



Comprehensive Study On Regulatory Requirements For Excipients In Eu

Ms. Tejaswi Jalindar Aher*, Dr. Kishor S. Salunkhe

Sanjivani College of Pharmaceutical Education and Research, Kopergaon

Abstract: The qualities of a formulation are affected by excipients, which are an important aspect in a dosage form. Excipients were once thought to be inactive components; however, it has now been discovered that they can have substantial negative effects. Many countries have experienced disasters in the past as a result of undiscovered excipient toxicity and mistreatment of excipients during transit. These tragedies call regulators' attention to the quality of excipients. Excipients can cause a variety of negative effects, such as hypersensitivity and allergies. When it comes to a novel excipient, preclinical research is much more important. New chemical excipients will be regulated in the same way as new APIs, according to the European Union (EU) directive 75/318/EEC. Within the EU, a regulatory dossier is necessary for any novel excipient (s). Excipients are employed as protecting agents, bulking agents, and in rare cases, to improve medication absorption. The International Pharmaceutical Excipients Council (IPEC) was founded in 1991 as a trade group that brought together excipient manufacturers and their pharmaceutical formulation clients.

Keywords: Excipients, Novel excipients, Dossier, CTD, CEP.

Introduction:

Drugs are always given in the form of a dosage form, which consists of a drug (or drugs) plus a variety of additional chemicals called excipients in varied amounts and proportions. Disintegrating agents, diluents, lubricants, suspending agents, colouring agents, flavouring agents, emulsifying agents, chemical stabilisers, and other excipients are among the most common. Excipients influence a formulation's various properties, such as absorption, efficacy, safety, bioavailability, solubility, stability, dissolution, and so on, and are increasingly being used as a key component in improving product branding, as well as the design of more patient-friendly dosage forms. They are in charge of the product's performance and ensure that the drug has the appropriate pharmacological effect. Excipients in pharmacological dosage forms are now

known to have well-defined functional activities. Modulating API solubility and bioavailability, enhancing active component stability in finished dosage form, preserving PH and osmolarity of liquid formulations, acting as an anti-oxidant, emulsifying agent, aerosols, tablet binders, and disintegrates are among their many roles. All ingredients of a medication formulation must comply with current cGMP rules and be assessed for safety and efficacy of the drug, according to regulatory criteria. (1) (3)

History:

The term excipient is assumed to have been originated from the Latin word *excipere* (Dorland's Medical Dictionary, 1974). It literally means to expect, gather, or receive something. Excipients were only recognised as a means for administering a medicament or subsequently as an inert support for the active medicament, according to The Nurse Dictionary.

Drugs derived from plants and animals have been utilised since the dawn of civilization. The medications used at the period were usually crude, and the methodology used was possibly extremely basic as well. Because of the existence of superstitions, drug use was limited, and knowledge of the drugs, their efficacy, and route of administration was limited to a small number of people.

A good example is the pharmacist Scheele, who discovered a variety of chemicals including citric acid, lactic acid, tartaric acid, arsenic acid, glycerine, and many others. Serturmer, a German chemist, discovered chemicals from plants in the early 1800s. A medicine is almost never given alone, but rather as part of or in combination with one or more nonmedicinal substances that perform a variety of common pharmacological roles. (4)

Novel excipient:

A new or novel excipient, according to current EU regulations, is a material that is used for the first time in a drug product or for the first time in a new route of administration. The rule applies to all excipients that have a new chemical structure or that have been chemically changed. The development of a new excipient is a difficult undertaking that must take into account a variety of factors, including performance, product safety, GMP, standards, analytical methods, stability, prices, and environmental concerns. (5)

Excipient composition profile:

Excipient composition profile include following components:

- **Nominal component:** The key components of an excipient are those that, in the majority of circumstances, help the excipient fulfil its role in the drug product(s) in which it is utilised.
- **Concomitant components:** The chemicals that are present in addition to the primary components should be regarded as part of the composition profile and should not be confused with the existence of added substances.
- **Additives:** Antioxidants, stabilisers, and other chemical substances are purposely added to excipients to improve their physico-chemical properties.
- **Processing aid:** Processing aids, such as filter aids, are chemical compounds employed in the manufacture of excipients for a specific processing necessity or advantage. During the excipient manufacturing process, processing aids may or may not be removed.

- **Degradants:** Due to a variety of circumstances, some excipients may degrade over time. It's also a good idea to figure out if the degradants have any hazardous potential.
- **Residual solvents:** Residual solvents are organic or inorganic liquids that have not been completely removed from the excipient during the production process.
- **Other components:** Other components that may be present, in addition to those described above, include organic or inorganic substances that are not the defined entity (main/concomitant components) of the excipient but are present as a result of variables in the excipient's manufacturing process. For example, Unreacted starting materials, residual catalyst, and metal reagents. (6)

Marketing Authorization procedures in EU (7) (8)

The European Union, which consists of 27 member states, has been working to improve and streamline the medication review and marketing authorization processes for many years. The following are the procedures that are now in use:

A. National procedure:

This type of authorization is granted on country-by-country basis by the competent authorities, in each member state. Products only intended for one market and not obliged to use the centralized procedure. To obtain marketing authorization in a country, the application must be submitted to the competent authority of that member state in its own language. The timeline for this procedure is 210 days. The fees for national procedure are affordable even for small firms also provides a base for Mutual recognition. It saves on translation cost to English or Regional languages.

B. Mutual recognition procedure:

Since 1995, the MRP has been in existence in the EU. When a pharmaceutical product has already been granted authorization by at least one country in the European Community, this procedure is used to gain marketing authorizations in one or more member states.

In this situation, the applicant proposes that one or more CMSs mutually recognise the RMS's authority. The holder of a marketing authorization must submit an application to the RMS and each of the CMS's authorised bodies (s). The RMS provides the Assessment Report, or changes any existing one, within 90 days of receiving a valid application, and sends it along with other papers to the CMS(s) and the applicant. Following receipt of the Assessment report and validation of the application by each of the CMS, the RMS starts the clock (s). The CMS(s) acknowledge the RMS's decision within 90 days.

