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Risk And Opportunities in Development of New Drug

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Abstract

The Certificate of Pharmaceutical Product (CoPP) was implemented to accelerate the 1availability of new drugs in developing countries by providing evidence of the quality of products and reducing the time to market through reliance on a prior trusted analysis. To determine current CoPP practices versus national regulatory guidelines and to inform recommendations for the efficient use of the CoPP based on the needs of the modern regulatory environment. This review includes basics of CoPP, origin of CoPP, types of drugs include in CoPP, procedure to obtain CoPP, requirement for CoPP, applicant, examples, format and content and benefits of CoPP. A CoPP is given by the drug regulator not before conducting an inspection of the manufacturing plant. Proper documentation is essential in almost every aspect of the pharmaceutical industry. Whether for product registration, factory inspection, or internal quality control, Adva Care employs the latest technologies to streamline and process information. All facilities possess up-to-date Good Manufacturing Practice (GMP), CE, TUV, and/or ISO certificates that reflect high quality standards and WHO rules and regulations and registration of documents.

Key words: food and drugs; health products; drug controller

Introduction:

Certificate of Pharmaceutical Product:

The Certificate of Pharmaceutical Product (abbreviated: CoPP) is a certificate issued in the format recommended by the World Health Organization (WHO), which establishes the status of the pharmaceutical product and of the applicant for this certificate in the exporting country1; it is often mentioned in conjunction with the electronic Common Technical Document (eCTD). A CoPP is issued for a single product, because manufacturing arrangements and approved information for different pharmaceutical forms and strengths can vary.2 The CoPP is mentioned in World Trade Organization documents, although the tightly regulated products are subject to bilateral trade agreements or regional trade agreements3. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has instituted standards for this purpose but it is unclear how the ex-ICH countries operate their health regulators [4,5]

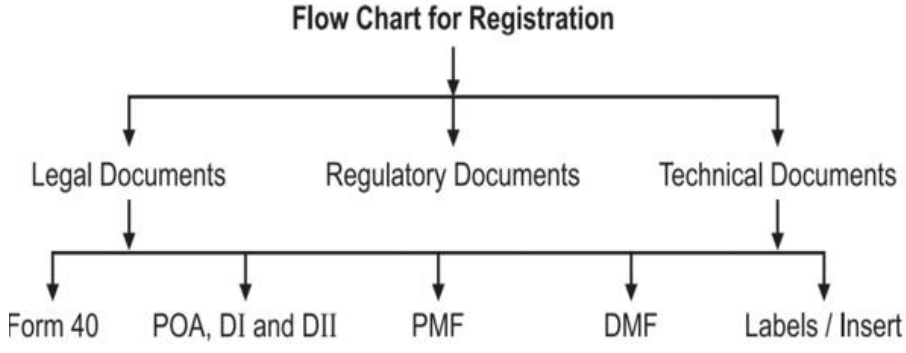

Figure 1: Certificate of Pharmaceutical Product

Scope of CoPP

The Certificate of a Pharmaceutical Product is needed by the importing country when the product in question is intended for registration (licensing, authorisation) or renewal (prolongation) of registration, with the scope of commercialisation or distribution in that country 2. Certification has been recommended by WHO to help undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities inimporting countries to assess the quality of pharmaceutical products as prerequisite of registration or importation.
In the presence of such CoPP, WHO recommends to national authorities to ensure that analytical methods can be confirmed by the national laboratory, to review and if necessary to adapt product information as per local labelling requirements, and to assess bioequivalence and stability data if necessary [6].
However, regulatory practices often vary in importing countries. Thus, in addition to CoPP, assessment of application dossiers to support drug registrations, with different levels and complexity of requirements are considered necessary to satisfy full assurance on the appropriate quality of drugs [7].

