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Review

Edqm Review Process For CEP

K. Serena*, P. Vedavahini, Dr. K. Nagasree, Dr. K. Shravankumar

Department Of Regulatory Affairs, Samskruti College Of Pharmacy In Ghatkesar, Telangana-501301.

*Author for Correspondence: K. Serena
Email: srenakokki@gmail.com

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Abstract

In addition to the possibility of Transmissible Spongiform Encephalopathy and an examination designed for manufacturing site Certification Suitability for Monograph of European has also been introduced by the European Directorate for Healthcare and Quality Medicines with respect to the regulation of the chemical purity of Pharmaceutical constituents. The most preliminary new applicant has the right to register in Europe for medication substances for authorization of certificate of suitability of active constituents list. Certificate of Suitability of active constituents can monitor any potential impurities from the production method for the product material. This is not compulsory but serves as an essential document by decreasing the time of accumulation and authorization. Transparency of the Certificate process and the monograph makes the Pharmacopoeia of Europe extremely relevant for the registration of medications in Eurpe. In 2018, certain types of nitrosamines (N-nitrosodiethylamine (NDEA) and N-nitrosodimethylamine (NDMA)) were detected in a number of active substances used in the treatment of hypertension and in related medicines.

Keywords: CEP

INTRODUCTION

Active Pharmaceutical Ingredients (APIs) and excipients are commonly manufactured by the company other than the manufacturer of the finished product. Pharmaceutical industries maintained their reputation with specific documentation in favour of providing the quality standards of drug substances. The international trade of this medicament is governed in the various countries in context to respective Pharmacopoeia guidelines. On the other hand European Pharmacopoeia (Ph. Eur.) commission deals of unique procedure for the drug substance with some Quality specifications. The existing drug substance/active substance information generally submitted for getting Certification of suitability to the monographs of the European Pharmacopoeia (CEP), active substance master file (ASMF) or European drug master file (EDMF) and full details of manufacture[1,2] .

In that circumstance, the certificate of suitability of the drug substance used for registration of product reduces the numerous amount of documentation. Far-reaching associations between the licensing authorities of the European Union (EU) and the other parties to the European Pharmacopoeia are successively reported in

certification suitability of monographs of the European Pharmacopoeia[3]. Subsequently again in Ethno pharmacological relevance, herbal drug must be well distinct monograph along with pesticide, heavy metal, aflatoxin B1, ochratoxin and aristolochic acid screening data[4] . Usually an ASMF can only be submitted for API(s) while CEP can be submitted for both API(s) and excipients(s). CEP is generally applicable for a) manufactured or extracted organic or inorganic substances (active or excipients), b) substances which are metabolites of microorganisms produced by fermentation as indirect gene products, c) products having risk of transmitting agents of animal spongiform encephalopathy (TSE)[5,6,7].

As a part of long term research effort, the present critical review in favour of certification procedure, briefly explained about CEP responsible to check the capacity of Ph. Eur. monograph(s) to control the possible impurities and contamination obtained from the drug substance manufacturing process. The CEP applicant is responsible to conform that the substance is manufactured as per Good Manufacturing Practices (GMP) requirements. European Directorate for the Quality of Medicines & Health Care (EDQM) issue CEP upon the compliance of GMP for respective drug substance. It will not provide GMP certificate nor is GMP certificate equal to CEP. EDQM is not accepting any application through paper format (except TSE risk and veterinary use substances only) since new existing guidelines. Applicant has to submit detail dossier in electronic format for drug substance via the "Common European Submission Platform (CESP)".The users should register with the CESP (https://cespportal.hma.eu/) before submitting application to the EDQM. On this way CEP is enlightened in a solid outline effort for the respective dossier, maintain their intellectual document for the EU and also create rationality in product registration which significantly influence certification , discuss in to the point renewal, sister file etc.[8]

Evolutionary history of european directorate for the quality of medicines & healthcare

The EDQM is a leading organization responsible for the issuing of CEP. First EDQM was restricted to controlling the chemical purity of the substance but later extended for risk of TSE and fermented product with inspection of manufacturing site applied for CEP. The key role of EDQM is to protect public health by enabling the development, supporting the implementation, and monitoring the application of quality standards for safe medicines and their safe use.