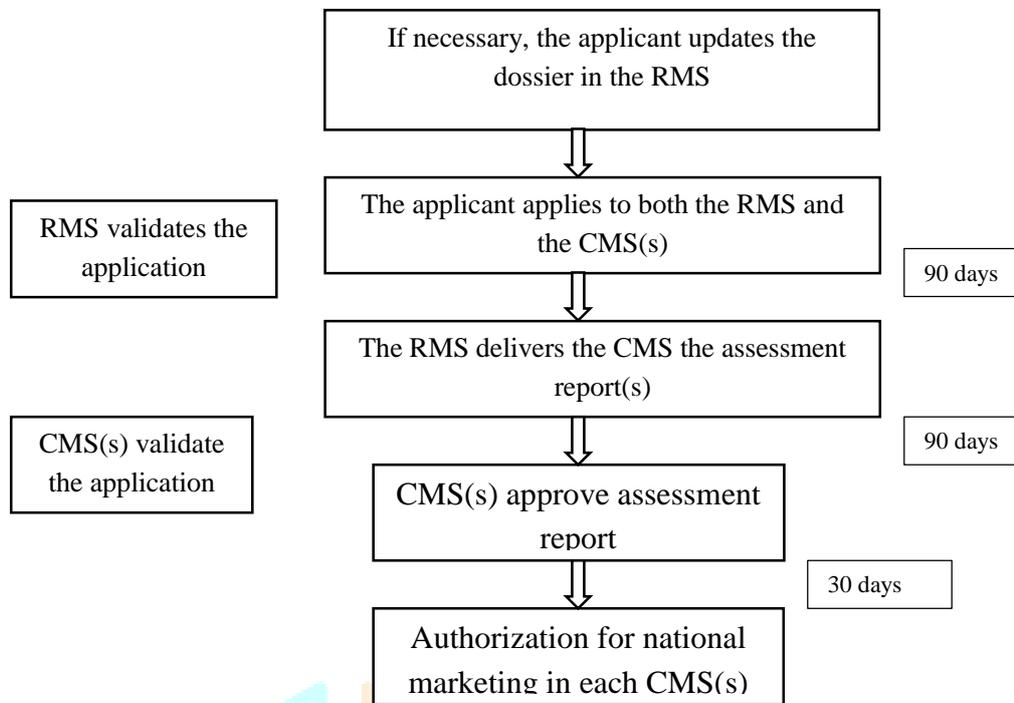


Fig.1 Mutual Recognition Procedure

C. Decentralized procedure (DCP):

In 2005, the EU implemented the new DCP. When no marketing permission has been given in the European Community, this approach is used to gain marketing authorizations in many Member States. The applicant must submit an application to each of the Member States' relevant authorities. The applicant has the option of naming a country as the Reference Member State (RMS). Within 70 days, the RMS sends the CMS(s) and the applicant a preliminary Assessment Report on the dossier. The CMS(S) has been asked to provide feedback on the proposed national prescription status as well as inform the RMS. On day 105, the RMS will send all comments to the application and, if necessary, pause the clock until the applicant submits a response document. On day 120, the RMS generates a Draft Assessment Report and, if the CMS(s) and the RMS reach an agreement, the procedure may be completed. Within 30 days of acknowledging their approval to the assessment report competent authorities of the RMS and the CMS(s) make a decision. A national marketing permission will be issued in the RMS and each of the CMS at the end of the DCP if there is a positive agreement (s).

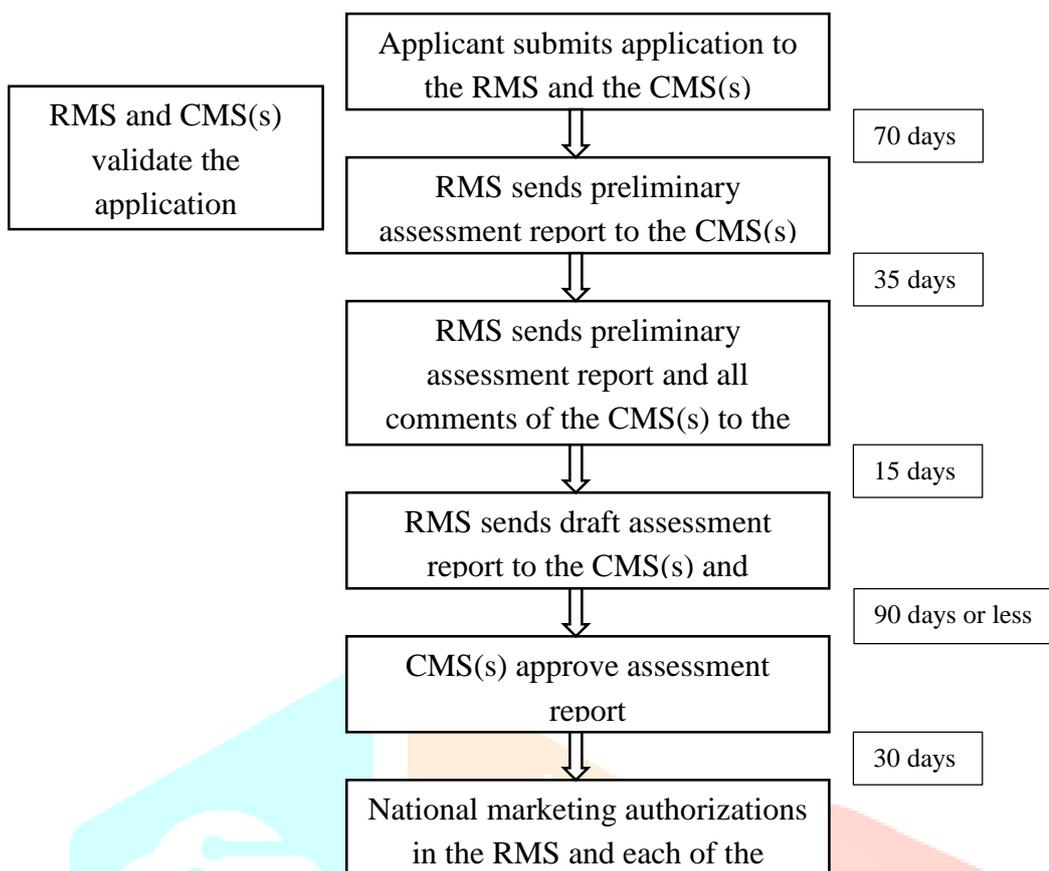


Fig.2, Decentralized procedure

D. Centralized procedure (CP):

In 1995, the European Union established a centralised procedure. When getting authorisation for certain pharmaceutical items, CP is required. In the Centralized Procedure, the applicant submits a marketing authorization request to the EMEA and receives a single European approval that is valid in all 27 EU countries. The EMEA informs the applicant of the CHMP position and whether the medical product is eligible for evaluation via the Centralized Procedure after discussion at CHMP. A Rapporteur is chosen from among the CHMP members to conduct any scientific examination. The rapporteur's job is to conduct the scientific review and provide an Assessment Report for the CHMP. The EMEA begins the procedure at the monthly starting date indicated on the EMEA website once the application has been approved as complete and the Rapporteur has confirmed that they have received the dossier. On Day 80, the CHMP members and EMEA receive the rapporteur's assessment reports. Members of the CHMP are tasked with conducting a peer review of the rapporteur's scientific examination and the scientific/regulatory conclusions obtained.