Content and format
The content of CoPP consists of the following main data:

- Exporting (certifying) country
- Importing (requesting) country
- Name, dosage (pharmaceutical) form and composition of the product [active ingredient(s) and amount(s) per unit dose]
- Information on registration (licensing) and marketing (presence on the market) status of the product in the exporting country
- Number of product license (including license holder details, license holder's involvement in manufacturing if any) and date of issue,if applicable
- Appended summary of technical basis on which the product has been licensed (if required by the issuing authority)
- Appended current product information
- Details on the applicant for the CoPP
- If marketing authorization is lacking in the exporting country, information about reasons

When applicable, information if the manufacturing site is periodically inspected by certifying authority and if the manufacturing site complies with Good Manufacturing Practice (GMP) as recommended by WHO.

Although issuing authorities claim that their CoPP conform to WHO format (a statement to confirm whether or not the document is issued in the format recommended by WHO should be included in the certificate), their format and content may vary from an issuing country to another. Also, some authorities do not issue CoPP if the respective drug is not licensed in the exporting country (e.g., Italy). In this last case, a Certificate of Exportation is issued instead, with a format and content similar to those of CoPP.

Special considerations in importing countries

Most competent authorities in importing countries require CoPP to be issued by the country of origin.
Also, even though this certificate is released in its original form, addressed to a specific importing country and stamped with the seal of issuing authority on each page, many authorities in importing countries may unnecessarily request authentication of such a document in the form of legalisation by their embassy in the exporting country or by apostillation ("Abuse of scheme").

Certificate of a pharmaceutical product (CoPP)

The Medical Products Agency (MPA) issues export certificates on request to assist exporters of medicinal products to satisfy the import requirements of other countries. The format of the certificates complies with that specified by the World Health Organization (WHO), except point 1.3 "Is this product actually on the market for use in the exporting country?" which is not included, as the MPA does not have access to that information.
The certificate can be ordered from the MPA using the form available on the website (see hyperlink to the right). The certificate of a pharmaceutical product (CoPP) will provide details about a single named medicinal product for human or veterinary use. A certificate can be issued for a medicinal product for which a Marketing Authorisation application is under consideration or refused or for a medicinal product which is licensed or withdrawn in Sweden. The certificate provides detailed information about the product including the Marketing Authorisation Holder (MAH), the complete composition and the manufacturing site(s).
The MAH or a representative of the MAH can apply for the certificate. The certificate is issued in English only. Certificates for medicinal products applied for through the centralised procedure are only issued by the EMA.
The MPA will issue a certificate within 30 days of the arrival of the request. The certificate is issued on specific certificate paper with an MPA stamp assigned. The requesting company is responsible for the legalization of the certificate when needed; this is not done by the Medical Products Agency.
The fee for issuing one CoPP is 950 SEK. The MPA will send an invoice to the applicant after the delivery of the certificate.
The medicinal product may have a different name in the importing country. If so, a statement of this can be attached to the certificate. The statement has to be written on the company's headed paper, be signed and dated and should state the trade name, pharmaceutical form and strength in both the exporting and the importing country.
If the Summery of Product Characteristics (SmPC) is to be attached to the certificate, the applicant is responsible for the translation of the latest approved Swedish SmPC from Swedish to English. The translated version should be enclosed to the request of the certificate.
If the medicinal product is authorised through the mutual or decentralised procedure with Sweden as Reference Member State (RMS), the latest approved English SmPC is already available at the MPA and can be attached to the certificate.[8]

Background
In 1967, the Twentieth World Health Assembly requested in resolution WHA20.34 that a draft text be prepared on good manufacturing practices (GMP). The text was subsequently submitted to the Twenty-first World Health Assembly in 1968, under the title "Draft requirements for good manufacturing practice in the manufacture and quality control of drugs and pharmaceutical specialities". In 1969, the Twenty-second World Health Assembly endorsed these requirements for "Good Practices in the Manufacture and Quality Control of Drugs" (resolution WHA22.50). These requirements have since been revised: the first revision was adopted by the World Health Assembly in 1975 (resolution WHA28.65) and the most recent - They have been replaced by Certificates of a Pharmaceutical Product (CPP) and are issued as a service to the industry when required by an importing country.