EDQM is involved in the harmonization of the standards and maintaining of the regulation and quality control of the medicine. EDQM is responsible for the maintenance and publication of Ph. Eur.Ph. Eur act as a reference work for the quality control of the medicine and main activity of EDQM. The methods mention in the pharmacopoeia is validated and is the collection of the good information for each parameter. It may be replaced by the other method by proving the better suitability. EDQM has done many changes in the period of more than 50 years, to improve the quality of drug and also other collaborative activities for harmonization. One department of EDQM is responsible for the Secretariat of the European Pharmacopoeia Commission, for preparing the General Chapters and Monographs of the European Pharmacopoeia.[10,11,12]

Rationality of the cep

The rationale behind this review article is to understand the benefits of CEP and various sections replaced in the Module-3: Quality (Drug substance Part) by the CEP when including it in the common technical document (CTD) for registration of the product with respect to different countries. The objective of the study is to provide introduction about CEP with its various types of applications. In addition, to identify that how a valid CEP act as a supportive document for the registration of medicine.



Fig 1: Benefits Of CEP

CEP procedure comes into force to evaluate the capacity of the European pharmacopoeia standards to control the quality of the drug substances used in the manufacturing process and generally avoid the subsequence re-assessment.[13]

Different Application Procedure in CEP

Applicant must send documents, while applying to obtain a CEP, to the certification of substance Division (DCEP) of the EDQM. DCEP is in charge of administration, coordination and execution of the Certification Procedure. describe the various application of CEP and the data required to submit in the Module 1,2 and 3.

New CEP Application

The applicant must send necessary documents in electronic format for getting a New CEP (except for TSE risk and veterinary use substances only), to the DCEP of the EDQM via the CESP. The applicant has to submit a single PDF containing Module 3 For TSE risk substances and eCTD, NeeS (for revisions/renewals) or VNeeS format for substances for veterinary use only. Upon receipt, the validation of application and assessment take place. After successful assessment the application is considered as complete and a new CEP is granted to the applicant as shown in. A new CEP is valid from the date of issue of original certificate. EDQM implement strict procedure to meet. official timeline and also clarified the possible outcomes for the assessment of CEP application.On the other side applications lacking necessary information after the maximum 2 EDQM deficiency letters are definitively closed.[14]

Renewal Application

The applicant should be submitted the renewal application approx. 6 months prior expiry date of the certificate. The procedure flow chart is shown in fig. 2(B). Late application for renewal may create the gap between date of expiry and the approval of the renewal application. If application has not been approved at the date of expiry, a provisional certificate may be granted[15,16]. CEP should be renewed after 5 years from the date of original certificate granted and are valid for an unlimited period after one time renewal except on EDQM request of one additional renewal as per Directives 2004/27/EC and 2004/28/EC of the European Council and of the Parliament. CEP holders should check the compliance of their current manufacturing process and if necessary they should revise the details submitted in their application. If application contain changes, in that condition applicant needs to provide the comparative changes in the form of table with their supportive data. CEP holder can submit renewal application with minor changes made in the dossier only. If there are major changes in the submitted documents, CEP holder should submit revision instead of renewal application[15,16].

Revision Application

CEP holder must inform the EDQM in case of any changes in the data submitted in the initial CEP application. In the conditions, when CEP is rejected for the revision by the EDQM, the current CEP will be valid

in that situation. Applications are closed/ rejected if lack the sufficient information to grant the CEP after maximum 2 EDQM deficiency letter(s) shown in fig2(B).