On Day 120, the applicant receives the acceptance of the CHMP List of Questions, as well as the general conclusions and review of the scientific evidence. Following receipt of the applicant's responses, the CHMP establishes a timeline for evaluating the submissions. The EMEA ensures that the CHMP's opinion is delivered within 90 days.

Following the adoption of a favourable CHMP opinion, the applicant submits final translations of all required papers to the EMEA in all EU languages. Finally, the EMEA delivers the CHMP opinion and other needed documents to the European Commission within 30 days, and the marketing authorization is

valid throughout the community in each of the Member States as a nationally granted marketing authorization.

Once the commission decision is issued, the European Public Assessment Report (EPAR) will be published on the EMEA website.

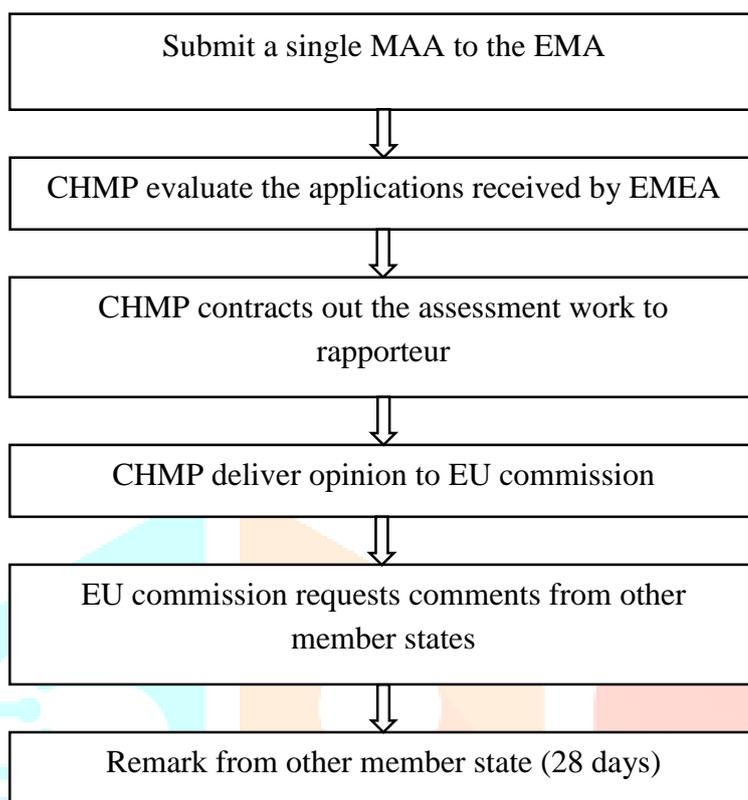


Fig.3, Centralized procedure

Need of preclinical evaluation of excipient

Excipients must be evaluated in a preclinical setting not only to meet regulatory requirements, but also because excipients are not inert and can induce undesirable toxicological effects on their own or in medication formulations. (9)

Excipients are responsible for a number of adverse events such as hypersensitivity, allergy, and anaphylactic nature in medication formulations. In the event of a novel excipient, preclinical research is more important. A new excipient is any inactive ingredient that is added to therapeutic and diagnostic products on a global scale, but it is believed that these inactive ingredients have no therapeutic effect at the intended dosage. (10)

Regulatory filing process for novel excipients:

European union (EU) directive 75/318/EEC states that new chemical excipients will be dealt with in an identical fashion to new API's. There is a requirement for a regulatory dossier within the EU region for any new excipient(s). All three ICH regions (US, EU, Japan) required formal registrations i.e., CMC (chemistry, manufacturing and controls) and safety data. European Master File (EMF) procedure is not currently available i.e., all data for the new excipient has to be included in the dossier for MA of a medicinal product. After successful worldwide registration company started preparation of pharmacopeial monographs within the various ICH region(s). Pharmaceutical European monograph for this excipient was first published in 2009 [macrogol poly (vinyl alcohol)] grafted copolymer. (11)

Guideline on Dossier preparation for excipients (12)

'Guideline on excipients in the dossier for marketing authorization of a medicinal product' This guideline outlines the information that must be supplied in connection to excipients, such as antioxidants and antimicrobial preservatives, and it applies to all excipients in human-use pharmaceutical goods. Excipients used in products in the clinical research stages of medication development are not covered by the guideline. The data should be supplied in the standard format described in Module 3 sections P.1, P.2, P.4, P.5, P.8 of the Common Technical Document (CTD).

I. Description and Composition of the Drug Product (section 3.2. P.1)

Excipients must be listed, with their common name, quantity, and use and reference to any relevant standard specified. When the common name isn't enough to express specifications, a brand name with a commercial grade should be supplied. Details on the composition of excipients represented as a mixture of compounds should be provided in both qualitative and quantitative terms. However, only the qualitative composition of flavouring agents and aromatic substances is permitted.

The Chemical Abstract Service Registry Number (RN-CAS) should be used to chemically characterise and construct antimicrobial preservatives and antioxidants.

II. Pharmaceutical development (section 3.2. P.2)

This section should include an explanation of the excipient selection, according to the Notes for Guidance on Pharmaceutical Development (CHMP/ICH/167068/04 and CHMP/QWP/055/96) (s). Excipient compatibility with active compounds and other excipients should be established. The excipients used, their concentrations, and other features that can affect the performance of a drug product. For antimicrobial preservatives and antioxidants, the applicant must demonstrate the following during the pharmaceutical development of the product:

- The need to add an antioxidant or preservative to the finished product at the desired level
- The antioxidant's and preservative's physical and chemical compatibility with other ingredients in the completed product, the container, and the closures.

The preservative concentration utilised must be justified in terms of efficacy and safety, with the least preservative concentration providing the appropriate degree of efficacy.

III. Control of Excipients (section 3.2. P.4)

i. Specifications (section 3.2. P.4.1)

The standards of Directives 78/25/EEC, as amended, and/or 94/36/EC, colours for use in foodstuffs, should be satisfied in all cases.

The references in Directive 78/25/EEC, as amended, are construed in a way that allows all of the colourants listed in Annex 1 of Directive 94/36/EC to be used in pharmaceutical products.

Excipients used in the manufacturing of sterile medical products must have bioburden and, if applicable, endotoxin limitations declared.