Applying for a Certificate

A CPP, in the format recommended by the WHO, establishes the status of the pharmaceutical product listed on the certificate, and the GMP status of the fabricator of the pharmaceutical product, in the exporting country. The Health Product Compliance Directorate issues a CPP to one of the following applicants:

- The Drug Identification Number (DIN) owner of the pharmaceutical product; or in the case of

radiopharmaceuticals the party to which a Notice of Compliance (NOC) has been issued

- The fabricator of the pharmaceutical product, if it is located in Canada and GMP compliant; or
- A third party that submits, along with the application, a written authorization for the issuance of the CPP from the DIN owner of the pharmaceutical product. (To be updated

Application Requirements:

Type	Requirements that must be met
Pharmaceutical product is fabricated and packaged/ labelled in Canada	• the fabricator and packager/labeller are GMP compliant • the pharmaceutical product has a valid DIN or NOC and a valid date of notification • or in the case of radiopharmaceuticals an NOC has been issued and the product has a valid date of notification • the pharmaceutical product is sold on the Canadian market.
Pharmaceutical product is fabricated in a foreign country and packaged/labelled in Canada or fabricated in Canada and packaged/labelled in a foreign country	• the packager/labeller and the fabricator are GMP compliant • the foreign establishment is GMP compliantand is listed on the Canadian Drug Establishment Licence (DEL) • the pharmaceutical product has a valid DIN or a NOC and a valid date of notification • the pharmaceutical product is sold on
Pharmaceutical product is fabricated and/or packaged/labelled in Canada but not marketed in Canada	• the fabricator and/or packager/labeller are/is GMP compliant • a DIN or an NOC has been issued, (that is the drug product has market authorization)
Pharmaceutical product is fabricated in Canada and not sold on the Canadian market, but the drug submission is under review	A CPP is issued if the fabricator is GMP compliant and if the applicant submits information on the formulation and active ingredients of the pharmaceutical product. Furthermore, the CPP issued will carry the following statement: "The product is manufactured for export only. The Health Products and Food Branch of Health Canada is currently reviewing an application to permit the marketing of this product in Canada."
The request for a certificate is not specific for a pharmaceutical product	A GMP Certificate is issued when the fabricator is GMP compliant. In this particular case, the certificate that is issued indicates the dosage forms only, instead of the product information.

Table 1: Conditions required for COPP

Importance of COPP :

It is needed by the importing country when the product is intended for registration (licencing , authorisation) , or renewal(prolongation) of registration.
Certificate has been recommended by WHO to help undersized drug regulatory authorities without proper quality assurance facilities in importing countries to acess the quality of pharmaceutical products as prerequisite of registration or importation .

WHO:

The application for the grant of WHO GMP certificate of pharmaceutical product shall be made to respective zonal officers as per the requirement. The CIOPP will be issued by the zonal officers on behalf of Drugs Controller General (India) after inspection and satisfactory clearance by CDSCO officers as per WHO-GMP guidelines .

General requirements for the submission of application for issue of COPP

- A application letter shall be addressed to DDC(1) / ADC(1) of respective CDSCO zonal/ subzonal offices with copy of covering letter and product summary sheet to DCG(1) by authorised person only .
- Application should clearly indicate for fresh(Grant) or reissue of products applied , accordingly it will be

scrutinized for the products applied .

- Applications will be reviewed by CDSCO officers and completed applications in all respects would be accepted for inspection on first come first serve basis.
- The forwarding letter or application shall be accompained with the list of products applied for grant of COPP , along with the product permission copy (manufacturing liscence issued by SLA) and notarised product summary sheet , site master file as per WHO-GMP requirements .
- List of major/master documents like master validation plan , quality manuals , specifications
- , master formula records maintained by firm and list of SOP'S (to indicate the documentation system of firm).
- Manufacturing layout
- List of personnel (with designation , quqlification and experience) , list of equipments , instruments , utilities along with make and model and capacity .
- List of primary and secondary impurity and reference standards /cultures available with the firm(relevant to the applied products for the grant of COPP) .