Sister File

Sister file is the fast-track procedure for the submission of similar CEP dossiers. An applicant containing a CEP may wish to apply for another CEP having same drug substance, due to some specifications, which was not covered by existing CEP or want separate CEP for different conditions of preparation. Then an applicant get benefit by submitting application as a sister file, if the following conditions are fulfilled.[17]
editions for sister file are as follow

- Same substance as covered by the original application
- Original application should be granted by the EDQM and respective CEP is valid
- The manufacture and holder is the same for the both CEP application
- Key intermediates of the process should be the same as original application

Any new concept should not be introduced i.e. Quality by design (QbD) or process analytical technology (PAT).[17] The requirement and process for the sister file is same as new CEP application shown in fig. 2(A). In addition, the applicant should include a comparative table of the difference between the new and original application. Sterile, TSE and herbal applications are not applicable for sister file.

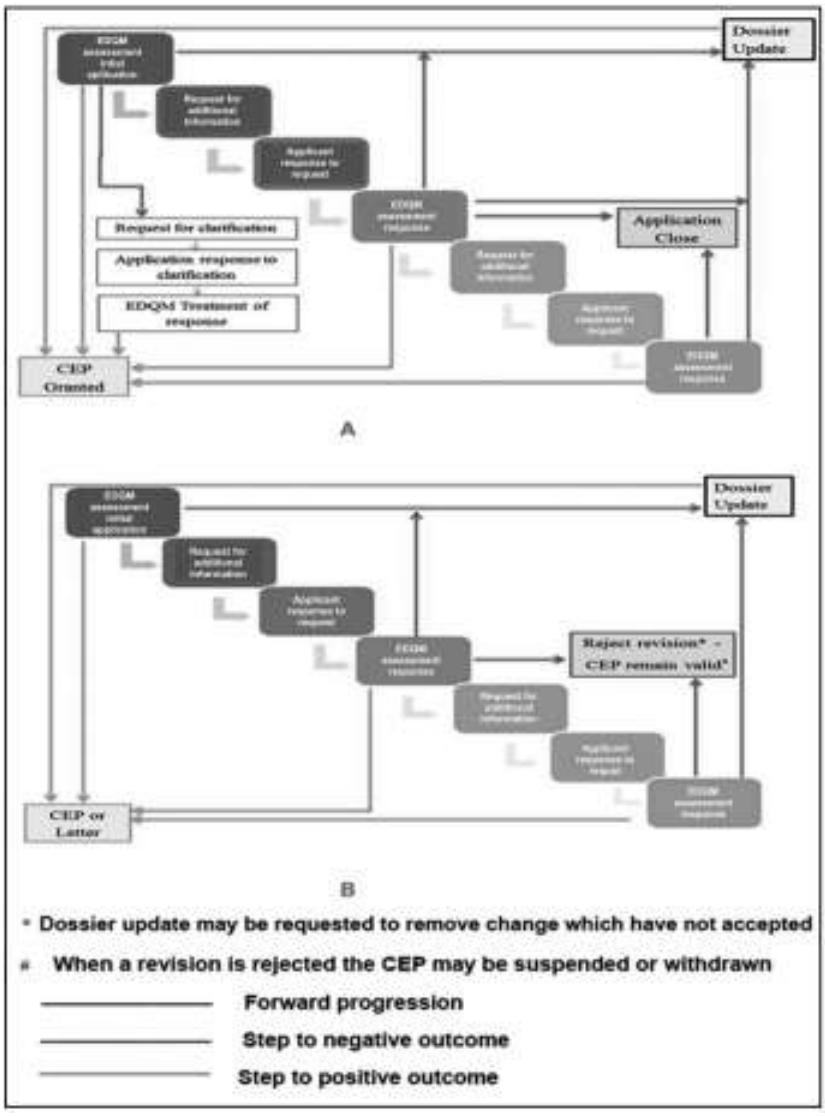

Fig 2: Flow diagram for (A) New CEP application and Sister file procedure (B)Revision or Renewal of CEP application.