- a) Excipients described in the European Pharmacopoeia or in the pharmacopoeia of an EU Member State:

Reference to the current edition of the pharmacopoeia should be included in the dossier for marketing authorisation. The routine tests which are to be carried out on each batch of starting materials must be stated in the application of marketing authorisation. If tests other than those

mentioned in the pharmacopoeia are used, proof must be supplied that the test methods used are suitable to establish that the starting materials meet the quality requirements of that pharmacopoeia. When the monograph covers a family of related products, the particular specifications chosen for the excipients must be submitted.

b) Excipients not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State:

Based on the following sorts of tests, an acceptable excipient specification should be established:

- Identification testing
- Physical parameters
- Purity checks, including overall and individual impurity limits
- If necessary, assay or limit tests, as well as validation parameters.

Compliance with the monograph of a third country pharmacopoeia, such as the US Pharmacopoeia or the Japanese Pharmacopoeia, can be acceptable where an excipient is neither described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State.

ii. Justification of Specifications (3.2. P.4.4)

Justifications of specifications consider the choice and usage of an excipient for a specific purpose: it will specify the features that must be evaluated during routine testing and that will be the subject of certain specifications in relation to the product's bioavailability. Justification of specifications is usually not necessary for excipients described in the European Pharmacopoeia.

iii. Excipients of Human or Animal Origin (section 3.2. P.4.5)

The applicable directives and instructions in European Pharmacopoeia General Chapter 5.1.7 Viral Safety and 5.2.8 Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents through Human and Veterinary Medicinal Products should be noted.

iv. Novel Excipients (section 3.2. P.4.5)

According to the drug substance format, full details of manufacture, characterisation, and controls, as well as cross references to supporting safety data, should be supplied for novel excipients.

- It is necessary to provide a full description of the excipient, its function, and its usage conditions. The composition should be indicated in qualitative and quantitative terms if the excipient is complex or consists of a mixture of substances.
- For all novel excipients, documentation on the chemistry of excipients is necessary, based on the CPMP Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96).

IV. Stability (section 3.2. P.4)

The characteristics and stability of excipients have a role in the maintenance of the medical product's physico-chemical qualities. Antioxidant levels are measured on a regular basis during the shelf life. Antimicrobial preservative content should be evaluated throughout the shelf life to ensure that antimicrobial preservative levels remain above the preservative efficacy challenge level and within specifications.

Excipients in the labelling and package leaflet of medicinal products for human use (12)

- According to Article 65(e) of Directive 2001/83/EC, the Commission shall prepare particular advice providing a list of excipients that must be listed on the labelling of medicinal products, as well as the manner in which these excipients must be listed.
- A list of those excipients known to have a recognised action or effect must be included in the specific guidelines provided pursuant to Article 65, according to Article 54(d). All excipients must be listed whether the product is injectable, topical, or eye preparation.
- The whole qualitative composition (in active substances and excipients) as well as the quantitative composition in active substances must be included in the package leaflet, according to Article 59(1)(f)(iv).
- The list of excipients whose knowledge is relevant for the safe and effective use of the pharmaceutical product and which are included in the detailed guidance provided pursuant to Article 65 is set forth in Article 59(2)(c).

The "Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use" guidance document is intended for use by competent authorities, applicants for a Marketing Authorization, and holders of a Marketing Authorization. Its Annex contains a list of excipients that must be declared on the label, as well as information for those that must be included on the package leaflet.

Nomenclature:

The requirements of names of all excipients on the labelling, package leaflet, and SmPC are as follows.

- Proprietary names should not be given to individual excipients. Excipients should be given the recommended international non-proprietary name (INN or INN modified).
- On the labelling, the E number alone may be used as an excipient if the entire name and the E number are specified in the package leaflet.
- Any known recognised activity or effect should be mentioned expressly, and proprietary flavours or perfumes may be declared in generic terms.
- Chemically changed excipients should be labelled differently than unmodified excipients to avoid confusion.
- The function and name of pH adjusters should be disclosed in the package leaflet.
- All components of compound excipients or mixtures should be listed under a common descriptive word and stated.
- Excipient abbreviations should not be use.

Excipients in the labelling:

All excipients in parenteral, ocular, and topical pharmaceutical preparations must be listed on the labelling, according to Directive 2001/83/EC (outer package or if no outer package on the immediate packaging). Only those excipients specified in this guideline that are known to have a recognised action or effect should be declared on the labelling of all other medical goods. The Annex contains a list of such excipients. When a pharmaceutical product contains any of the excipients mentioned in the Annex, the name of the excipient and/or the E number, if applicable (e.g., for colourants), must be listed on the labelling, along with a statement like "see leaflet for further information."

Excipients in the package leaflet

All excipients must be listed by name on the package leaflet, according to Article 59(1)(f)(iv) of Directive 2001/83/EC. As a result, all excipients should be declared using the nomenclature prescribed in this guideline, as described in the section on Definitions and Examples above.

The fourth column (information for the package leaflet) in the Annex includes information relating to each excipient, in accordance with Articles 59(1)(c)(iv) and 59(2)(c) of Directive 2001/83/EC.

By default, the package leaflet should include the text of this information, expressed in plain and intelligible words for the patient. When the Annex requires a warning or information statement, the package leaflet and SmPC should make it clear that the statement is linked to the presence of a specific excipient.

The EU excipient risk assessment guidelines (14)

Pharmaceutical manufacturers must do a structured risk assessment for each excipient and identify the appropriate GMP, according to the EU's falsified Medicines Directive, which was enacted in 2011. The EU Excipient Risk Assessment Guidelines, based on this legislation, were prepared in 2013, published in March 2015 after much debate, and went into effect one year later on March 21, 2016. The EU Excipient Risk Assessment Guidelines cover both the intended use and the source of excipients in terms of substance.

The major topics are covered in chapters 2 to 4, which include:

- Chapter 2: 'Determining appropriate GMP based on excipient type and use', provides guidance on how to assess and rank the risk presented by the excipient.
- Chapter 3: 'Determining the excipient manufacturer's risk profile', covers identification of appropriate GMP and assessment, ranking and control of the risk profile of the excipient manufacturer.
- Chapter 4: 'Confirming the implementation of appropriate GMP', presents guidance on how to manage the risks of use of the excipient on an on-going basis.
- Two sets of criteria, based on the EU Guideline, capture the risks associated with excipients: one from a manufacturing or supply perspective, and the other from an application viewpoint.

Two lists of criteria capture risks related to excipients based on the EU Guideline: on the one hand from a manufacturing or supply perspective and, on the other hand, from an application point of view.