Procedure For Acceptine The Application For Issue Of Copp

- Applications forwarded by before 1-10-2009 will be considered provided they should resubmit the application in the revised format with forwarding letter , notarised product summary sheet and other documents which were not submitted earlier as per requirment on first come first serve basis .
- A ll applications received will be scrutinized by CDSCO officials after receipt and query letter will be sent to applicant , if any or otherwise will be considered for inspection .
- Inspection will be carrid out by CDSCO officers ads per WHO GMP guidelines of TRS 822/902 for sterile products and other relevent guidelines in TRS937 , TRS 929 , TRS 863 etc.as applicable from time to time .
- Self apprisal cheklist should be filled and submitted to CDSCO officer before inspection .
- inspection team verify the checklist at the time of inspection .
- Inspectors brief the inspection findings at the exit meeting .
- The report should clearly define defeciencies as per WHO GMP guidelines .
- Respective zonal/subzonal certifying authority prepare "Review Report" based on review of observations of checklist and written inspection report as per WHO GMP guidelines .
- Firm may reapply if required after proper compliance after 5 months from date of rejection.
- If the same firm applies after 5 months , scrutiny of such application should be asked for earlier compliance with documentary evidences in addition to the usual general requirements for submission of application for issue of COPP .

The WHO Certification Scheme and International Pharmaceutical Product Marketing :

The World Health Organization (WHO) is the United Nations' leading regulatory authority for international public health. According to WHO, access to essential and quality medicines is a basic human right.1 Because of the unique way the pharmaceutical industry impacts human health and well-being, WHO plays an important role in regulating international drug approval and marketing. Quality, safety and efficacy (QSE) are the fundamental requirements for marketing a drug in any country.

Any new drug must meet adequate quality standards and have sufficient clinical evidence to demonstrate its safety and effectiveness before it can enter the market.2 New drug approval is a highly complex process that requires a high level of expertise and resources, and large, well- trained, experienced multidisciplinary teams with the capability to review and evaluate all aspects of new products. Only a few regulatory agencies, mainly in welldeveloped, industrialized countries, are competent to effectively evaluate new drugs to assure their quality, safety and efficacy.

From a drug regulatory competence perspective, the world is divided into three groups of countries: those that have well-developed Competent Authorities with the knowledge, scientific and technical capabilities to perform full regulatory review and evaluation; countries with varying levels of development and drug regulatory capabilities for their pharmaceutical markets; and those that have very limited or no drug regulatory capability. The last two groups of countries cannot undertake full assessment of new pharmaceutical products; therefore, they depend to differing extents upon evaluations by such established regulatory bodies as the US Food and Drug Administration (FDA), European Medicines Agency (EMEA), UK Medicines and Healthcare products Regulatory Agency (MHRA), Australian Therapeutic Goods Administration (TGA), etc.

Certificate of Pharmaceutical Product:

Drug approval by one of these major authorities provides a valid basis for marketing a product in these less-developed countries unless there are specific issues to be considered such as population related differences in metabolic pathways. Consequently, the Competent Authorities of developed countries where drugs are manufactured and exported should provide documentation and evidence of approvals for specific pharmaceutical products to importing countries unable to fully evaluate new drugs. Most commonly, such evidence of approval is via a standard document, the Certificate of Pharmaceutical Product (called a Certificate of Medicinal Product in the EU), generally referred to as a CPP. The CPP represents a source- intensive, full QSE assessment.

WHO recommends the CPP as part of a broad scheme detailed in its guidelines.3 This scheme is an administrative instrument that requires each participating member state to attest to another's health authority that: a specific product is authorized to be placed on the market within its jurisdiction, or if not authorized, the reason why that authorization has not been accorded; the plant in which the product is manufactured is subject to inspections at suitable intervals to ensure that the manufacturer conforms to GMP standards recommended by WHO; and all submitted product information, including labeling, is currently authorized in the certifying country.

The CPP is a confidential document provided by the exporting country's regulatory authorities to the approved product's license holder or its agent in the importing country. It is to be presented in the filing application to the target country's health authority when the product in question is under consideration for new registration for authorized importation and sale, or when action is required to renew, modify or review a prelicensed product. As such, Competent Authorities that perform a full quality, safety and efficacy review should not request a CPP but rather provide the CPP based upon their assessment.

WHO provides a recommended model certificate4 in three languages: English, French and Spanish. The templates' formats and wording, and conditions and terms of certification may vary from one country to another. However, certificate contents are consistent with those suggested by WHO. All CPPs should include a statement to confirm they are consistent with the WHO certification scheme.

