14 Nicht zutreffend bedeutet, dass die Herstellung in einem anderen als dem das Produktzertifikat ausstellenden Land stattfindet und die Inspektion im Auftrag des Herstellungslandes durchgeführt wird.</p> <p>15 Die Anforderungen an Gute Praktiken bei der Herstellung und Qualitätskontrolle von Arzneimitteln, auf die im Zertifikat Bezug genommen wird, sind im 32. Bericht des Expertenausschusses für Spezifikationen für pharmazeutische Zubereitungen (WHO-Fachschriftenreihe Nr. 823, 1992, Anlage 1¹⁾) enthalten. Speziell für biologische Produkte zutreffende Empfehlungen wurden durch den WHO Expertenausschuss für biologische Standardisierung (WHO-Fachschriftenreihe, Nr. 822, 1992, Anlage 1¹⁾) formuliert.</p> <p>16 Dieser Abschnitt sollte vervollständigt werden, wenn der Zulassungsinhaber oder Antragsteller dem Status (b) oder (c), wie unter Nr. 8 oben beschrieben, entspricht. Dies ist besonders wichtig, wenn ausländische Vertragspartner in die Herstellung des Arzneimittels eingebunden sind. Unter diesen Umständen sollte der Antragsteller die zertifizierende Behörde entsprechend unterrichten, um die Vertragsparteien, die für die einzelnen Herstellungsstufen des Fertigarzneimittels verantwortlich sind und den Umfang und die Art der Kontrollen, die bei jeder dieser Parteien durchgeführt werden, zu ermitteln.</p> | <p>11 This refers to product information approved by the competent national regulatory authority, such as a Summary of Product Characteristics (SPC).</p> <p>12 In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission must be provided to the authority by the applicant.</p> <p>13 Please indicate the reason that the applicant has provided for not requesting registration:
 (a) the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the country of export;
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 (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
 (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
 (e) any other reason, please specify.</p> <p>14 Not applicable means that the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.</p> <p>15 The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No.822, 1992, Annex 1).</p> <p>16 The section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.</p> |
|---|---|

Annex IV – EMA CPP Application Form

APPLICATION FORM FOR CERTIFICATES OF MEDICINAL PRODUCTS(1)

Part A Organisational information(2)

Each Part A is subject to a processing charge

Boxes in red must be completed

A.1 Certifying Authority (3)
European Medicines Agency
7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Website: <http://www.ema.europa.eu>

Certificates Team

Fax: (44-20) 7418 8595, Tel: (44-20) 7418 8400

E-mail (standard): certificate@ema.europa.eu(urgent): certificate_urgent@ema.europa.eu

**A.2 Marketing Authorisation Holder(s) or Holder(s) of CHMP Positive Scientific Opinion
(Art. 58 Regulation (EC) No. 726/2004) (4)**

Company Name SME (5) ☐
Company Address
Company Postcode Country

A.3 Certificate Requesting Company (6)

Contact person (7) Title First Name Last Name
Fax (8) Telephone (9)
E-Mail (10)
Company Name (11) Certify requesting company (12) ☐
Company Address
Company Postcode Country

I declare that the last permission letter, if available, remains valid (13) ☐

A.4 Precondition for acceptance of a request for certificates (14)

Application for marketing authorisation has been submitted to the Agency via centralised procedure
Application under Article 58 of Regulation (EC) no.726/2004 has been submitted to the Agency

☐ Yes (15)☐ Yes (15)

GMP compliance status confirmed and based on recent GMP inspections by an EU/EEA or Mutual Recognition Agreement partner Inspectorate

☐ Yes ☐ Restricted

Product(s) is free from recently reported, serious hazards

☐ Yes ☐ Restricted

A.5 Fees

Customer Number (16)
Application processing ☒ Standard (10 working days) ☐ Urgent (2 working days)
Number of sets of certificates (17) x € 140 = € 0
Request fee (18) = € 140
TOTAL (19) = € 140

Reference/purchase order to appear in the invoice (20)

A.6 I, the undersigned, declare that all information in this request and its annexes is correct

Date Name

APPLICATION FORM FOR CERTIFICATES OF MEDICINAL PRODUCTS

Part B Table for requested certificates (21)

1

Sections in red are compulsory.**B.1 Product Information**

Trade name of the medicinal product (22)

Pharmaceutical form(s) (23)

Trade Name in the importing country (24)

Has an opinion under Article 58 of regulation (EC) No. 726/2004 (cooperation with WHO for the evaluation of certain medicinal products for human use intended exclusively for market outside the EU) been issued for the product?

☐ Yes (25)

Name(s) address(es) and activity(ies) of the site(s) involved in the manufacturing of the finished products (drug products), to be mentioned in the certificates (26)

Add	Name	Address	Activity
X			<input type="checkbox"/> Manufacture of the finished product <input type="checkbox"/> Manufacture of the finished product:solvent/diluent <input type="checkbox"/> Batch Release <input type="checkbox"/> Quality Control of the finished product <input type="checkbox"/> Primary Packaging <input type="checkbox"/> Secondary Packaging

B.2 Sets of certificates for the product(27).**Each set of certificates is subject to an additional charge**

Add	Importing Country	MA Numbers	EU Lang.	Number of Certificates	Annexes in addition to SPC	Available on the market in the EU
X			EN			

Total Sets 0

Total Certs.

New Product

X

Annex V – FDA CPP Application Form

Department of Health and Human Services Food and Drug Administration	SUPPLEMENTARY INFORMATION CERTIFICATE OF A PHARMACEUTICAL PRODUCT
1. Requestor Information	
Name Firm	Address
Telephone number	FAX number
Firm Tax ID code	Email address
2. Section 1.0	
Proprietary name	
Dosage form	
3. Section 1.1	
Active ingredient	
Amount per unit dose	
Note: The information for this section may be provided in the approved product labeling and may be attached to the certificate. For certificate requests for more than one country, provide a copy of the attachments for each country. Provide one copy of the attachments for FDA. Attachments are limited to a total of 5 pages for CDER and 10 pages for CBER and CVM.	
4. Section 2A.1 & 2A.2	
Applicant name	Address
FDA product approval (AADA, ANDA, BLA/PLA, NADA, NDA)	Date of issue
<i>Also, provide a copy of the approval letter as verification of the product license or NDA or NADA number and approval date.</i>	
5. Section 2A.3 or 2B.2	
Status of Product license holder (mark appropriate item(s)): <input type="checkbox"/> Manufacturer <input type="checkbox"/> Packager and/or Relabeler <input type="checkbox"/> Neither	
6. Facilities involved in the manufacturing of the exported product (A maximum of three facilities may be listed for CDER and four facilities for CBER and CVM.)	
Facility name (1)	Address
License number (if applicable)	
Registration number	Date of most recent inspection
Facility name (2)	Address
License number (if applicable)	
Registration number	Date of most recent inspection
CDER instructions begin on page 4.	
CVM instructions begin on page 5.	
CDER instructions begin on page 6.	

6. Facilities involved in the manufacturing of the exported product (*continued*)

Facility name (3)	Address
License number (<i>if applicable</i>)	
Registration number	Date of most recent inspection
Facility name (4)	Address
License number (<i>if applicable</i>)	
Registration number	Date of most recent inspection

7. Section 2A.3.1

<p>Do you want the manufacturing location(s) listed on the certificate?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
--

8. Importing countries (list in columns)

--	--

9. Number of certificates requested: _____

10. Section 2B.3

<p>For unapproved biological drugs, mark the category that indicates why authorization is lacking:</p> <p><input type="checkbox"/> Not required <input type="checkbox"/> Not requested <input type="checkbox"/> Under consideration <input type="checkbox"/> Refused</p>

Department of Health and Human Services Food and Drug Administration	EXPORTER'S CERTIFICATION STATEMENT "CERTIFICATE OF A PHARMACEUTICAL PRODUCT" for CBER and CVM
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FIRM NAME

As the responsible official or designee of the company named above, I hereby certify to the United States Food and Drug Administration that: <ul style="list-style-type: none"> the company, the manufacturing plant, and the product being exported, as identified in the Supplementary Information, continue to be, to the best of my knowledge, in compliance with all applicable requirements of the Federal Food, Drug, and Cosmetic Act; the product being exported has been manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practice requirements; and the product labeling provided with the Supplementary Information is a true and accurate representation of the product labeling approved by the FDA.
--

SIGNATURE	DATE
-----------	------

NAME AND TITLE

<div> Making or submitting false statements on any documents submitted to FDA may constitute violations of the United States Code Title 18, Chapter 47, Section 1001 with penalties including up to \$250,000 in fines and up to 5 years imprisonment. </div>

Department of Health and Human Services Food and Drug Administration	EXPORTER'S CERTIFICATION STATEMENT "CERTIFICATE OF A PHARMACEUTICAL PRODUCT" for CDER
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The information, contained in this request for a Certificate of a Pharmaceutical Product, is true and accurate based upon the current approved application or other legal basis permitting marketing of the product. We acknowledge that any false or fictitious statements, made in the application, that are used by FDA to process the certificate, will be in violation of the United States Code Title 18, Section 1001.