SOURCE criteria: Risks from the excipient manufacturer or supplier perspective

- Quality Management System applied by the excipient supplier
- Contamination potential, Impurities
- TSE, Viral safety, Microbiological contamination
- Dedicated equipment/facilities
- Environmental control and storage conditions

USE criteria: Risks regarding the application of excipients

- Dosage form
- Route of administration
- Functionality
- Quantity, daily intake

The case study was divided into four steps based on these initial considerations.

Step 1: Supplier qualification:

The EU directives were turned into a checklist, or supplier questionnaire. In an Excel spreadsheet, the responses were harmonised and collected.

Step 2: Excipient risk ranking:

An excipient risk ranking template covering all elements of the EU guidelines was developed. It provides a three-part risk score; low, medium, high for each excipient, which reflects both the individual criteria and the resulting overall risk score. As guidance for risk prioritization, ICH Q9 Quality Risk Management was used.

Step 3: Supplier risk assessment:

Step 3 involved determining the supplier risk, based on the previous definition of minimum requirements derived from documents such as the IPEC-PQG GMP Guide and EXCiPACT.

Step 4: Gap analysis: supplier risk profile:

In step 4, a risk profile for each supplier was established based on a gap analysis, with the purpose of also identifying effective mitigation alternatives, such as updating the Quality Assurance Agreement (QAA) or tightening incoming goods control.

Excipient certification

EXCiPACT is a voluntary international scheme that provides independent third-party certification of pharmaceutical excipients manufacturers, suppliers, and distributors around the world. The European Fine Chemical Group, the International Pharmaceutical Excipients Council (IPEC), the European Association of Chemical Distributors, and the Pharmaceutical Quality Group collaborated to create EXCiPACT (PQG). Manufacturers of pharmaceutical excipients are covered by EXCiPACT GMP, while distributors of pharmaceutical excipients are covered by EXCiPACT GDP.

EXCiPACT Certificates can only be issued by Certifying Bodies that have been audited and certified by EXCiPACT and have completely implemented the Scheme rules into their management systems, as well as auditors who have gone through a rigorous assessment procedure to become EXCiPACT registered.

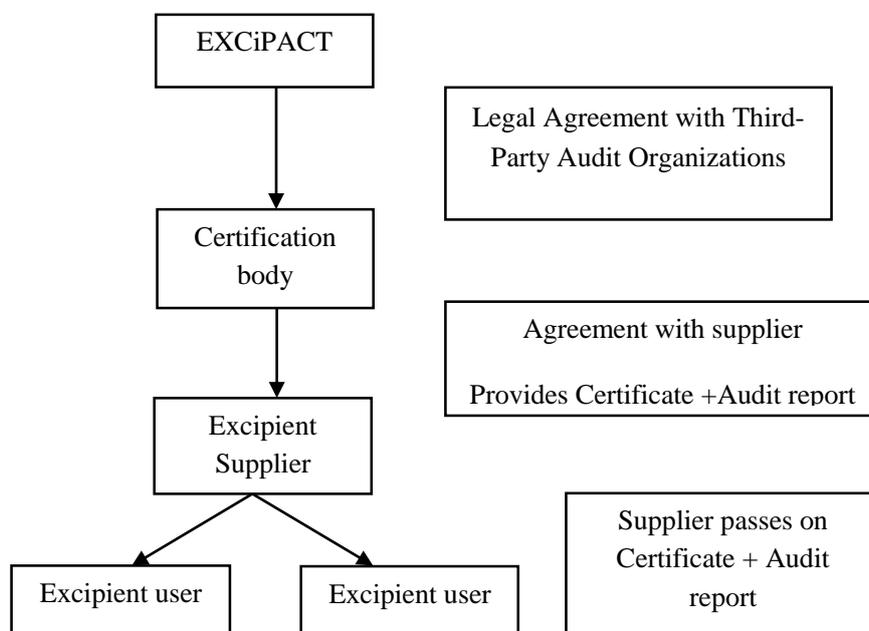


Fig. The EXCiPACT certification scheme process and relationships

Certificate of Suitability (CEP): (17)

The Certification of Suitability (CEP) is a document that verifies that Active Pharmaceutical Components (API) or pharmaceutical ingredients (excipients) meet the requirements of the European Pharmacopoeia's monograph (EP).

The chemical composition of the compounds should be explicitly described in the CEP. The manufacturer must show that the substance's quality is governed by EP monographs and is certified by the European Directorate for the Quality of Medicines' Certification Secretariat (EDQM).

The "ordinary" CEP can be obtained by excipient producers for an excipient detailed in a European Pharmacopoeia monograph by submitting a file to the European Directorate for the Quality of Medicines in the Common Technical Document (CTD) format. The CEP functions similarly to a Type 4 Drug Master File in the United States, allowing the excipient provider to keep proprietary information that is not shared with excipients for which there is no European Pharmacopoeia monograph.

A second kind of CEP exists to demonstrate that TSE (Transmissible Spongiform Encephalopathies) is not a concern, and it is open to APIs and excipients. The CEP signifies that the excipient has little or no risk of transmitting TSE to people via the medicinal product.

Applicants must submit the following documentation to the EDQM's Certification of Substances Department (DCEP) in electronic format to acquire a certificate of suitability to the European Pharmacopoeia monographs:

- Application form
- A Dossier in CTD format written in one of the two official languages of the Council of Europe (English)
- A single copy of the Quality Overall summary (QOS)

As soon as the application is received, it is validated and placed on a list for evaluation. The EDQM may contact the applicant with questions after the assessment. The EDQM grants a CEP to the applicant when

they have been addressed, which is valid for 5 years from the date of issue and indefinitely following the 5 years renewal term. The "Guidance for electronic submissions for Certificates of Suitability (CEP) applications" should be followed by all electronic submissions made to EDQM in the context of CEP applications.

a. Content and structure of a CEP application (18)

The following are the three modules that should be included in an application:

Module 1

- Cover letter
- EDQM application form including signed declarations
- Information about the expert, cv as relevant
- Applicants should attach a document/file containing the questions with the corresponding responses and supporting data when responding to an EDQM deficiency letter.
- Additional information: a section/folder containing, if applicable, a toxicological study, a signed copy of a CEP, and so on.
- Revisions: a finished comparative table laying out the accepted and proposed modified text for module 3.

Module 2: (new CEP applications)

- Quality overall summary, prepared preferably using the EDQM template

Module 3:

- Technical documentation designed in compliance with the CTD as defined by ICH guidance publications for a new CEP application.
- Module 3 does not allow the usage of annexes or attachments.

b. eCTD submission format:

The structure of the eCTD should correspond to the most recent versions of the relevant documents, which can be found at <http://esubmission.ema.europa.eu>.

