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ROLE OF COPP IN PHARMACEUTICAL EXPORT

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ABSTRACT:
MHRA (Medicines And Health Products Regulatory Agency) is the regulatory authority body for pharmaceuticals approval in the UK union. MHRA is formed by the merging of two separate agencies in 2003 i.e., Medicines Control Agency and Medical Device Agency. This agency works to maintain safety, quality and ef cacy of the drug product before it enters into the country. The main aim of this work is to know about the practice and the regulatory requirements for the registration of a drug in the UK as per the regulations of MHRA. They are responsible for ensuring that the medicines and medical devices are acceptably safe and don't cause any harm to the patients. MHRA provides a license which is a marketing authorization to the manufacturer, required before a drug is being used by the patients of that country. Good Manufacturing Practice (GMP) is the minimum requirement that a manufacturer should possess during the period of production of the drug product. New drugs are being invented and also being distributed as per the needs of the patients. It is known that no drug product is completely safe or is 100% safe for use, but MHRA tries to minimize as many problems regarding the drug so that patients will be provided with the best drug with minimal risk.
Key words: MHRA, United Kingdom, Product license, eCT
This review includes basics of CoPP, origin of CoPP, types, types of drug includes 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, AdvaCare 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. Essential product registration documents, such as the Certificate of Pharmaceutical Product (COPP), Free Sales Certificate (FSC), Certificate of Origin (COO), and Marketing Authorizations are among the many documents our registration department frequently submit for registration purposes.

Keywords: *Pharmaceutical Industry, COPP , GMP , COO , Drug Regulator.*

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INTRODUCTION:

Certificate of pharmaceutical product : [1]

The certificate of pharmaceutical product (abbreviated: CPP) 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 country. It is issued for a single product, because manufacturing arrangements and approved information for different pharmaceutical forms and strengths can vary. [2]

Scope:

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. Certification has been recommended by WHO to help undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities in importing countries to assess the quality of pharmaceutical products as prerequisite of registration or importation.

In the presence of such CPP, 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 bio equivalence and stability data if necessary. [3]

However, regulatory practices often vary in importing countries. Thus, in addition to CPP, 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.[4]

Content and format:

The content of CPP 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 licence (including licence holder details, licence 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 CPP
- If marketing authorisation 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 CPP 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 CPP 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 CPP.

Special considerations in importing countries:

Most competent authorities in importing countries require CPP 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").

Proper documentation is essential in almost every aspect of the pharmaceutical industry. Whether for product registration, factory inspection, or internal quality control, AdvaCare 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. Essential product registration documents, such as the Certificate of Pharmaceutical Product (COPP), Free Sales Certificate (FSC), Certificate of Origin (COO), and Marketing Authorizations are among the many documents our registration department frequently submit for registration purposes. Likewise, technical files are repeatedly checked for consistency and accuracy for both internal quality control purposes and in preparation of inspections.

AdvaCare is highly specialized in the export process and has vast experience with documentation for product registration. Our customers realize the value in registering our products - the value of quality, time, and reliability.[5]

Certificate of a pharmaceutical product (CPP):
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 (CPP) 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 legalisation of the certificate when needed; this is not done by the Medical Products Agency.

The fee for issuing one CPP 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. [6]

Importance of COPP :
It is needed ny 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 .

Master of Drug Regulatory Affairs:
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 Commitee (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. Table 1 provides an overview on the areas of work within one sub department of the Essential Medicines and Health Products (EMP):

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

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

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.
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.
4. 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 Heath 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 marketingauthorization 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 Productsmoving 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 DirectorGeneral 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.

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 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 ICH standard participating 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.

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).

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 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.

According 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 warranty 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.

CONCLUSION:

Any medicinal agent to be marketed in the United Kingdom has to follow the guidelines and regulations framed by MHRA, a regulatory authority which approves the drug products. The objective of this review article is to highlight information regarding the requirements, the different types of submissions for the registration of a medicinal product in a market in the UK. It also includes all the details about the fee for the application and the time period for the approval of the application after the submission of the application. By knowing the requirements of the MHRA guidelines and regulations, it is easy for a product to get into the
UK market.

- Know the requirements of the importing countryprior to submitting an application while obtaining CoPP.
- Complete Application Form no. 3613b.
- Submission of required documentation.

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