Different Conditions Related to CEP

• Suspension: Temporary cancellation of a granted CEP. Under certain conditions, the CEP may be restored.
• Withdrawal: Definitive cancellation of a granted CEP.
• Closure: Cancellation of an on-going CEP application
• Hearing: Re-consideration of a decision taken by the EDQM Ad hoc Committee regarding the validity of a CEP or an application for a CEP.[18]

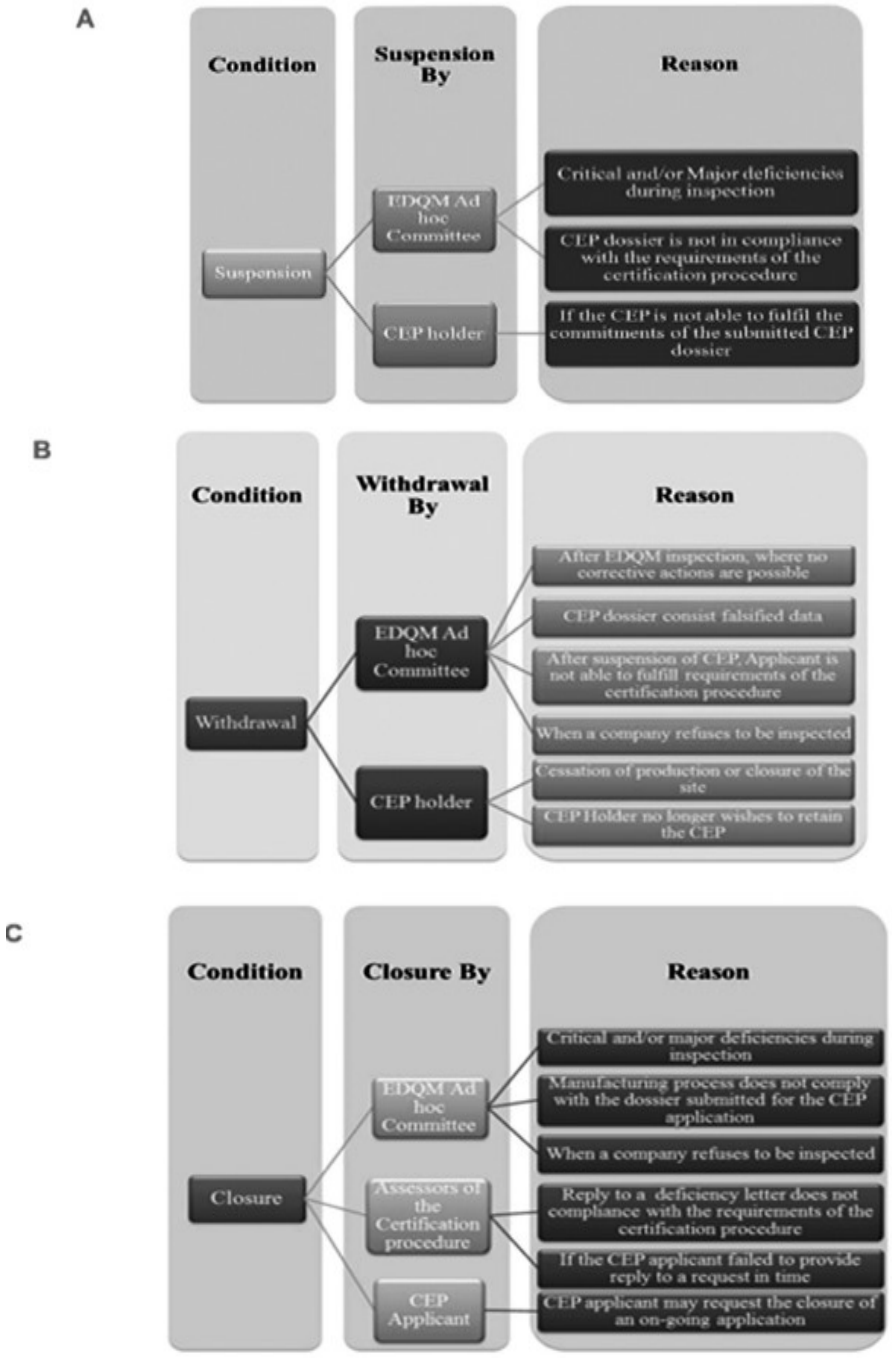

Fig 3: (A) Suspension of CEP (B) Withdrawal of CEP (C) Closure of CEP

Contain information about CEP in Australia, New Zealand and Canada except South Africa. At the time of Product registration application, the applicant has to submit following information in the Module 3 (Drug Substance Part) of CTD, if CEP is included as drug substance information.[19,20] Elucidation of Structure and Other

Characteristics Studies to identify polymorphs when the CEP specifies a polymorphic form and particle size distribution, where applicable. Specifications This section should contain the listed Impurities, residual solvents and additional test (if any) that are not controlled in the CEP.

Analytical Procedures and Validation Additional methods used by Finished Pharmaceutical Product (FPP) manufacturer to those in the CEP and Ph. Eur. Monograph should be included.

Batch Analyses this section should contain CoA(s) from the drug substance manufacturer for minimum two batches. Reference Standards or Materials Information about reference standards used by FPP manufacturer Container-Closure System Specifications containing descriptions and identification of primary packaging components. If not specifies by the applicant in CEP. Stability When CEP is not reflecting the retest period, Stability data as per stability guideline showing the API stability should be included. The CEP may not necessarily contain all parameters, in this case the applicant should add the documents, data to show the validation, specification acceptance limits e.g. stability data to support the retest period (if retest date is not mentioned in CEP), Physicochemical characteristics etc. Many licensing authorities are accepting CEP as their requirement to support fully or partially, the quality section of the registration file submitted for substances used in medicinal products. Countries like Albania, Algeria, Australia, Azerbaijan, Canada, Georgia, Ghana, Israel, Kyrgyzstan, Moldova, Morocco, New Zealand, Saudi Arabia, Singapore, South Africa, Malaysia, Tunisia, Uzbekistan etc. are also accepting CEP.[21]