AUTHORIZATION TO RELEASE STATEMENT

We authorize the Food and Drug Administration to release this information in the certificate format. I understand that we will be billed a fee for each certificate not to exceed \$175.00. If you have any questions, or require additional information regarding this correspondence, please call me at _____ (phone number).

SIGNATURE	DATE
-----------	------

NAME AND TITLE

Department of Health and Human Services
Food and Drug Administration

EXPORT CERTIFICATION
Submission Requirements for Requesting Certificates for
Exporting Products to Foreign Countries (for CBER)

Background

Firms exporting products from the U.S. are often asked by foreign customers or foreign governments to supply a certification relating to products subject to the Federal Food, Drug, and Cosmetic Act and other acts the Food and Drug Administration (FDA) administers. Under the FDA Export Reform and Enhancement Act of 1996 (the Act), FDA is authorized to issue certificates for drugs, animal drugs, and devices within 20 days of receipt of a request for such a certificate. A fee of up to \$175 may be charged for each certificate issued. In addition to issuing export certificates for approved or licensed products, the FDA will also issue export certificates for unapproved products that meet the requirements of Sections 801(e) or 802 of the Act.

General Instructions:

- The “**Certificate to Foreign Government**” is for the export of products legally marketed in the United States. Certificate requests should include the information listed in **Supplementary Information – Certificate to Foreign Government Requests** (*PDF, Text*). Please ensure that the Exporter’s Certification Statement is signed by a responsible official of the exporting firm and is enclosed with the certificate request. Please ensure that the appropriate Exporter Certification Statements for Certificate to Foreign Government Requests for Human Cells, Tissues, and Cellular and Tissue-Based Products (procured prior to May 25, 2005, or on or after May 25, 2005) is signed by a responsible official of the exporting firm and is enclosed with the certificate request.
- The “**Certificate of Exportability**” is for the export of products not approved for marketing in the United States (unapproved products) that meet the requirements of Sections 801(e) or 802 of the Act. Certificate requests should include the information listed in **Supplementary Information - Certificate of Exportability Requests** (*PDF, Text*). Please ensure that the Exporter’s Certification Statement is signed by a responsible official of the exporting firm and is enclosed with the certificate request.
- The “**Certificate of a Pharmaceutical Product**” conforms to the format established by the World Health Organization (WHO) and is intended for use by the importing country when the product in question is under consideration for a product license that will authorize its importation and sale or for renewal, extension, amending or reviewing a license. WHO Certificate requests should include the information listed in **Supplementary Information – Certificate of a Pharmaceutical Product Requests** (*PDF, Text*). Please ensure that the Exporter’s Certification Statement is signed by a responsible official of the exporting firm and is enclosed with the certificate request.
- The “**Non-clinical Research Use Only Certificate**” is for the export of a non-clinical research use only product, material, or

component that is not intended for human use which may be marketed in, and legally exported from the United States under the Federal Food, Drug, and Cosmetic Act. Certificate requests should include the information listed in **Supplementary Information - Non-clinical Research Use Only Certificate Requests** (*PDF, Text*). Please ensure that the Exporter’s Certification Statement is signed by a responsible official of the exporting firm and is enclosed with the certificate request.

- Please type certificate requests or print clearly.
- In most cases, one product will be listed per certificate. However, products that were approved under the same PLA / BLA, NDA, PMA or 510(k) application or similar unapproved products may be listed on the same certificate based on the available space for a one page certificate. Certificate requests for listing multiple products will be evaluated on a case-by-case basis.
- If information is omitted in the application by the requester or if clarification is needed on the supplied information, the requester will be contacted via telephone or FAX. If the requester does not provide the necessary information within 48 hours, the request for certificates will be returned and will need to be resubmitted for FDA review.
- Questions may be directed to the Import/Export Team at 301-827-6201.
- Send the request and supporting documents to:

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
1401 Rockville Pike, Attention: HFM-624
Rockville, MD 20852-1448
or via FAX at 301-594-0940
- On October 1, 1996, CBER was given the authority to charge \$175 for the first two certificates and \$85 for any subsequent certificates issued for the same product(s) in response to the same certificate request. Please do not submit a check with your request, as FDA will bill you quarterly for issued certificates.
- You may enclose a completed FEDEX form to expedite the return of Certificates.

Issuance of a “Certificate to Foreign Government”, “Certificate of Exportability” or “Certificate of a Pharmaceutical Product” will not preclude regulatory action by FDA, if warranted, against products covered by the Certificate.

A “Certificate to Foreign Government”, “Certificate of Exportability” or “Certificate of a Pharmaceutical Product” is issued by FDA solely for export purposes and may not be used for domestic advertising.

Department of Health and Human Services
Food and Drug Administration

**INSTRUCTIONS FOR COMPLETION OF
APPLICATION FOR CERTIFICATES
(for CVM)**

1. The Export Certificate to Foreign Governments is for the export of products legally marketed in the United States. An application form must be completed and signed. The form is to be completed by the responsible head or designee of the exporting firm. Please enclose labels for each product.
 2. The Certificate of Exportability is for the export of products unapproved for distribution and sale in the United States. The requestor must meet the requirements of Section 801(e) of the Act.
 3. The **“Certificate of a Pharmaceutical Product”** conforms to the format established by the World Health Organization (WHO) and is intended for use by the importing country when the product in question is under consideration for a product license that will authorize its importation and sale or for renewal, extension, amending or reviewing a license. WHO Certificate requests should include the information listed in **Supplementary Information – Certificate of a Pharmaceutical Product Requests**. Please ensure that the Exporter’s Certification Statement is signed by a responsible official of the exporting firm and is enclosed with the certificate request.
 4. If the requested information on the application form is not provided by the exporting firm or if clarification is needed on the supplied information, the exporting firm will be contacted via telephone or FAX. If the exporting firm does not provide the necessary information within 48 hours, the request for certificates will be returned and will need to be resubmitted. You may enclose a completed FEDEX form to expedite return of the Certificates. A certificate will be issued for each product.
 5. Requests for certificates should be sent to:

Kim Bell
Center for Veterinary Medicine Division of
Compliance (HFV-235)
7519 Standish Place
Rockville, MD 20855
(240-276-9212- for inquiries)
 6. The fee for preparing and issuing a single certificate is \$175; 1st duplicate original \$155 and \$70 for each subsequent duplicate. No fee will be charged for animal food/feed products. Please do not include the fee payment with your requests; the exporting firm will be billed quarterly.
 7. The instructions and applications will be available on the *CVM Home Page* (www.fda.gov/cvm/exportcertificate.htm).
- PLEASE NOTE: Making or submitting false statements on any documents submitted to FDA represents violations of the United States Code, Title 18, Chapter 47, Section 1001 with penalties including up to \$10,000 in fines and up to 5 years imprisonment.**
- Issuance of an Export Certificate for Approved Products or Certificate of Exportability will not preclude regulatory action by FDA, if warranted, against products covered by the Certificate. Certificates issued by the FDA are solely for export purposes and may not be used for domestic advertising.**

Department of Health and Human Services
Food and Drug Administration

**CERTIFICATE OF A PHARMACEUTICAL PRODUCT
APPLICATION INSTRUCTIONS (for CDER)**

INTRODUCTION

The Food and Drug Administration has historically issued various types of certificates to firms exporting products to foreign countries. The Center for Drug Evaluation and Research (CDER) has revised its procedures for the issuance of Certificates of a Pharmaceutical Product (examples are attached) for the following types of requests:

- Drug products that are legally marketable in the U.S.;
- Products not authorized for sale in the U.S. which may be legally exported to foreign governments (Certificate of a Pharmaceutical Product for Export of an Unapproved Product under Sections 801 (e) or 802 of the FD&C Act); and
- Foreign Manufacturer (products manufactured outside of the U.S.).

GENERAL INFORMATION

A separate application must be made for each drug product. However, before preparing your application, please consult with the importing country to determine exactly what type of information is being required for the certificate.

- Products approved with the same NDA number and the same dosage form, but with different potencies, can be processed on the same certificate.
- Foreign names for the drug products may be included and noted as "International Tradename" in the "Remarks" section of the certificate.
- DO NOT submit applications in binders or put the attachments in plastic sleeves.

Additional Information

To maintain conformity with the certificate format, additional information or statements must not exceed **three** lines of text. Text that exceeds three lines must be typed on a separate 8½" x 11" sheet of paper and will be attached to the certificate.