It is vital to highlight that the eCTD CEP dossier is a stand-alone document that is technologically unattached to any marketing authorization dossier. When sending the initial ECTD submission, the starting sequence should be 0000. Any material that has been previously evaluated and authorised in a "baseline" sequence 0000 should be included when moving from another submission format to eCTD.

Before submitting an eCTD to EDQM, it should be technically examined using an appropriate validation tool. If pass/fail problems are discovered during EDQM validation at the time of receipt, the submission will be blocked or rejected.

c. NeeS submission format:

The structure and specification of NeeS, as well as the validation criteria, should be in accordance with the rules and publications found at <http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html>.

The structure and name of the CTD file/directory must be followed, with a Table of Contents appended as needed.

d. When to submit a baseline Module 3?

Module 3 is an electronic "baseline" that shows all of the CTD sections that match to the regulatory information that has already been filed and accepted. When switching from a paper to an e-submission, it is strongly advised that you submit a baseline Module 3. When submitting a renewal, revision, or notification, it is strongly advised to provide a baseline Module 3.

e. Validation by the EDQM

When EDQM receives a submission, it goes through a validation process. Validation entails checking the submission format and ensuring that it complies with the requirements outlined in the "Guidance for electronic submissions for CEP applications" paper as well as the EU validation rules for NeeS and eCTD.

f. Pathways of submission:

The "Common European Submission Portal" should be used to submit electronic contributions (CESP). Before sending submissions to the EDQM, users must first register with the CESP site.

g. Security:

There should be no password protection, encryption, or other security settings in the files supplied; such files will not be allowed during the validation step at EDQM. Before sending any electronic submission to EDQM, the applicant should scan it for viruses.

GMP and quality standard for excipients

In 1937, the antibacterial drug was initially dissolved in diethylene glycol (DEG). DEG also improved the taste and appearance of the drug for children. As a result of taking it, more than 100 children died of kidney failure. As a result of this incident, the federal Food, Drug, and Cosmetic Act of 1938 was enacted.

The usefulness of an excipient in a drug product, the evaluation of the excipient's toxicity, and the likelihood of cross contamination during its manufacturing are all inherent characteristics of the excipient. GMP compliance may be required because of the nature of excipients. When making excipients, proper GMP must be observed. The International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Guide (PQG), commonly known as the Joint Good Manufacturing Guide, should be followed when processing excipients. (20)

Excipient GMP Implementation (21)

Once it has been confirmed that a chemical is intended for use as a component of a drug product, GMP must be followed. The manufacturing of excipients should be done in compliance with the GMP ideas outlined in this Guide. The goal of GMP for excipients is to ensure product integrity, avoid contamination, and keep track of all data. Manufacturing processes should be controlled and documented, and GMP procedures as stated in the 'IPEC and PQG' should be followed at some logical processing step, as established by the producer.

Quality Management System (Excipients Quality Systems)**General Requirements:**

The parts of the quality management processes should be applied in a proportionate and suitable manner to each stage of the product lifecycle, taking into account the various goals and knowledge available at each stage. The excipient manufacturer retains responsibility for quality, and control mechanisms should be outlined.

Documentation Requirements:

The excipient manufacturer should have a system in place to keep track of papers and data related to the quality management system's requirements. To assist general understanding and consistent execution, the organization's overarching aims and approach to GMP should be specified and documented.

- **Quality Manual:** The excipient manufacturer should have a written statement of the quality management system, quality policy, and the organization's commitment to following the GMP and quality management standards outlined in this Guide. The documentation should identify and justify the moment at which each manufacturing step is subject to the complete excipient GMP regulations.
- **Control of Documents:** Identification, collecting, indexing, filing, storage, security, maintenance, and disposition of controlled documents, including regulatory papers and documents of external origin that are part of the quality management system, should be established and maintained by the excipient manufacturer. In addition, formal controls for process approval, amendment, and distribution should be in place. These controls should ensure that the most recent version of a procedure is being used throughout all operational regions and that earlier document versions have been eliminated. If a regulatory filing exists, such as an excipient DMF or CEP, procedures should be in place to examine and update it on a regular basis. If electronic signatures are used on papers, they should be monitored to ensure that they provide the same level of security as a handwritten signature.
- **Control of Records:** Records should be kept to show that the required quality was met and that the quality management system was functioning properly. Records should be readable and easily distinguishable. Entries in records should be clear and indelible, made immediately after the activity is completed, and signed and dated by the individual who performed the observed work. At all times, precautions should be taken to ensure data integrity. Analytical outputs and calculations, for example, should be traceable back to the original data and observations. Manual (paper) and electronic data are both subject to data integrity rules. Control processes for certifications of analysis or conformance should be documented.

Development and specification process of excipient: (3)

- **Consistency and control of excipients:** The manufacturing process should be monitored to ensure that the excipient fulfils the specified standards on a consistent basis. Actual samples should be used for in-process controls, such as inspection and/or testing. Excipient composition profile specifications for these components should be based on relevant toxicological data as well as manufacturing methods.
- **Performance indicators:** Consistent excipient quality can be established simply by adhering to monograph standards or product specifications. Manufacturers should design acceptable performance indicators for the planned commercial use of excipients because they perform functional tasks.

- Limits in the process, product specifications, and batch records: Excipient production and release specifications may be developed separately. Production specifications are usually more restrictive than release specifications.
- Excipient manufacturers should make information like sales specifications (including in-house test techniques), Safety Data Sheets (SDS), excipient information package (EIP), and technical literature (including storage and stability information) available to excipient consumers.
- After the product launch, new excipients are frequently introduced with only a few batches manufactured. Excipient manufacturers' capacity to generate a more consistent product improves as they gain production experience.
- Excipient users may demand excipient producers to provide extensive manufacturing and quality information for inclusion in their drug registration papers. Some information may be considered confidential by excipient manufacturers.

Excipient selection criteria: (3)

When analysing and specifying excipients, users identify a number of criteria. Excipient parameters, performance qualities, and prospective supply sources based on dosage form and method of administration are among these criteria.