Each certifying authority agrees to inform WHO and all national Competent Authorities of any serious problems associated with a certified product exported under the scheme's provisions, or of any criminal abuse of the scheme directed to the export of falsely labeled, counterfeited or substandard pharmaceutical products. Upon receipt

of such notification, WHO will transmit the message immediately to the competent national authority in each concerned member state. In general, a product cannot be certified during the assessment of a serious safety or quality defect.

Prior to implementation of the CPP, "Certificates of Free Sales" were used to attest that pharmaceutical products were fabricated in compliance with GMPs. These certificates are discouraged by WHO and no longer issued by most authorities, since they have been replaced by the CPP. Certificates of Free Sale are occasionally issued by some authorities as a service to manufacturers when required by importing countries. However, most countries have adopted the CPP format as recommended by WHO

When requesting a CPP, the applicant should indicate the type of information required. Supplementary information may be attached to the CPP at the applicant's request and at the certifying authority's discretion. The certifying authority is responsible for assuring the authenticity of the certified data. For example, EMEA is only obliged to attach the relevant Summary of Product Characteristics (SPC).

At the applicant's request, the package leaflet, labeling, European Public Assessment Report (EPAR) and/or Statement of Quantitative Composition (SQC) can also be attached.6 EMEA issues certificates only if the Marketing Authorization Application is assessed through the Centralized Procedure. National health authorities for European Economic Area countries can issue certificates for any medicinal products for which the marketing authorization is valid in their territories. Not every regulatory authority can issue a CPP. To issue a CPP, the country must be a party to the scheme and must meet the conditions specified by WHO guidelines for its implementation.17

Literature Review:

Céline Rodier ET AL., (2021): The certificate of pharmaceutical product (CPP) was implemented to accelerate the availability of new drugs in developing countries by providing evidence of the quality of products and reducing the time to market through reliance on a prior trusted analysis. However, the CPP format, issuing process and use have not been revised since 1997 and there are significant differences among countries in regard to requirements for CPP timing, terminology, and format. We sought to determine current CPP practices versus national regulatory guidelines and to inform recommendations for the efficient use of the CPP based on the needs of the modern regulatory environment. We conducted a comparative analysis of company practice versus agency guidelines across 18 maturing pharmaceutical markets using data from the Cortellis for Regulatory Intelligence® (CRI) and the Centre for Innovation in Regulatory Science (CIRS) Emerging Markets Regulatory Review Times (EMaRReT) databases and regulatory authorities' websites. Of the studied 18 countries, 16 require the CPP for submission of new registrations; many accept alternative documentation but most still require legalization of the CPP and many are not compliant with the complex CPP format. Additional complicating factors include language requirements and varying local guidelines for CPP submission timing and validity dates. With the implementation of a number of suggested improvements, the CPP can continue to serve an important role in streamlining regulatory efficiency and provide confidence in new medicines, ensuring a more efficient and effective approval process and expediting patient access to safe and effective medicines worldwide.

Meena Pooja et al ., (2015) : Certificate of pharmaceutical product CoPP . This review includes basics of CoPP, origin of CoPP, types, types of drug includes in CoPP, procedure to obtainCoPP, requirement for CoPP, applicant, examples, format and content and benefits of CoPP. A CoPP is given bythe drug regulator not before conducting an inspection of the manufacturing plant. The Indian pharmaceuticalmarket is at around Rs65, 000 crore and out of this, export for around Rs30, 000 crore and certificate is valid for a two years period.