Attachments

All attachments must be sent in duplicate. For certificate requests, for more than one country, please provide the container label, package container, and package insert for each country as follows:

An application for **one** country requires **two** sets of attachments (one set for the certificate and one for our files).

- Requests for **two or more** countries require **one** set of attachments for each country, plus **one** additional copy for our files (e.g., for two certificates, provide three sets of attachments; one set for each certificate and one set for our files).
- Attachments must not exceed **five** pages per certificate.

Ribbons

The following colors are being used to designate the type of certificate requested:

- **Red** will be affixed to all (regular) Certificates of Pharmaceutical Product.
- **Blue** will be affixed to Certificates for Export of an Unapproved Product.
- **Yellow** will be affixed to Certificates with Foreign Manufacturing sites.

Fees

Under the FDA Export Reform and Enhancement Act of 1996, FDA is authorized to charge a fee for certificates issued within **20 calendar days** of receipt of an application. The fee, for each certificate, shall not exceed **\$175.00**. **Do NOT send payment with the application; invoices are issued quarterly.**

- Second certificate, for the same country, in the same application **\$90.00**
- Third and subsequent certificates, for the same country, in the same application **\$40.00**

Expiration Date

Certificates will expire **24** months from the date of notarization. After expiration, a new application must be submitted. Certificates cannot be reissued.

REQUIRED INFORMATION

An application for an export certificate **must** include the following information:

Federal Tax Identification Number

To facilitate the billing process, the following information must be included in all certificate applications:

- Federal tax identification number
- Billing address and contact

Marketing Status in the Exporting Country (U.S.)

- Is the product currently marketed in the United States?
Yes or No.

Certification of Exportation from the U.S. for Foreign Manufacturing Sites

Please include the following statement in the cover letter: "***We certify that (Product Name) is manufactured and/or packaged in (Name***

Certificate of a Pharmaceutical Product – Application Instructions (for CDER) (Continued)

of Foreign Country) and is exported from the United States.” Unless a product is sent from the U.S., directly to the requesting country, a Certificate of a Pharmaceutical Product (CPP) will not be issued.

Country of Destination

Certificate requests, for multiple countries, can be made in one application. A certificate will be issued for each country, but only one certificate number will be assigned per application.

U.S. Tradename (the drug product’s brand name) or Generic Name

- The trade or generic name on the product as it is marketed in the U.S.
- Labels with foreign tradenames must be accompanied by the U.S. equivalent.

Container Label(s)

- An original sample of the current product label, approved for marketing in the U.S., must be mounted on a plain sheet of 8½” x 11” paper. Loose, paper clipped, or labels in plastic sleeves will not be accepted. *(1 copy per certificate plus 1 copy for our files)*
- One label for each potency requested must be submitted. *(1 copy per certificate plus 1 copy for our files)*
- If the label is silk-screened onto the container, please send a copy of the silkscreen or the art layout of the label mounted on a plain sheet of 8½” x 11” paper. DO NOT send the container (e.g., bottles, tubes). *(1 copy per certificate plus 1 copy for our files)*
- To remain within the five-page attachment maximum, several container labels can be mounted on one sheet of paper. Labels can also be double mounted on both sides of the paper.

Package Container

- An original sample, of the current package container, must be mounted on a plain sheet of 8½” x 11” paper. If the package container is a box, collapse it before mounting. *(1 copy per certificate plus 1 copy for our files)*
- If the carton is bulky, please send the art layout of the container mounted on 8½” x 11” paper. *(1 copy per certificate plus 1 copy for our files)*

Package Insert

An original sample of the current package insert must be mounted on a plain sheet of 8½” x 11” paper. *(1 copy per certificate plus 1 copy for our files)*

NOTE: For OTC products, the product sample and promotional literature are no longer needed.

Name and Address of Manufacturing Facility, Including Zip Code

- Include the name of the manufacturing site, with a complete street address.

- Provide the registration number for the manufacturing facility.
- Provide a **brief** explanation, and/or documentation (e.g., FDA Form 356 H), if there have been any changes in the corporate structure or in the company name.

Marketing Authority

New drug and abbreviated new drug approval letters are considered to be the only “license” to market a drug product. If the product does not have an approval letter, provide the legal basis permitting marketing of the product. Over-the-Counter drugs and those with grandfathered status are marketed under OTC monographs and Compliance Program Guide (CPG 7132c.02), respectively.

NDA, ANDA, or AADA Approval Letter

- Copy of the *original* approval letter as verification of the NDA, ANDA, or AADA number, approval date, application holder, product name, dosage form, and potency of the drug product. ***If the NDA holder has changed, please provide the name of the new application holder.***
- Copy of *supplemental* approval letters for new dosage forms, new potencies, new indications, and Rx to OTC switches. DO NOT submit supplemental approval letters for new manufacturing sites or stability studies.

Over-the-Counter (OTC)

- Provide the title and date of the applicable monograph. DO NOT attach a copy of the publication.

Grandfathered Status

- Provide a statement addressing the grandfathered status of the drug product.

Sections 801(e) and 802 of the Food, Drug, and Cosmetic Act

- Export of unapproved drug products that are not authorized for sale in the U.S. may be legally exported to foreign countries under § 801(e) and 802 of the FD&C Act.
- A copy of the product formulation, to be attached to the certificate, must be included with the application.

Status of Product-license Holder

The product-license holder is the name of the company that owns the new drug or abbreviated new drug application. Please indicate, in the cover letter, the name of the **current** product-license holder of the NDA or ANDA. For purposes of complying with the WHO scheme, the product-license holder is classified as one of the following:

- Manufacturer
- Packager/Labeler
- Neither (Distributor)

Certificate of a Pharmaceutical Product – Application Instructions (for CDER) (Continued)

Status of Applicant

The applicant is the name of the firm or person who submits an application for an export certificate. For purposes of complying with the WHO scheme, the applicant is classified as one of the following:

- Manufacturer
- Packager/Labeler
- Neither (Distributor)

Certification Statement

The information contained in this request for a Certificate of a Pharmaceutical Product is true and accurate and based upon the current approved application or other legal basis permitting marketing of the product. We acknowledge that any false or fictitious statements made in the application, which are used by FDA to process the certificate, will be in violation of the United States Code Title 18, Section 1001.

Product Identification Statement (required for unapproved products)

For certificate requests for unapproved drug products, a product identification statement must be included affirming that the company and the product to be exported are in compliance with applicable provisions of the Act as amended by the FDA Reform and Enhancement Act of 1996. This statement also identifies the provision of Sections 801 or 802 of the FD&C Act permitting export as follows:

We certify that the product to be exported is in compliance with the applicable provisions of § 801(e) and 802 of the Act as amended by the FDA Reform and Enhancement Act of 1996.

Authorization to Release Information

Each application must include a statement authorizing release of the information contained in the certificate and attachment(s) as follows:

We authorize the Food and Drug Administration to release this information in the certificate format. I understand that we will be billed a fee for each certificate, not to exceed \$175.00.

ACTIVE PHARMACEUTICAL INGREDIENTS (API) and Excipients

The active pharmaceutical ingredient (API) is the bulk drug substance (raw material) that has not been processed into a final dosage form (e.g., tablet, capsule).

- Provide an original sample of the current bulk container label, for the API, mounted on a plain sheet of 8½" x 11" paper.
- Export certificates are **NOT** issued for inactive ingredients (excipients).

INCOMPLETE APPLICATIONS

To obtain a certificate, the applicant must provide all required information. An application with incomplete information, or improperly mounted labels, will be returned to the submitter.

CORRECTION OF ERRORS

- Errors made by FDA during the preparation of export certificates will be corrected, at no cost to the applicant, within 45 days after issuance.
- Errors made in the application, by the submitter, cannot be corrected. A new application must be submitted.

MAILING ADDRESS

Please include self-addressed return labels with your application and mail it to the following address. Please note that we are only able to accept FEDEX for overnight mailing of the export certificates.

Food and Drug Administration
Center for Drug Evaluation and Research
Export Certificate Program
10903 New Hampshire Avenue
Building 51, Room 4249
Silver Spring, MD 20993-0002

If additional information is needed, please call one of the following members of the Export Certificate Team: Betty McRoy at 301-796-3218 or Marta E. Gonzalez-Piñeiro at 301-796-3283.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF ADDRESS BELOW.