- **Specifications:** Although compendial excipient specifications are frequently sufficient, excipient users should assess whether additional specifications or requirements, such as procurement specifications, are required. These would necessitate both parties' discussion and written agreement. When compendial materials are unavailable, the excipient user creates a documented risk assessment to justify the use of a non-compendial excipient.
- **Additional Compositional Considerations:** Compositional information may be included in an excipient information package; however, this information may be regarded confidential.
- **Performance Characteristics:** Users of excipients must show that they are compatible with the drug component, other excipients in the formulation, and the packaging materials. Excipient users must also show that at the recommended concentration, excipients deliver the requisite functionality and stability in the medical product.
- **Supply Considerations:** Excipient users should;
 1. Evaluate the need to qualify multiple sources for each excipient used in a medicinal product formulation.
 2. Consult any internal list of currently approved excipients and suppliers.
 3. Identify original manufacturers and manufacturing sites/locations.
 4. Consider the supply chain complexity and security, including whether excipients are being purchased directly from original manufacturers or through distribution channels.
 5. Establish quality agreements in alignment with the IPEC QA Guide.
- **Excipient Manufacturer Qualification:** Audit history, production experience and reliable sourcing should be considered during excipient manufacturer qualification and, as applicable, during ongoing performance review.

Excipient users should generate audit information for all excipients and their distribution through site visits, using either internal audit resources or qualified third-party audit providers. Users of excipients should check for any additional regional regulatory requirements. **Regulatory Considerations:** Users of excipients should be aware of excipient regulatory obligations (e.g., US FDA SUPAC, EU variation regulation and other regional regulatory requirements). For example:

- assessment of the excipient regulatory status in the intended market(s)
- ensure sufficient “novel excipient” information is available to support filing(s)
- evaluate safety aspects as part of their own regulatory assessment.

Resource management: (21)

To establish, maintain, and develop the quality management system, the organisation should determine and provide the appropriate qualified individuals and resources, such as equipment, materials, buildings, and facilities.

a. Human resources:

The excipient manufacturer should design and maintain systems for identifying training requirements and providing personnel with the relevant training. Training records should be kept in a proper manner. Management should provide comprehensive and ongoing personnel hygiene training to personnel who handle materials so that they are aware of the steps that must be taken to prevent excipient contamination. To prevent contamination of excipients, the company should conduct a documented risk assessment to identify areas where the excipient is at risk of contamination by individuals or their activities. Only authorised personnel should have access to the restricted areas of the buildings and facilities. Personnel should dress in clean, appropriate clothing for the activity in which they are engaged, and this clothing should be changed as needed.

b. Infrastructure:

To assure excipient quality and avoid contamination, the infrastructure should be built, managed, operated, cleaned, and maintained in compliance with GMP principles.

Buildings and facilities: Contamination prevention should be considered in the design of manufacturing processes, and facilities used in the production, processing, packaging, testing, or storage of an excipient should be kept in good repair and be of appropriate size, construction, and location to facilitate cleaning, maintenance, and proper operation appropriate to the type of processing.

c. Equipment:

Process equipment should be built so that contact surfaces are not reactive, additive, or absorptive, affecting the excipient's quality. To reduce the danger of contamination, equipment with moving parts should be examined for the integrity of seals and packaging materials. These records can be kept in the form of a log, a computer database, or other suitable documentation.

d. Utilities:

Excipient quality should be reviewed and appropriate action taken to control the risk of contamination and cross-contamination using utilities such as nitrogen, compressed air, and steam utilised in the manufacture, storage, or transfer of products.

e. Water:

Water used in excipient manufacturing should be proven to be of sufficient quality for its intended usage. Process water should, unless otherwise specified, fulfil WHO requirements for drinking (potable) water quality. If potable water is insufficient to ensure quality, or if stricter chemical and/or microbiological water quality specifications are required, appropriate controls and specifications, such as physical and chemical attributes, total microbial counts, and limits on objectionable organisms and/or endotoxins, should be established.

f. Work environment:

When an excipient is exposed throughout the manufacturing process, it should be in a clean environment to avoid contamination, including cross contamination. To determine the appropriate controls, a documented risk assessment should be conducted, such as:

1) Air handling:

The air handling systems in excipient production units should be designed to prevent contamination and cross contamination. It is permissible to recycle a portion of the exhaust air back into the same area for specialised areas processing the same excipient.

2) Controlled environment:

To avoid contamination or degradation caused by exposure to heat, air, or light, a controlled environment may be required. The gas should be treated as a raw material when an inert environment is required. If the controlled environment is disrupted, sufficient evidence and rationale should be provided to indicate that the excipient's quality has not been harmed.

3) Cleaning and Sanitary Conditions:

Buildings used in the production, processing, packaging or holding of an excipient should be maintained in an appropriately clean.

Where maintenance of clean and sanitary conditions is critical to excipient quality, documented procedures should assign responsibility for cleaning and sanitation, describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used in cleaning the buildings and facilities.

4) Pest control:

Structures should be free of rodents, birds, insects, and other vermin infestations. The pest management programme should be documented by the excipient producer. The use of appropriate rodenticides, insecticides, and other pesticides should be documented.

5) lighting:

Cleaning, maintenance, and correct operations should all be made easier with adequate lighting. Lighting should be shatter-proof or otherwise shielded where the excipient is exposed to the work environment or kept.

6) Washing and toilet facilities:

Appropriate personnel washing facilities, including hot and cold water, soap or detergent, air dryers, or single-service towels, should be supplied to ensure that appropriate hygiene standards may be maintained.

7) Waste:

Waste should be separated, appropriately labelled, and disposed of in accordance with its nature, such as chemical, biological, or hazardous waste.

Monitoring and measurement of product:

The excipient maker should set test methods and procedures to ensure that the product fulfils specifications on a consistent basis.

a) Laboratory controls:

Measures should be taken at all times to ensure data integrity. Laboratory reagents and solutions should be prepared, labelled, handled, and stored according to documented procedures. The supplier should label purchased reagents and solutions with the right name, concentration, and expiration date.

b) Finished excipient testing and release:

Finished excipient testing should be performed on each batch to ensure that the excipient conforms to documented specifications. There should be a procedure to ensure that appropriate manufacturing documentation, test results, is evaluated prior to release of the finished excipient. The quality unit should be responsible for the release of the finished excipient.

c) Retained samples:

Unless otherwise justified and recorded, a representative sample of each batch of the excipient should be kept. The retention time should be justified and determined by the date of expiration or re-evaluation. The retained samples should be kept in a safe area that is easily accessible and in settings that are compatible with the final excipients' specified storage conditions.

d) Certificates of analysis:

For each batch of excipient, the organisation should give certificates of analysis that meet the specified specifications.

e) Impurities:

Excipient manufacturers should detect and set acceptable limits for impurities whenever possible. Impurities should not exceed such defined limitations if manufacturing processes are properly controlled. Organic solvents are used to extract or purify many excipients. Drying is usually used to get rid of these solvents.

f) Stability:

Excipient stability is an essential aspect contributing to the overall quality of the medication product. While many excipient products are stable and may not require comprehensive testing to ensure stability, excipient stability is an important factor contributing to the overall quality of the drug product.

g) Expiry/Re-evaluation Periods:

Each excipient should have an expiry or re-evaluation period assigned to it, and the client should be informed of it.

h) Control of Nonconforming Products:

Nonconforming raw materials, intermediates, and finished excipients should be properly identified and regulated to avoid unintended usage or release for sale. Nonconforming product's record should be maintained.

i) Reprocessing:

When an activity that is a routine component of the manufacturing process is repeated, it should only be done after it has been reviewed and documented that the excipient can be made in that way. Reprocessing record should be maintained.

j) Returned excipients:

A documented procedure defining the process for handling returned items should be in place. Records for returned products should be kept, and they should include the excipient's name and batch number, the reason for the return, the quantity returned, and the excipient's final disposal.

k) Analysis of data:

Consumer complaints, product reviews, process capability studies, and internal and customer audits can all provide this information. Such data analysis could be used as part of a management review.