Conventions for identifying therapeutic drugs vary greatly between drug classifications systems across the world. Standardizing the identification of medicinal products would facilitate the development of an international drug information database to support greater interoperability of prescription information, enable improved global health surveillance to assess pandemic risks, enable transnational medical trials studying multiple patient populations, and maximize interoperability of medical data related to rare diseases.[22,23] A directive issued in the European Union in 2011 mandated cross-national recognition of prescriptions and provided measures to facilitate verifying legitimacy of prescriptions issued by other member states. While this directive requires that prescriptions be written using a "common name" there are also significant variations in medication names and formulations across Europe markets.[24]

A standardized drug identification system must be established to create this global drug database. The Identification of Medicinal Products (IDMP) standard was created in 2012 by the International Organization for Standards (ISO) to outline key characteristics of medicinal product classification systems for international harmonization . One key component of IDMP is ISO 11616, which defines the elements required to construct universal Pharmaceutical Product Identifiers (PhPID). PhPIDs are internationally recognizable identifiers for drug products and are composed of three main attributes: the active pharmaceutical substance, dosage form, and strength, allowing pharmaceutically equivalent drug products to be recognized as synonymous regardless of regional differences in branding. While representations of active pharmaceutical substance and strength are similar across drug nomenclature systems, representations of drug dosage forms vary significantly. This variation between regional terminologies presents a substantial obstacle to achieving interoperability between drug nomenclature systems and generating universal PhPIDs.[25]