The burden time for this collection of information is estimated to average 1 hour per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
1350 Piccard Drive, Room 400
Rockville, MD 20850

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Annex VI – Malaysia CPP Application Form

L	O	I															
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**AKTA JUALAN DADAH 1952 (DISEMAK 1989)
PERATURAN-PERATURAN KAWALAN DADAH DAN KOSMETIK 1984**

PERATURAN 16(1)

**PERMOHONAN PERAKUAN KELUARAN FARMASEUTIKAL/ *CERTIFICATE OF A
PHARMACEUTICAL PRODUCT***

ARAHAN

- Borang ini hendaklah **DITAIP** dalam satu salinan asal sahaja.
- Bayaran pemprosesan : RM50.00 bagi setiap salinan perakuan. Pembayaran pemprosesan hendaklah dibuat melalui draf bank/kiriman wang/wang pos di atas nama '**Biro Pengawalan Farmaseutikal Kebangsaan**'.
- Borang yang telah lengkap hendaklah dihantar kepada **Pusat Pendaftaran Produk, Biro Pengawalan Farmaseutikal Kebangsaan, Kementerian Kesihatan Malaysia, Jalan Universiti, Peti Surat 319, 46730 Petaling Jaya, Selangor Darul Ehsan.**

1. Nama Keluaran :

2. a) Nombor Pendaftaran Keluaran:

b) Tarikh Kelulusan Pendaftaran:

3. Nama, Alamat Penuh , No. Telefon dan Fax Syarikat Pemohon:

4. Nama, Alamat Penuh , No. Telefon dan Fax Pengilang:

**5. Nombor Lesen Pengilang Yang Dikeluar oleh PBKD dan Tarikh Dikeluarkan:
(Sila lampirkan bersama salinan lesen pengilang terkini)**

6. Negara yang memerlukan Sijil Perakuan:

7. Nombor Sijil Perakuan terkini yang pernah dikeluarkan oleh PBKD untuk keluaran ini:

8. Sila kemukakan perkara-perkara berikut:

- ☐ Label dan sisip bungkusan yang diluluskan dan digunakan untuk pasaran tempatan. (Satu salinan Asal bagi setiap negara yang dipohon dan dilekatkan pada kertas ukuran A4.) *
- ☐ Formulasi Keluaran terkini. (sila tandakan bahan aktif) dan (komposisi lengkap termasuk semua eksipien) *
- ☐ Bukti jualan i.e. invoice jualan/ nota hantaran terkini.*

*** Permohonan tidak akan diproses jika keperluan di atas tidak dipenuhi.**

9. Bayaran pemprosesan :

(semua jenis pembayaran hendaklah dibuat di atas nama 'Biro Pengawalan Farmaseutikal Kebangsaan')

No. draf bank/kiriman wang/wang pos:

--

Jumlah (RM)

--

*Bayaran pemprosesan bagi permohonan Perakuan Keluaran Farmaseutikal ialah **RM 50.00 sahaja** bagi setiap keluaran ke satu Negara.*

PERAKUAN PEMOHON:

Saya yang bernama seperti di bawah sebagai mewakili syarikat yang memohon mengaku bahawa semua kenyataan di atas dan lampiran yang disertakan adalah benar.

Tandatangan Pemohon : _____

Nama Penuh (huruf besar) : _____

Nombor Kad Pengenalan : _____

Jawatan dalam Syarikat : _____

Tarikh : _____

Cop Rasmi Syarikat disini:

UNTUK KEGUNAAN PEJABAT SAHAJA:

Tarikh Diterima:

--	--	--	--	--	--	--	--

Tarikh Diproses:

--	--	--	--	--	--	--	--

Nombor Perakuan Keluaran Farmaseutikal

c	p	p	:						
---	---	---	---	--	--	--	--	--	--

Tarikh Dikeluarkan:

--	--	--	--	--	--	--	--

Tandatangan Pegawai : _____

Nama Pegawai : _____

Catatan:

Jun 2009/Pind.01/2012

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Annex VII – Argentina CPP Application Form

Certificado de Producto Farmacéutico
Certificate of Pharmaceutical Product

**Este certificado se extendió conforme al formato recomendado
por la Organización Mundial de la Salud**

**This certificate was extended according to the format
recommended by World Health Organization**

País (Titular del certificado) Exportador: **REPÚBLICA ARGENTINA**
Exporting (Certifying) Country: **ARGENTINE REPUBLIC**

País (solicitante) Importador: -----
Importing (applicant) Country: -----

1. Nombre y forma farmacéutica del producto:
Name and pharmaceutical form of the product:

- 1.1 Principio(s) activo(s) y cantidad (es) por unidad de dosis:
Active ingredient(s) and amount(s) per unit dose:

- 1.2 Excipientes:
Inactive Ingredients:

- 1.3 ¿Está este producto autorizado para ser puesto en el mercado del país
exportador?
Is this product licensed to be placed on the market for use in the
exporting country?

1.4 ¿Está este producto siendo comercializado en el mercado del país exportador?

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

2.A.1 Número de Certificado del producto y fecha de emisión

Number of product license and date of issue:

Certificado N° -----, emitido el -- de ----- de ----

Certificate N° -----, issued on -----, -----, ----- (month, date, year)

2.A.2 Propietario del Certificado del producto (nombre y dirección):

Product license holder (name and address):

2.A.3 Estado del propietario del certificado del producto:

Status of product license holder:

A- Fabrica la forma farmacéutica final / Manufactures the final pharmaceutical form. ☐

B- Empaca y/o etiqueta una forma fabricada por otra empresa/ Packages and/or label a pharmaceutical form manufactured by other company. ☐

C- No realiza ninguna de las operaciones arriba mencionadas / It does not make any of the operations above mentioned. ☐

(marcar con una "X" la opción que corresponda)

2.A.3.1 Nombre y dirección de quién fabrica la forma farmacéutica:

Name and address of the manufacturer of the pharmaceutical form.:

(En caso de haber seleccionado A en 2.A.3 no completar)

2.A.4 ¿Se adjunta "summary basis for approval"?

Is a summary basis for approval attached?

No Aplica Not Apply

- 2.A.5 La información de las condiciones de aprobación del producto que se Adjunta, ¿es completa y conforme con la autorización?
The information of the conditions of approval of the product that is attached, is complete and it conforms to the license?

- 2.A.6 Solicitante del certificado, si es diferente del titular de la autorización (nombre y dirección):
Applicant for Certificate, if it's different from the license holder (name and address):

3. La Autoridad Sanitaria realiza inspecciones periódicas a la planta de manufactura donde se elaboran las diferentes concentraciones ?
Does the Sanitary Authority make periodic inspections to the manufacture plant where the different concentrations are produced?

- 3.1 Periodicidad de rutina de inspección (años):
Regularity of inspections routine (years):

Una cada dos años Every two years

- 3.2 Ha sido inspeccionado quién manufactura este tipo de concentraciones?
Has the manufacture of this type of concentration been inspected?

- 3.3 ¿Las instalaciones y procesos, responden a la GMP, según las recomendaciones de la Organización Mundial de la Salud?
Do the facilities and process respond to the World Health Organization GMP recommendations?

-
4. ¿La información suministrada por el solicitante, satisface a la Autoridad Sanitaria en todos los aspectos del procedimiento de manufactura del producto?
The information provided by the applicant satisfies the Sanitary Authority in all the aspects of the manufacture procedure of the product?
-

Dirección de la autoridad que certifica:

Address of Certifying Authority:

INAME (Instituto Nacional de Medicamentos).-

Avenida Caseros 2161

Ciudad Autónoma de Buenos Aires- República Argentina.-

Número Telefónico: 0054 – 11- 4305-8674

Telephone number: 0054 -11- 4305-8674

Nombre de la persona autorizada: **Lic. Marta E. Spinetto.-**

Name of the authorized person: **Lic. Marta E. Spinetto.-**

Válido por doce meses

Válid for twelve months

Fecha: **dejar en blanco**

Date: **dejar en blanco**

Nº de Trámite: **dejar en blanco**

Nº of Proceeding: **dejar en blanco**

Lic. Marta E. Spinetto

Directora

Instituto Nacional de Medicamentos

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

¹ This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

² Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

³ The formula (complete composition) of the dosage form should be given on the certificate or be appended.

⁴ Details of quantitative composition are preferred but their provision is subject to the agreement of the product-licence holder.

⁵ When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.

⁶ Sections 2A and 2B are mutually exclusive.

⁷ Indicate, when applicable, if the licence is provisional, or the product has not yet been approved.

8 Specify whether the person responsible for placing the product on the market:

- (a) Manufactures the dosage form;
- (b) Packages and/or label a dosage form manufactured by an independent company
- (c) Is involved in none of the above

9 This information can only be provided with the consent of the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product license. If the production site is changed, the license has to be updated or it is no longer valid.

10 This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

11 This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC)

12 In this circumstance, permission for issuing the certificate is required from the product-license holder. This permission has to be provided to the authority by the applicant.

13 Please indicate the reason that the applicant has provided for not requesting registration.

- (a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;
- (b) the product has been reformulated with a view to improving its stability under tropical conditions;
- (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
- (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
- (e) any other reason, please specify.

¹⁴ Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.