J. Balasubramanian et al ., (2015) : Vitality Of COPP In Pharmaceutical Exports. When registering a pharmaceutical product overseas, the Government body in charge of approving the application will usually require a Certificate of Pharmaceutical Products (COPP) to ensure that the product is being sold as a commercial finished product in the country that is producing it. A certificate issued by the Inspectorate establishing the status of the pharmaceutical, biological, radiopharmaceutical product listed and the Good Manufacturing Practices (GMP) status of the fabricator of the product. This certificate is in the format recommended by the World Health Organisation (WHO). Every country has its own system and requirements in order to register a pharmaceutical product. Although the required documents and procedures vary quite a bit most have many similar requirements for documents in order to ensure that the product being registered meet their standards for efficacy, safety and quality. To ensure quality standards are met, the appropriate regulatory authority in the intended drug market may request documents about the drug in question such as the COPP. The COPP is the legal document that declares a certain manufacturing company is legally allowed to sell their pharmaceutical product in the country they are producing. The COPP is mandatory in many countries that require WHO accreditation for pharmaceutical products being imported. As laid down by the WHO, the GMP certification is also necessary for the same. The WHO has time and again expressed concerns on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce.

Alistair Davidson et al ., (2002) : The Value of the Certificate of Pharmaceutical Product in Registration of Medicinal Products . This article reviews the value and importance of the World Health Organisation Certificate of Pharmaceutical Product (CPP) scheme. The scheme has largely streamlined a part of the registration procedure associated with imported medicines. It provides a significant assurance to regulatory authorities that imported medicines have been evaluated against rigorous and publicly-defined standards of quality, safety, and efficacy and have been approved for marketing. It also provides confirmation that the product is manufactured in accordance with the requirements of Good Manufacturing Practice. A more effective use of the scheme may provide drug regulatory authorities with an opportunity to deploy their resources to other areas of medicines regulation to the greater benefit of the public health. Six recommendations are made regarding how use of the scheme could be enhanced to improve patients' access to new medicines more rapidly: 1. CPPs should be required at the regulatory approval stage rather than at submission of the application; 2. Regulatory agencies should develop goals to approve products within one month after receiving the CPP; 3. CPPs should be acceptable from nonsource countries, that is, a selection of issuing authorities recognized for their highly developed regulatory review processes; 4. CPPs should be accepted from recognized authorities regardless of marketing status in that country; 5. Health authorities with limited resources should consider approving the product on the basis of a CPP alone; and 6. Legalization of CPPs should not be required.

Aim :

Role of CoPP in pharmaceutical export

Objective(s):

- To provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce.
- Certificate of pharmaceutical products demonstrates that imported medication is of the relevant standard of quality, safety and efficacy to allow marketing, rigorous testing and inspection in the exporting country to be carried out

by regulatory authorities and shows that it meets the relevant standards and procedures of Good Manufacturing Practice.

- This certificate shows whether a certain product is to be sold in the country or not.
- Certificate of Pharmaceutical Product (CPP) is an international voluntary agreement to provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce.

Discussion:

The Certification Scheme is an international voluntary agreement originally developed in the late 1960s with the objective of providing assurance to its members about the quality of the pharmaceutical products moving in international trade. The CoPP contains summarized information of the regulatory status of the medicine, of its manufacturer in the CoPP's issuing country and, according to the WHO's model, the commercialization status of the product in the territory of the CoPP's issuing country.

The CoPP is widely required by emerging countries in new drugs' submission processes, post- approval changes and renewal of drugs' registrations. In many Latin American countries, the CoPP is a mandatory document for new marketing applications and several other applications related to the drug's life cycle.

Despite its origin in a WHO international agreement, there is a significant diversity of CoPP- related regulatory models and practices in the Latin American region. Differences have been identified in the Region with respect to the regulatory authorities whose CoPPs are accepted, the required information contained in the CoPP template, the applications where the CoPP is required and when such a document must be submitted. In several cases the CoPP is a pre- requisite for submissions of, or decisions on, drug applications and in such situations marketing authorizations in the Region cannot be obtained until the drug or its variation is approved by an accepted regulatory authority.

CoPP-related regulations and procedures have been discussed in view of the new global regulatory environment and the current characteristics of the pharmaceutical market. In this context, the WHO Expert Committee on Specifications for Pharmaceutical Preparations, during its 43rd meeting, recommended that the WHO Certification Scheme should be reviewed "in light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector coupled with changes in the make-up of both the regulators and the groups involved in procurement." This position has been reinforced with the adoption by this Committee of the revised document of questions and answers about the Scheme in October 2015, as an opportunity to advocate for active support of the effective functioning of this quality tool.