In response to the ISO standards, the European Directorate for the Quality of Medicines and Healthcare (EDQM) reorganized its controlled vocabulary by relating dose forms to key dosage form characteristics. Additionally, the European Union commissioned a project called Up-Scaling the Global Univocal Identification of Medicines (UNICOM) to better adhere to IDMP standards and establish a unified global drug database. The UNICOM project identified EDQM as the most promising nomenclature for describing dosage forms due to EDQM's adherence to a structured ontology and to IDMP standards. [26,27]

Choosing EDQM as the standard for describing dosage forms implicated that drugs outside the EU must either be reclassified using EDQM terminology or that regional terminology must align with EDQM. The World Health Organization, United States Food and Drug Administration (FDA), Uppsala Monitoring Centre, and UNICOM completed a pilot project to reclassify dosage form descriptions of US drug products from the FDA's Terminology for Structured Product Labelling (SPL) to EDQM. The pilot results were discussed in a June 11th, 2021 webcast identifying the main challenge in standardizing dosage form descriptions to EDQM as the large number of US drug products on the market needing manual reclassification. This spurred interest in alignment of existing drug nomenclature systems with EDQM, rather than conversion, to avoid the cumbersome process of manual reclassification.[28]

While EDQM is of growing significance for its adherence to IDMP standards, the drug terminology system operated by the United States National Library of Medicine, known as RxNorm, is of prevalent utility both nationally and internationally. RxNorm is the basis for the U.S. Department of Veterans Affairs National Drug File-Reference Terminology, the Drug Ontology (DrOn)[28], and the Observational and Medical Outcomes Partnerships (OMOP) open-source common data model used across the United States and Europe to conduct multinational drug studies. Interoperability between the Canadian drug ontology OCRx and RxNorm has also been demonstrated, further contributing to the international significance of RxNorm.[29]

While studies have evaluated interoperability between FDA SPL and SNOMED-CT [30], to EDQM, there no studies have evaluated alignment of dosage form descriptions between RxNorm and EDQM. Overall, there are few published works on this topic as the initiative to align regional nomenclatures with EDQM is currently predominated by governing agencies rather than researchers. Given the national and international significance of RxNorm, the objective of this paper is to experimentally align RxNorm and EDQM dosage forms, using EDQM descriptors and RxNorm dosage forms, and by creating an ontology encompassing both RxNorm and EDQM dosage forms.

In recent years, there has been a firm ambition to establish a worldwide system for global identification of medicinal products (IDMP). Each nationally authorized medicinal product anywhere in the world would receive a global identification number, so that the active substance, the dose form and the strength of the medicinal product can be recognised by health care workers and patients, anywhere in the world.[31] This will allow the flow of prescriptions across borders, but also the flow of information about medicinal products, facilitating the development of decision support systems and patient-centred mobile applications.

It started in 2012, with the publication of a series of ISO/CEN IDMP standards, addressing the crucial aspect of information on medicines in research and development, market authorisation, prescribing and dispensing, drug information, and pharmaco-epidemiology. These standards provide guidance for the standardisation of substance representation, dose form terminology and expression of strength, the three basic elements for the identification of a Medicinal Product. The ISO/CEN 13499:2012 standard and its technical specification focuses on dose forms. This triggered, in 1995, a first reorganisation of the European Terminology for Dose forms in the European Pharmacopoeia, managed by the European Directorate for Quality in Medicines & Healthcare (EDQM). This Directorate is an administrative entity under the Council of Europe, grouping countries from Europe and beyond.[32]