¹⁵ The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

¹⁶ This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

Instrucciones Generales

Para más amplias informaciones sobre el Sistema de Certificación OMS y los conceptos que aparecen en el certificado, referirse a la documentación de OMS. El formato del certificado permite su informatización.

Los certificados tienen que ser proporcionados con las anotaciones impresas en lugar que escritas a mano.

Si necesario, se agregarán hojas adicionales para proporcionar aclaraciones y comentarios.

Notas explicativas

1- Este certificado, cuyo formato cumple con las recomendaciones de la OMS, describe la situación en el país exportador de un producto y de quien solicita el certificado. Cada certificado se refiere a una única presentación porque la fabricación y la situación regulatoria puede ser diferente para diferentes formas y concentraciones.

2- Use, cuando posible, la Denominación Común Internacional (DCI) u otra denominación no protegida.

3- La composición completa de la forma farmacéutica debe aparecer en el certificado o ser anexada.

4- Es preferible proporcionar la fórmula cuali-cuantitativa completa si el titular de la autorización de comercialización (registro) lo permite.

5- Cuando corresponda, proporcionar información sobre restricciones de venta, distribución, o uso del producto que se aplican en el país exportador.

6- Las secciones 2A y 2B se excluyen recíprocamente.

7- Indicar, cuando corresponda, si la autorización de comercialización es provisoria o el producto aun no está aprobado.

8- Especificar si la persona responsable de la comercialización:

- (a) fabrica la forma farmacéutica final;
- (b) empaca y/o etiqueta una forma fabricada por otra empresa; ó
- (c) no realiza ninguna de las operaciones arriba mencionadas.

9- Esta información puede ser proporcionada solamente cuando el titular de la autorización de comercialización o, en el caso de productos sin autorización, el solicitante del certificado lo permita. La ausencia de esta información indica que la persona correspondiente no ha permitido su inclusión. Cabe subrayar que la información sobre el lugar de fabricación es parte de la autorización de comercialización. Si ese lugar cambia, la autorización debe ser actualizada o dejará de ser válida.

10- Esto se refiere al documento, que algunas autoridades acostumbran preparar, que constituye la base técnica sobre la cual se ha emitido la autorización de comercialización.

11- Esto se refiere a la información sobre el producto (indicaciones, contraindicaciones, etc.) aprobada por la autoridad competente.

12- En este caso, es necesario que el titular de la autorización de comercialización permita que se otorgue el certificado. El solicitante debe obtener este permiso.

13- Indicar por cual razón el solicitante no ha pedido autorización de comercialización:

- (a) el producto ha sido desarrollado exclusivamente para tratar enfermedades - sobre todo tropicales - que no son endémicas en el país exportador;
- (b) el producto ha sido reformulado para mejorar su estabilidad en clima tropical;
- (c) el producto ha sido reformulado para excluir excipientes que no son aceptados en el país importador;
- (d) el producto ha sido reformulado para respetar límites máximos diferentes para un ingrediente activo;
- (e) otra razón, por favor explicar.

14- No se aplica significa que la fabricación tiene lugar en un país diferente del que emite el certificado y la inspección es responsabilidad de la autoridad del

país de fabricación.

15- Los requisitos para buenas prácticas en la fabricación y el control de calidad de medicamentos mencionados en el certificado son los incluidos en trigésimo-segundo informe del Comité de Expertos de la OMS en Especificaciones de Preparaciones Farmacéuticas (OMS, Serie de Informes Técnicos, No. 823, 1992, Anexo 1). Recomendaciones específicas para productos biológicos han sido preparadas por el Comité de Expertos de la OMS en Patrones Biológicos (OMS, Serie de Informes Técnicos, No. 822, 1992, Anexo 1).

16- Esta parte se completa cuando el titular de la autorización o el solicitante del certificado pertenecen a los casos (b) y (c) de la nota 8 indicada arriba. Es particularmente importante cuando empresas extranjeras intervienen en la fabricación. En estos casos, el solicitante debe proporcionar a la autoridad certificadora toda información que permita identificar los fabricantes responsables por cada etapa de la producción de la forma final, y el grado y tipo de control que el solicitante eventualmente tenga sobre éstos.

Annex VIII – Brazil FDA CPP Application Form



**AGÊNCIA NACIONAL DE VIGILÂNCIA
SANITÁRIA**
National Agency of Sanitary Surveillance

GERÊNCIA GERAL DE MEDICAMENTOS
General Management of Drugs

CERTIDÃO DE EXPORTAÇÃO DE PRODUTO FARMACÊUTICO
EXPORT CERTIFICATE OF PHARMACEUTICAL PRODUCT

Esta Certidão está de acordo com o formato recomendado pela Organização Mundial da Saúde
This Certificate conforms to the format recommended by the World Health Organization

País exportador (*Exporting Country*): **Brasil (Brazil)**

País importador (*Importing Country*): xxxxxxxxxxxxxx

1.Nome e forma farmacêutica do produto: xxxxxx
(*Name and dosage form of the product*):

1.1. Nome do produto no país importador: xxxxxxxxx *
(*Product name in the importing country*):

1.2.Princípio(s) ativo(s) e quantidade(s) por unidade de dose: xxxxxxxxxx
(*Active Ingredient(s) and amount per unit dose*): xxxxxxxxxx
Para a composição completa, ver no verso.
(*For complete composition, see at the verso*)

1.3.Vencimento do registro: xx/xxxx
(*License expiration*): xx/xxxx

1.4. Este produto está autorizado para ser comercializado no mercado do país exportador? Sim <i>Is this product licensed to be marketed in the exporting country? Yes</i>		1.5. Este Produto está realmente no mercado do país exportador? Sim <i>Is this product actually on the market in the exporting country? Yes</i>	
2.A.1.Número do registro do produto e data de emissão: xxxxxxxxxxxx (<i>Number of product license and date of issue</i>): xxxxxxxxxxxx		2.A.2.Detentor do registro, nome e endereço (<i>Product license holder, name and adress</i>): xxxxxxxxxxxxxxxxxxxx	
2.A.3.Condição do Detentor do registro do produto: Fabricante, Embalador ou Detentor do registro do produto <i>Status of product license holder:</i>			
2.A.3.1. Nome e endereço do local de fabricação do produto: xxxxxxxxxxxxxxxxxxxx (<i>Name and address of the manufacturer of the product</i>): xxxxxxxxxxxxxxxxxxxx			
2.A.3.2. Nome e endereço do local de embalagem primária e/ou secundária: xxxxxxxxxxxxxxxxxxxx (<i>Name and address of packages</i>): xxxxxxxxxxxxxxxxxxxx			
2.A.4.O resumo básico para aprovação está anexado? Não <i>Is a summary basis for approval appended? No</i>		2.A.5.A informação sobre as condições de aprovação do produto está anexa? Não <i>Is a summary basis for approval appended? No</i>	
3.A autoridade certificadora efetua inspeções periódicas da planta de fabricação na qual se produz a forma farmacêutica? Sim <i>Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? Yes</i>			
3.1.Periodicidade das inspeções de rotina (anos): 2 anos <i>Periodicity of routine inspections (years): 2 years</i>			
3.2.A fabricação deste tipo de forma farmacêutica tem sido inspecionada? Sim <i>Has the manufacture of this type of dosage form been inspected? Yes</i>			

3.3.As instalações e operações cumprem as Boas Práticas de Fabricação como recomenda a Organização Mundial de Saúde? <i>Do the facilities and operations conform to GMP as recommended by the World Health Organization?</i>	Sim Yes
4. A informação apresentada pelo solicitante satisfaz a autoridade certificadora em todos os aspectos da fabricação do produto? <i>Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product?</i>	Sim Yes

Data (Date): **Brasília, xx/xxxxxx/xxxxx**

NOME DO GERENTE GERAL
GERENTE GERAL DE MEDICAMENTOS
ANVISA-MS

Esta Certidão somente será válida com o Selo Seco da ANVISA (*This Certificate only will be valid with the Dry Seal of the ANVISA*)

* Informação de responsabilidade exclusiva da empresa detentora da certidão. O medicamento comercializado em outro país com o nome **XXXX**, não registrada no Brasil, não poderá circular no mercado brasileiro com este último nome. (** This information is the responsibility of the company holding the certificate. The product marketed in another country with XXXX name not registered in Brazil, does not circulate in the Brazilian market with the latter name.*)

FÓRMULA / FORMULATION:

Número de componentes na fórmula (*Number of components in the formulation*) =xx

APRESENTAÇÕES DO PRODUTO
(PRESENTATIONS OF THE PRODUCT):

Esta Certidão somente será válida com o Selo Seco da ANVISA (*This Certificate only will be valid with the Dry Seal of the ANVISA*)