Storage and stability requirements of excipient:

The purpose of the stability guideline is to give excipient manufacturers with methodologies for assessing the stability of their excipients. This guideline outlines how to set up a stability study programme for a pharmaceutical excipient for an excipient manufacturer. All excipients, including new or unique chemical excipients, are covered by the IPEC Excipient Stability Program Guide. When applying for a CEP in Europe, the EDQM only considers stability data in accordance with ICH Q1A(R2) if the applicant requests a retest interval on the certificate. The primary goal of an excipient stability study is to demonstrate that the excipient will continue to meet standards from the time of manufacture until the package is opened.

A final report should be written when the data has been collected and analysed. The report should include an assessment of the stability data as well as the conclusions reached, as well as a list and explanation of any deviations. A Confidential Disclosure Agreement may apply to summary reports. The excipient grade(s) and packaging type(s) for which the stability data is applicable, the suggested storage conditions, acceptability criteria, and the expiry interval should all be defined in the report. (19)

Conclusions:

Excipients have recently been reported to have several major side effects, and regulatory control over excipient use is still unclear when compared to API use. Excipients should undergo multiple analyses before being used in a formulation. New chemical excipients will be treated in the same way as new APIs, according to European Union Directive 75/318/EEC. Excipients are covered under IPEC's GMP guidance document, however there is no clear GMP requirement for excipients. For any novel excipient, a regulatory dossier is required inside the EU territory (s). Excipients require strict regulation and law in order to avoid unwanted side effects and interactions with the medicine (s). In the European Union, the Certificate of Suitability is a mandatory document that validates that the API or pharmaceutical components (excipients) match the European Pharmacopoeia's monograph standards.

References:

1. *Pharmaceutical excipients: A regulatory aspect*. Verma, Surender, et al. s.l. : The Pharma Innovation Journal, 2016. 2277-7695.
2. *Pharmaceutical Excipients: A review*. Chaudhari, Shilpa P and Patil, Pradeep S. s.l. : INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY, 2012, Vol. 1(1).
3. Qualification of Excipients for Use in Pharmaceuticals Guide and Checklist. <https://www.ipeceurope.org>. [Online]
4. Kar, Mousumi, et al. Current Developments in Excipient Science: Implication of Quantitative Selection of Each Excipient in Product Development. *Basic Fundamentals of Drug Delivery*. 2019.
5. *Novel excipients- from concept to launch*. Guth, Felicitas, Schiffter, Heiko A and Kolter, Karl. s.l. : Chimica Oggi - Chemistry Today, 2013, Vol. 31(5).
6. [Online] <https://www.slideshare.net/Pankaj2014/regulatory-aspects-on-excipients>.
7. *Marketing authorization procedures in the European Union- Making the right choice*. Ghalamkarpour, Arash. s.l. : LIFE SCIENCE TECHNICAL BULLETIN SGS, 2009.
8. Singh, Gajendra, Agarwal, Gaurav and Gupta, Vipul. *Drug Regulatory Affairs*. s.l. : CBS Publishers & Distributors Pvt Ltd, 2015. 978-81-239-2881-4.
9. *Pharmaceutical Excipient Development: The Need for Preclinical Guidance*. Baldrick, Paul. s.l. : Regulatory Toxicology and Pharmacology, 2000.
10. *Design and international harmonization of pharmacopoeial standards*. Calam, D. H. s.l. : Journal of Pharmaceutical and Biomedical Analysis, 1995.
11. *Pharmaceutical excipients - Quality, regulatory and biopharmaceutical considerations*. Elder, David P, Holm, Rene and Kuentz, Martin. s.l. : European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical sciences, 2015.
12. Committee for medicinal products for human use (CHMP): Draft GUIDELINE ON EXCIPIENTS IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORIZATION OF A MEDICINAL PRODUCT. <http://www.emea.europa.eu>. [Online] November 6, London 2006.
13. VOLUME 2C Guidelines Excipients in the labelling and package leaflet of medicinal products for human use. <http://www.emea.europa.eu>. [Online]
14. *EU Excipient Risk Assessment Guidelines - Practical Implementation Experience*. Holtz, Firthjof. s.l. : SAFC Pharma & Biopharma Raw Material Solutions.
15. Guidelines on the Formalised Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use. <http://www.emea.europa.eu>. [Online] February 5, 2013.
16. HOW CAN YOU ENSURE PATIENT SAFETY THROUGH SUPPLIER QUALITY. [Online] <https://www.sgsgroup.in/-/media/local/india/documents/flyers-and-leaflets/sgs-excipient-certification-services.pdf>.
17. [Online] [https://www.freyrsolutions.com/what-is-certification-of-suitability-cep-and-sister-cep-submissions#:~:text=The%20Certification%20of%20Suitability%20\(CEP,the%20European%20Pharmacopoeia%20\(EP\)..](https://www.freyrsolutions.com/what-is-certification-of-suitability-cep-and-sister-cep-submissions#:~:text=The%20Certification%20of%20Suitability%20(CEP,the%20European%20Pharmacopoeia%20(EP)..)
18. Guidance for electronic submissions for Certificates of Suitability (CEP) applications. <https://www.edqm.eu>. [Online] January 2018.
19. The IPEC Excipient Stability Program Guide. <https://www.ipeceurope.org>. [Online] 2010.
20. *Excipient GMP Quality Standards: One is Enough*. Silverstein, Irwin. s.l. : Pharmaceutical Technology, 2002.
21. The International Pharmaceutical Excipients Council & The Pharmaceutical Quality Group THE JOINT GOOD MANUFACTURING PRACTICES GUIDE For Pharmaceutical Excipients. [Online] <https://www.ipeceurope.org/uploads/publications/20170517-ipece-pqg-gmp-guide-final-1536242212.pdf>.