The Food and Drug Administration (FDA) in the US expressed a clear intention to adopt IDMP and to welcome international collaboration [33]. The European Medicines Agency (EMA) developed a close cooperation with the FDA regarding the cleansing of pharmaceutical substance terminology. In 2019, the FDA and the World Health Collaborating Centre for Pharmacovigilance in Uppsala (WHO_UMC), and EMA developed a collaboration to test procedures to generate global identification numbers, now evolving to a global working group between these parties. In 2020, EMA engaged in an ongoing process of writing an implementation guide for the implementation of IDMP within National Agencies[34]. Further, the pharmaceutical industry prepares for IDMP implementation in the submission of new applications for marketing authorisation. A number of consultancy companies has emerged, specializing in the issue.Next to substance identification, the identification and descriptive terminology for dose forms of medicinal products is crucial. The EDQM multilingual terminology on dose forms, revised in 2015 to adapt to the ISO/CEN standard, is used in the regulatory sphere in Europe, recommended by the International Council for Harmonisation, and used in many non-European countries[35]. In the US, the less granular RxNorm terminology of the National Library of Medicine is used. In clinical care, the SNOMED-CT terminology has a separate chapter for dose forms, also inspired by the ISO/CEN standard.[36]

All these pilot initiatives in the implementation of IDMP led to deeper insight in the theoretical aspects of the CEN/ISO standards. This experience is now fed into a revision cycle of these standards, currently on-going. This process runs synchronically with the UNICOM project, a large-scale Action Program of 4 years, launched at the end of 2019, to coordinate the efforts of 41 Partners (National Medicines Agencies and stakeholders), and to stimulate transatlantic cooperation.[37]

It is clear that in the coming years, a decision will have to be taken on the choice for a global terminology for dose forms, as this is instrumental for creating global identification numbers for national medicinal products, ensuring semantic interoperability across information systems, languages and borders. EDQM is a trusted international terminology, but in this pivotal moment of IDMP implementation, it is important to describe its unique features, which make it fit for purpose as a global terminology, and to examine some possible improvements.[38]

The aim of this study is to propose recommendations for improvements to the current EDQM in the light of its use as a global terminology in the identification of medicinal products, by describing and analysing the features of the EDQM terminology; by formulating possible minor changes, and by creating a small ontology of dose forms, based on the basic attributes of dose forms in EDQM, and suitable for alignment with other dose form terminologies.

The European Directorate for the Quality of Medicines & HealthCare (EDQM) plays a crucial role in ensuring the quality and safety of medicines and healthcare products across Europe.[39] As part of its mandate, the EDQM conducts rigorous reviews of various aspects related to pharmaceuticals and healthcare, aiming to uphold high standards and protect public health.

The EDQM review process encompasses a wide range of activities, including the evaluation of pharmaceutical substances, the establishment of quality standards, the certification of reference standards, and the inspection of manufacturing facilities. These reviews are conducted with meticulous attention to detail and adherence to established regulatory frameworks.

One of the primary objectives of the EDQM review is to facilitate the harmonization of standards and practices within the European Union (EU) and beyond. By establishing common quality standards and procedures, the EDQM helps to streamline regulatory processes and enhance the accessibility of safe and effective medicines for patients throughout Europe.[40]

Furthermore, the EDQM review process promotes transparency and accountability in the pharmaceutical industry. Through its rigorous evaluation mechanisms, the EDQM ensures that manufacturers comply with relevant regulations and adhere to best practices in pharmaceutical production, thereby safeguarding the integrity of medicines and healthcare products.

Aim and objectives

The aim of the study was to validate two quality indicators for community pharmacy care focusing on patient involvement. As part of the EDQM Pharmaceutical Care Quality Indicators Project (Council of Europe), at least 10 patients per indicator were recruited in each community pharmacy. Pharmacists targeted patients aged 18-65 years starting chronic treatment (Indicator 1) and elderly patients with polymorbidity receiving at least five chronic treatment medicines (Indicator 2). Based on patients' answers to a questionnaire, patient-pharmacist consultations took place. For Indicator 2, patients were also offered a medication review.

CONCLUSION

As CEP is not mandatory to submit for medicinal product registration but by providing the CEP the applicant get various benefits related to approval and content of dossier, because CEP replaces many sections from Module 3 (Drug Substance Part). CEP demonstrated that the drug substance quality controlled by standards in Ph. Eur., which contribute major role in registration of medicine and have wide international acceptance. This review established a framework to maintain CEP with various conditions applicable to CEP.

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