Annex IX - Country Questionnaires

Country Region	Argentina, Latin America
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología médica)
Size of you HA	
<ul style="list-style-type: none"> How many employees? 	This information is not available
<ul style="list-style-type: none"> How many Employees are working on reviewing NDAs? 	This information is not available
<ul style="list-style-type: none"> Budget of the HA per year? 	This information is not available
<ul style="list-style-type: none"> How many applications are usually processed by your HA per year? 	This information is not available
How long does a NDA usually take until approval?	12 months
Does the local authority require CPPs (according WHO format)?	Yes
For which processes is a CPP mandatory? (please amend as required)	
<ul style="list-style-type: none"> NDA for an imported finished product 	<p>CPP is required but is not the exclusive document that can be submitted.</p> <p>CPP with marketed status mentioning the product is on the market of any annex I country (USA, Japan, Sweden, Switzerland, Israel, Canada, Austria, Germany, France, UK, Netherlands, Belgium, Denmark, Spain, Italy) and this CPP must include the legal name and address of the manufacturer, shelf life, material packaging and the composition of the product.</p>
<ul style="list-style-type: none"> NDA for a locally manufactured product 	<p>Any local evidence of marketing or from Annex I country.</p> <p>CPP is a good alternative if in Argentina is a new API or a new combination of APIs</p>
<ul style="list-style-type: none"> variation during Lifecycle management of a registered product 	CPP is required in some cases, e.g. new indication, new manufacturing site
How many CPPs are required for imported products in case of:	
<ul style="list-style-type: none"> NCE 	One
<ul style="list-style-type: none"> New Indication 	One
<ul style="list-style-type: none"> New formulation 	One
<ul style="list-style-type: none"> Generics 	One
<ul style="list-style-type: none"> Variation submissions 	One
From which countries are CPPs :	

Anna Sahl

Answer received: 06.03.2013

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<ul style="list-style-type: none"> required? 	USA, Japan, Sweden, Switzerland, Israel, Canada, Austria, Germany, France, UK, Netherlands, Belgium, Denmark, Spain or Italy
<ul style="list-style-type: none"> accepted? 	USA, Japan, Sweden, Switzerland, Israel, Canada, Austria, Germany, France, UK, Netherlands, Belgium, Denmark, Spain or Italy
Validity of the CPP :	
<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	Yes, because we submit a certificated copy of the CPP (by notary).
<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	

Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	The submission of a CPP is required. If a CPP is not available then we must submit clinical trials and in this case the approval takes longer time.
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	Our HA makes a complete review always but keep in mind that the HA required fewer documents if a CPP is available (e.g you don't need to submit clinical trials) CPP is required but does not mean fewer steps.
On which time of submission is the CPP required? e. g.	The CPP is required at the time of submission
<ul style="list-style-type: none"> at the time of submission? 	
<ul style="list-style-type: none"> before review starts? 	
<ul style="list-style-type: none"> before approval? 	

Is the CPP accepted as alternative to a GMP certificate?	No.
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	GMP certificate is required in some cases to check the manufacturing site.

For which process might a CPP be helpful but is not mandatory?	
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	Our HA require fewer documents if a CPP is available (e.g you don't need to submit clinical trials)
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	No, the same legislation applies for OTC and Rx

Does your Health Authority issue CPPs?	Yes
How long does it take your HA to issue a CPP?	About 1 month
Fees for a CPP issued by your HA	U\$S 120

Any additional comments?	
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Anna Sahl
Answer received: 06.03.2013

Country Region	Brazil, Latin America
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	ANVISA
Size of you HA	
<ul style="list-style-type: none"> How many employees? 	Year 2011 effective employees (total of 934): <ul style="list-style-type: none"> - 146 administrative analysts; - 656 health and regulatory surveillance specialists; - 132 administrative technician;
<ul style="list-style-type: none"> How many Employees are working on reviewing NDAs? 	For novel medicines, total of 20 technicians: <ul style="list-style-type: none"> - 6 for clinical studies evaluation; - 14 to evaluate registration and post-registration submissions and international inspections;
<ul style="list-style-type: none"> Budget of the HA per year? 	Year 2011, total authorized amount: R\$ 680,425,141.00
<ul style="list-style-type: none"> How many applications are usually processed by your HA per year? 	Year 2011, total medicine registrations granted: 531 (39 novel, 69 innovative, 18 biological, 2 dynamized, 31 specific, 19 phytotherapeutic, 531 generic and similar)
How long does a NDA usually take until approval?	Novel drug: 12-19 months Innovative drug: 15-24 months
Does the local authority require CPPs (according WHO format)?	Does not need to be according to the WHO format
For which processes is a CPP mandatory? (please amend as required)	
<ul style="list-style-type: none"> NDA for an imported finished product 	Yes
<ul style="list-style-type: none"> NDA for a locally manufactured product 	Yes, if possible. Generally speaking, CPP is a core requirement, it is unlikely to ANVISA to give a product its first worldwide registration
<ul style="list-style-type: none"> variation during Lifecycle management of a registered product 	Yes, depending on the subject. For instance, a new concentration is considered to be a post registration approval by ANVISA and requires a CPP
How many CPPs are required for imported products in case of:	
<ul style="list-style-type: none"> NCE 	1
<ul style="list-style-type: none"> New Indication 	0
<ul style="list-style-type: none"> New formulation 	1
<ul style="list-style-type: none"> Generics 	0
<ul style="list-style-type: none"> Variation submissions 	Yes, depending on the subject
From which countries are CPPs :	
<ul style="list-style-type: none"> required? 	Country of origin
<ul style="list-style-type: none"> accepted? 	From countries where the product is duly registered and marketed (preference to FDA and EU countries)

Anna Sahl

Answer received: 07.03.2013

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Validity of the CPP :	
<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	Usually they are valid for 2-3 years and used within the specified timeframe
<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	Depending on the variation and contents of the CPP, e.g., a new dosage form or new concentration where PI texts are part of the CPP
Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	No; and not presenting a CPP prevents approval
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	No
On which time of submission is the CPP required? e. g.	At the time of submission, can be amended along the process prior to approval, but deficiency letter will be issued for that matter if analysis of the process starts
<ul style="list-style-type: none"> at the time of submission? 	
<ul style="list-style-type: none"> before review starts? 	
<ul style="list-style-type: none"> before approval? 	
Is the CPP accepted as alternative to a GMP certificate?	No; sometimes GMP can be proven through CPP, but not the best scenario
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	Yes; not presenting a GMP prevents approval, can be amended along the process, prior to approval, but deficiency letter will be issued for that matter (this step is harder to control with regards to the timeframes and predictions)
For which process might a CPP be helpful but is not mandatory?	
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	CPP is a core requirement, it is unlikely to ANVISA to give a product its first worldwide registration
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	In general, OTC are medicines which comply with a pre-approved list of indications per product category and chemical entity; may not be presented as injectable formulations and if formulated with vitamins and minerals, there are limits for such APIs
Does your Health Authority issue CPPs?	Yes
How long does it take your HA to issue a CPP?	Electronic document
Fees for a CPP issued by your HA	No cost
Any additional comments?	ANVISA may issue a WHO format CPP, takes about 3-4 months to be issued – this is submitted in paper

Anna Sahl
Answer received: 07.03.2013

Country Region	Uruguay, Latin America
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	Ministerio de Salud Pública, Departamento de Medicamentos
Size of you HA	
• How many employees?	14
• How many Employees are working on reviewing NDAs?	7
• Budget of the HA per year?	Data not available
• How many applications are usually processed by your HA per year?	Data not available
How long does a NDA usually take until approval?	Fast track(if accepted) : 10 to 45 days Normal track : 15 to 18 months Existing drugs and presentation : 4 months
Does the local authority require CPPs (according WHO format)?	CPP can have different formats but no electronically issued CPPs are accepted
For which processes is a CPP mandatory? (please amend as required)	
• NDA for an imported finished product	X
• NDA for a locally manufactured product	
• variation during Lifecycle management of a registered product	X (Labeling var.:new indication, or changes that must be justified CMC var.: changes in shelf life or DP composition)
How many CPPs are required for imported products in case of:	
• NCE	1
• New Indication	1
• New formulation	1
• Generics	There are no generics defined in UY
• Variation submissions	1
From which countries are CPPs :	
• required?	Origin country with marketed status and EU country or FDA
• accepted?	If origin country CPP doesn't have marketed status another EU or FDA CPP with MS can be added
Validity of the CPP :	
• can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year?	CPP can be used until its expiration date

Anna Sahl

Answer received: 27.02.2013

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<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	No
Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	CPP are mandatory for submission of imported products
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	No
On which time of submission is the CPP required? e. g.	At the time of submission (if not, the submission is not accepted)
<ul style="list-style-type: none"> at the time of submission? 	
<ul style="list-style-type: none"> before review starts? 	
<ul style="list-style-type: none"> before approval? 	
Is the CPP accepted as alternative to a GMP certificate?	No
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	GMP certificate is mandatory at the submission time but it can be included
For which process might a CPP be helpful but is not mandatory?	-
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	-
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	No
Does your Health Authority issue CPPs?	Yes, but with local format
How long does it take your HA to issue a CPP?	Depends on what you need it for
Fees for a CPP issued by your HA	Aprox.160 US dollars (it has a slight variation each month due to local currency)
Any additional comments?	-