To assess this complex scenario as it relates to American countries and promote a discussion on the opportunities to update and improve CoPP-related regulations and practices in the Region, the Steering Committee of the Pan-American Network for Drug Regulatory Harmonization of the Pan-American Health Organization (PANDRH/PAHO) approved in December of 2017 the project "Assessing CoPP requirements for drug registration processes in the Region of the Americas towards more timely access to medicines and more convergent regulatory approaches", which is being coordinated by the Cuban regulatory authority (Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos – CECMED) and the Latin American Federation of the Pharmaceutical Industry – FIFARMA.

The CoPP project is the first PANDRH project that will be conducted jointly by a National Regulatory Authority (NRA) and a pharmaceutical industry's association. The project's Work Plan comprises the development of a comprehensive mapping of how PANDRH members regulate CoPP-related requirements and a structured discussion among National Regulatory Authorities, the pharmaceutical industry and, occasionally, other stakeholders with appropriate expertise, on the current public health role of such requirements and their adequacy to meet the evolving needs of patients, regulators and the industry. Expected outcomes are intended to facilitate the identification of opportunities to improve the convergence and updating of CoPP regulation in the area, optimizing NRA's good regulatory practices and performance. Ultimately, the project's aims are to provide a contribution to faster patient access to new health technologies.

The CoPP project's final report is expected to be submitted to PANDRH's Steering Committee in March 2019. Interested parties may follow the project, consult relevant documentation and know the CoPP project's agenda by registering at PAHO's Regional Platform on Access and Innovation for Health Technologies (PRAIS) and joining PANDRH's CoPP project Community of Practice.

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 ,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.

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. Rägo mentioned in a presentation on this point that "A certificate is as good as the certifying authority" (Rägo, 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 CoPP 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 CoPP from the exporting country, which is qualified and eligible to issue a CoPP, 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 CoPP prior to approval and to reduce the delay of the time to market.

The CoPP 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 CoPP is often required in the countries which were included to the evaluation via the questionnaires. Some local HAs accept one CoPP 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 CoPPs for every single submission, since issuing a CoPP 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 CoPP 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. CoPPs 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 CoPP 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 CoPP 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 CoPP additionally to the NDA of imported finished medicinal products but it is mentioned that a WHO format is not required. But a CoPP 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 CoPP 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 CoPPs are issued by local HA which are mandatorily requesting CoPPs. It might be needed that HAs in countries like Argentina, Brazil or countries with even smaller HAs have to issue CoPPs 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 CoPP as evidence for GMP even though the CoPP 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 CoPP. But some HAs from countries like China or Russia will waive on the requested GMP certificate, if the inspection date is included in the CoPP presenting the GMP status. But this information on the inspection date is not necessarily reflected in the CoPP, for example in the German CoPP 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 CoPP (WHO, World Health Organization - 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 CoPPs from ICH countries only. The CoPP 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 CoPP 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 CoPPs 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 CoPPs 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 CoPP 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 CoPPs are required for filing of NDAs in several countries. Regulatory submission planning could follow a wave concept; countries needing a CoPP for filing have to follow in a second wave, when CoPPs are available due to first approvals by SRAs.

There are already associations by stakeholders working in detail on the use of a CoPP. 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 CoPP Network. They are also

conducting reviews and collecting industry experience of certification (e. g CoPP, 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 CoPPs 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 CoPPs is not supportive regarding timesaving proceedings.

Conclusion:

The CoPP can continue to serve an important role in streamlining regulatory efficiency and provide confidence in new medicines, ensuring a more efficient and effective approval process and expediting patient access to safe and effective medicines worldwide. CoPPs should be required at the regulatory approval stage rather than at submission of the application. Regulatory agencies should develop goals to approve products within one month after receiving the CoPP. CoPPs should be acceptable from no source countries, that is, a selection of issuing authorities recognized for their highly developed regulatory review processes. CoPPs should be accepted from recognized authorities regardless of marketing status in that country. Health authorities with limited resources should consider approving the product on the basis of a CoPP alone and Legalization of CoPPs should not be required.

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