Anna Sahl
 Answer received: 27.02.2013

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Country Region	Malaysia, Asia Pacific
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	National Pharmaceutical Control Bureau
Size of you HA	
<ul style="list-style-type: none"> How many employees? 	Estimated 100
<ul style="list-style-type: none"> How many Employees are working on reviewing NDAs? 	5
<ul style="list-style-type: none"> Budget of the HA per year? 	Unknown
<ul style="list-style-type: none"> How many applications are usually processed by your HA per year? 	Unknown
How long does a NDA usually take until approval?	Varies between 12-18 months
Does the local authority require CPPs (according WHO format)?	Yes
For which processes is a CPP mandatory? (please amend as required)	
<ul style="list-style-type: none"> NDA for an imported finished product 	Yes
<ul style="list-style-type: none"> NDA for a locally manufactured product 	No (CPP is only for purpose of exporting goods)
<ul style="list-style-type: none"> variation during Lifecycle management of a registered product 	No
How many CPPs are required for imported products in case of:	
<ul style="list-style-type: none"> NCE 	1
<ul style="list-style-type: none"> New Indication 	Not required
<ul style="list-style-type: none"> New formulation 	1
<ul style="list-style-type: none"> Generics 	1
<ul style="list-style-type: none"> Variation submissions 	Not required
From which countries are CPPs :	
<ul style="list-style-type: none"> required? 	Reference countries: United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland
<ul style="list-style-type: none"> accepted? 	All from the above. Other countries may be accepted as well (upon negotiation with the local HA with valid justification)
Validity of the CPP :	
<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	Usually, one CPP to be used for 1 submission. Cross-referencing may be allowed upon negotiation with the local HA.

Anna Sahl
 Answer received: 25.02.2013

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<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	Refer above.
Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	No
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	CPP is a mandatory document required by the local HA.
On which time of submission is the CPP required? e. g.	CPP is usually required at time of submission. In certain scenarios and upon negotiation with the local HA, applicant may submit using certified true copy of approval letter first. CPP will then be submitted at a later date, prior to approval.
<ul style="list-style-type: none"> at the time of submission? 	
<ul style="list-style-type: none"> before review starts? 	
<ul style="list-style-type: none"> before approval? 	
Is the CPP accepted as alternative to a GMP certificate?	
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	Yes
For which process might a CPP be helpful but is not mandatory?	
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	CPP is used for submission purpose of a NDA as the local HA require that the product be approved first in country of reference. CPP does not help to expedite approval timelines.
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	Both require CPP for submission
Does your Health Authority issue CPPs?	Yes
How long does it take your HA to issue a CPP?	1 month
Fees for a CPP issued by your HA	RM50
Any additional comments?	NOne

Anna Sahl
 Answer received: 25.02.2013

Country Region	Korea, Asia Pacific
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	MFDS (Ministry of food and drug safety)
Size of you HA	
<ul style="list-style-type: none"> How many employees? 	1,760
<ul style="list-style-type: none"> How many Employees are working on reviewing NDAs? 	About 300 (sum of reviewers in department of drug evaluation, biologic product evaluation, administrative department for NDA and BLA and department of drug quality and biologic products quality)
<ul style="list-style-type: none"> Budget of the HA per year? 	308,7 billion Korean won (KRW) (205.8 mil euro)
<ul style="list-style-type: none"> How many applications are usually processed by your HA per year? 	1002 for ETC, 406 for OTC
How long does a NDA usually take until approval?	Normally 10-12 months for NDA, > 18 months for BLA
Does the local authority require CPPs (according WHO format)?	Yes, but with additional requirements e.g. composition with reference to standard of APIs, marketing status (yes) and GMP compliance statement
For which processes is a CPP mandatory? (please amend as required)	CPP is required for all NDA for imported finished products
<ul style="list-style-type: none"> NDA for an imported finished product 	Yes
<ul style="list-style-type: none"> NDA for a locally manufactured product 	No
<ul style="list-style-type: none"> variation during Lifecycle management of a registered product 	Line extension such as new indication and variations – no New strengths, new formulation - Yes
How many CPPs are required for imported products in case of:	
<ul style="list-style-type: none"> NCE 	1
<ul style="list-style-type: none"> New Indication 	0
<ul style="list-style-type: none"> New formulation 	1
<ul style="list-style-type: none"> Generics 	1
<ul style="list-style-type: none"> Variation submissions 	0
From which countries are CPPs :	
<ul style="list-style-type: none"> required? 	Generally CPP from sourcing country is required, but not mandatory for chemical drug.
<ul style="list-style-type: none"> accepted? 	CPP from sourcing country is mandatory for biologic products
Validity of the CPP :	
<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	

Anna Sahl

Answer received: 30.05.2013

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<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	1 CPP for 1 submission
Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	No
On which time of submission is the CPP required? e. g.	Before approval
<ul style="list-style-type: none"> at the time of submission? before review starts? before approval? 	
Is the CPP accepted as alternative to a GMP certificate?	
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	Not required in case GMP review is conducted for NDA
For which process might a CPP be helpful but is not mandatory?	
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	CPP could be supporting data in some cases including new indication, but it can't replace complete review.
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	No
Does your Health Authority issue CPPs?	Yes
How long does it take your HA to issue a CPP?	3 working days
Fees for a CPP issued by your HA	25,000 KRW (about 17 euro)
Any additional comments?	

Country Region	China
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	CFDA(China Food and Drug Administration)
Size of you HA	
<ul style="list-style-type: none"> How many employees? 	345 including CDE (center for Drug Evaluation) and CFDA.
<ul style="list-style-type: none"> How many Employees are working on reviewing NDAs? 	99
<ul style="list-style-type: none"> Budget of the HA per year? 	USD 167 million for 2012
<ul style="list-style-type: none"> How many applications are usually processed by your HA per year? 	CDE has been assigned around 7,000 applications in 2012.
How long does a NDA usually take until approval?	22 months
Does the local authority require CPPs (according WHO format)?	Yes for imported drug applications including IND and NDA.
For which processes is a CPP mandatory? (please amend as required)	
<ul style="list-style-type: none"> NDA for an imported finished product 	Yes
<ul style="list-style-type: none"> NDA for a locally manufactured product 	No
<ul style="list-style-type: none"> variation during Lifecycle management of a registered product 	Yes for any changes regarding the items listed in the IDL.
How many CPPs are required for imported products in case of:	
<ul style="list-style-type: none"> NCE 	1 for each submission
<ul style="list-style-type: none"> New Indication 	1 for each submission
<ul style="list-style-type: none"> New formulation 	1 for each submission
<ul style="list-style-type: none"> Generics 	1 for each submission
<ul style="list-style-type: none"> Variation submissions 	For changing the items listed in the IDL, 1 for each submission. For other changes, no CPP needed.
From which countries are CPPs :	Not specified.
<ul style="list-style-type: none"> required? 	
<ul style="list-style-type: none"> accepted? 	
Validity of the CPP :	
<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	No. One CPP is used for one submission.
<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	Some variations may not need CPP. See above explanation.

Anna Sahl
 Answer received: 08.05.2013

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Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	No.
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	No.
On which time of submission is the CPP required? e. g.	At the time of submission.
<ul style="list-style-type: none"> at the time of submission? before review starts? before approval? 	
Is the CPP accepted as alternative to a GMP certificate?	If the CPP can state the GMP status and the inspection information it could be accepted as alternative to a GMP certificate.
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	See above.
For which process might a CPP be helpful but is not mandatory?	To support the approval for the drug substance as a certificate to state that the DS has been approved for another drug.
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	N.A.
Any Difference between Rx and OTC registrations? (if yes, please explain in detail)	For imported OTC, we firstly need get Rx approval then could apply for OTC switch after several years usage in China populations.
Does your Health Authority issue CPPs?	No
How long does it take your HA to issue a CPP?	N.A.
Fees for a CPP issued by your HA	N.A.
Any additional comments?	<p>CPP is mandatory for an imported drug application in China at IND stage, and copy of CPP could be used when we make NDA submission if at that time the previous CPP is still valid.</p> <p>For IMCT application, CPP is not mandatory but GMP certificate is mandatory.</p>

Country Region	Russia
Name of your Health Authority (HA) responsible for granting Marketing authorizations for finished Drug Products	Ministry of Health, Russian Federation (scientific evaluation is performed by substructure 'FGBU' – federal state institution)
Size of you HA	
• How many employees?	NA
• How many Employees are working on reviewing NDAs?	NA
• Budget of the HA per year?	NA
• How many applications are usually processed by your HA per year?	About 5 000 including NDA, variations, renewals ¹
How long does a NDA usually take until approval?	<p>1) If NDA local clinical data was obtained during International clinical trials with Russian patients participation – NLT 210 working days</p> <p>2) If NDA has no local clinical data – NLT 210 working days + time for clinical trials (clock - stop)</p>
Does the local authority require CPPs (according WHO format)?	CPPs according WHO format are not obligatory for submission, but it is preferable
For which processes is a CPP mandatory? (please amend as required)	
• NDA for an imported finished product	Yes
• NDA for a locally manufactured product	No
• variation during Lifecycle management of a registered product	Yes (only for NDA, Product transfer, content changes, shelf life)
How many CPPs are required for imported products in case of:	
• NCE	1
• New Indication	1
• New formulation	1
• Generics	1
• Variation submissions	1 (for each variation)
From which countries are CPPs :	
• required?	Country of origin
• accepted?	In case if CPP of origin country cannot be obtained – CPP from other country is accepted (EU countries and US – are preferable)
Validity of the CPP :	

Anna Sahl
 Answer received: 14.03.2013

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<ul style="list-style-type: none"> can one CPP used for a specific timeframe, e. g. for several submissions on the same product within 1 year? 	Yes, in case if all information is corresponded to the information included to variation
<ul style="list-style-type: none"> or do you need a new CPP for every submission e. g. variation etc.? 	No (in case if something included in CPP is changed)

Does the submission of a CPP accelerate the registration procedure? (If yes: how much is the time saving?)	No
<ul style="list-style-type: none"> Will the HA accept the CPP as alternative to a complete review (please amend in detail) 	No
On which time of submission is the CPP required? e. g.	at the time of submission
<ul style="list-style-type: none"> at the time of submission? 	
<ul style="list-style-type: none"> before review starts? 	
<ul style="list-style-type: none"> before approval? 	

Is the CPP accepted as alternative to a GMP certificate?	CPP can be alternative to GMP in case if CPP includes information about GMP inspection with date
<ul style="list-style-type: none"> Is a GMP certificate always required for NDAs? 	Yes ²

For which process might a CPP be helpful but is not mandatory?	No any process
<ul style="list-style-type: none"> In which way is a CPP helpful? (e.g. faster approval since no complete review will be required when a CPP is available?) 	No any process
Any Difference between R_x and OTC registrations? (if yes, please explain in detail)	No

Does your Health Authority issue CPPs?	No
How long does it take your HA to issue a CPP?	-
Fees for a CPP issued by your HA	-

Any additional comments?	1- 745 NDA submissions to Russian MoH for half a year (2 nd half of 2012)
	2 - GMP is needed for all stages (sites) of manufacturing process (for substance also)

Anna Sahl
Answer received: 14.03.2013

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Annex X – IDRAC Global Module on CPPs

IDRAC Global Module on CPPs (extract) (IDRAC, 2013)

Country Region	Argentina, Latin America	Brazil, Latin America	Malaysia, Asia-Pacific	China	Russian Federation
CPP Issuing Authority	Instituto Nacional de Medicamentos (INAME)	Gerência Geral de Medicamentos (GGMED) / General Office of Medicinal Products of the ANVISA	Drug Control Authority (DCA)	State Food and Drug Administration (SFDA)	Not applicable
Notes on CPP	N/A	N/A	Registration of product for export purposes is not necessary if there is no change in the formulation or appearance of the product. An "export notification" procedure allows an applicant to apply for Free Sale Certification for the product whereby the applicant need only declare to the DCA the differences in the product for export compared to the registered product marketed in Malaysia (such as a product being exported under a different name). A CPP will be issued to the applicant for the registered product together with an explanation of any difference(s) to the importing country.	N/A	Russian Federation does not issue CPPs. The following documents are issued locally: Manufacturing License (which confirms that the product is manufactured in accordance with local requirements) and Registration Certificate (which confirms that product has got a Marketing Authorization). Not all local manufacturers are GMP certificated, GMP certification will be mandatory from 01 Jan 2014.
WHO Format	Yes	Yes	Yes	No	Not applicable
Turnaround time	1 month	Not specified	2 weeks	2 weeks	Not applicable
Fees	200 ARS (Argentine Peso)	No fee	50 MYR (Malaysian Ringgit)	150 CNY	Not applicable
Language	English and Spanish	Portuguese/English, Spanish/English	English	Simplified Chinese and English	Not applicable
Validity	1 year	Not specified	2 years	2 years	Not applicable

Procedure	Applicants are encouraged to check agency's requirements before requesting CPPs	The exporter has to file an application including the following documents: General Front page, Petition Formulary 1 and 2; Copy of the publication in the Official Journal of the Product Registration granted by ANVISA, a document to support the request for the CPP, the renewal publication, the GMP Certificate and approved Package insert.	Online application process to register the product for export purpose and apply for CPP.	Submit application form for export plus SFDA required dossier	Not applicable
Link to CPP form or guideline 1	Form: Certificate of Pharmaceutical Product, 2013 (Spanish and English Versions) (IDRAC 88212)	Form: Certificate of Pharmaceutical Product-CPP, 25-Jan-2012 (Portuguese and English Versions) (IDRAC 99259)	Form: BPFK-412.2 - Application for Certificate of Pharmaceutical Product, Apr-2012 (IDRAC 156369)		
Does the local authority require CPPs ?	Yes	Yes	Yes	Yes	Yes
For which regulatory submission are CPPs required?	Registration	Product registration. Without CPP the application may be filed but registration will not be granted.	Registration Re-registration	Registration Renewal	Registration, CMC changes (i.e. change of manufacturing site, of pharmaceutical Formulation / composition). In case a CPP is not available a GMP certificate, a Free Sales certificate and a manufacturing license can be submitted.

Which authority should issue CPPs?	Accepted CPPs are those issued by Health Authorities of the following countries: USA, Canada, Japan, Australia, New Zealand, Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, UK, Israel, Brazil, Cuba, Chile, Mexico, China.	CPPs should be issued by the Health Authority of the country of origin.	CPPs shall be issued by the Competent Authority of the country of origin. CPPs issued by EMEA for products registered through the centralized procedure in EU will be accepted; CPPs issued by the manufacturer or other authorities are not accepted. In the event a CPP is not available from the country of manufacture (e.g. where a product is not licensed for sale in said country but manufactured under contract only for product owner from another country), the following alternatives may be considered: GMP Certification/Manufacturing License for the manufacturer from the relevant Competent Authority, together with : (1) CPP from the country of the product owner; or (2) CPP from the country of release, if (1) is not available. If more than one manufacturer is involved, GMP certificates should be available for all the manufacturers. The Drug Control Authority reserves the right to conduct an inspection on any manufacturing site.	An original CPP (WHO format) issued by the Competent Authority in the exporting country of origin is required.	According to the Federal Law N 61-FZ CPPs should be issued by the Health Authority of the country, where medicinal product is registered. Although Agreement about Collaboration in Circulation of Medicinal Products and Medical Devices of State-members of Eurasian Economic Community of 28-Sep-2012 refers CPP to the country of origin.
Need for Legalisation	CPPs should be legalized (apostille certificate or consular legalization). The CPP should have a legal translation.	The CPP has to be notarized at the Brazilian consulate and a legal translation of the notarized copy provided.	No need for legalization of original CPP. It is recommended that CPP is in the format of Who Certification Scheme.	If it is a original, legalisation is not required. If it is a copy of the original CPP it should be locally notarized and legalized. A copy of CPP is notarized by local notary public and legalized by Chinese embassy.	Should be legalised.

Definition of "Country of Origin"	Country where the final product has a marketing authorization.	Country where the company is located.	Country of origin means country of manufacturer. However for registration submission purposes Malaysian authority does accept CPP from country of product owner. For the case of CPP from country of manufacturer, only CPP is OK. For the case of CPP from product owner, CPP + GMP/Manufacture License of the manufacturer are required. See "Drug Registration Guidance Document (Malaysia)" for more details.	The first preferable option is CPP is from the country of origin as country where finished products is manufactured, the secondary option is CPP is from country of Marketing Authorization holder, the last option is CPP is from country of company's head quarter.	Not provided in Russian legislation. Although Agreement about Collaboration in Circulation of Medicinal Products and Medical Devices of State-members of Eurasian Economic Community of 28-Sep-2012 defines country of origin as country, where product is manufactured.
Regulatory Summary 1	<u>Import / Export (IDRAC 27644)</u>	<u>Import / Export (IDRAC 26658)</u>	<u>Import / Export (IDRAC 33487)</u>	<u>Import / Export (IDRAC 46812)</u>	<u>Import / Export (IDRAC 51678)</u>

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Mettmann,

Anna Sahl