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A STUDY ON REGULATION OF PHARMACEUTICAL EXCIPIENTS IN EUROPEAN UNION (EU)

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ABSTRACT

Excipients are known to be pharmacologically inert, plays a vital role in the formulation of medications. Inert substances called excipients are added to drugs in order to improve formulations or the therapeutic effects of active pharmaceutical ingredients (APIs) in the final dose form. As such, an active substance and an additive are present in practically in all medicinal products. Scientists studying about pharmaceutical excipients have demonstrated over time that excipients are not inert and can affect the quality, safety, and efficacy of prescribed medications when taken as indicated. Today, with adverse affects patient outcomes from pharmaceutical excipient adulteration, pharmaceutical businesses and regulatory agencies view control over excipient distribution and manufacturing as a key concern. Because they maintain the efficacy, safety, and functioning of the active pharmaceutical ingredients (APIs), which are found in almost all marketed medications, excipients are essential to the pharmaceutical production process. This study aims towards the regulatory aspects of pharmaceutical excipients and their function in dosage forms, with a focus on excipient qualification for use, novel excipient regulations, challenges, and the role of the International Pharmaceutical Excipients Council (IPEC) in regulating excipient quality in the European Union (EU).

Keywords: IPEC, FDA, API, CPMP, QWP, CFR, DMF, CTD, GMP, EMA, EDQM, CEP, QRM, ICH, NDA, MAA, GRAS, CDER, QbD, MAH, ISO.

I. INTRODUCTION

The final pharmaceutical product typically contains inactive components, also referred to as excipients, such as co-solvents, colorants, surfactants, preservatives, or sweeteners, in addition to the active pharmaceutical ingredient (API). "Any component of a drug product other than the active ingredient" is what the US Food and Drug Administration (FDA) defines as an inactive ingredient. Excipients are regarded as necessary for a number of reasons, such as making the production of products easier, assisting with identification, adjusting stability, preservation, and delivery, and raising the acceptance of the products. Excipients can be made chemically, through other processes like fermentation, or from natural sources. [1]

Regulatory bodies are currently passing new rules mandating that pharmaceutical companies guarantee the quality of their ingredients as they grow more worried about the safety and quality of excipients. [2] Inadequate control over excipient quality may affect the drug's stability, effectiveness, or quality, which could result in a product recall or worse, problems with patient safety. [3] The manufacturing authorization holder's pharmaceutical quality system need to include the excipient risk assessment/risk management approach. [4]

In order to ensure the safety and effectiveness of a medicine, all ingredients in a formulation must comply with current cGMP rules and undergo testing in accordance with those guidelines [5]. An appropriate level of GMP should be established, implemented, and maintained during the production, packaging, repackaging, labeling, quality control, release, storage, distribution, and other related activities of pharmaceutical products in order to achieve the goal of guaranteeing that the excipients used in those products are of appropriate quality.[6]

In addition to the ingredients that make up the outer layer of pharmaceutical products, such as gelatin capsules, excipients also include things like fillers, disintegrants, lubricants, coloring agents, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilizers, permeation enhancers, flavoring, and aromatic substances. [7] Given the significance of excipients in pharmaceutical formulations, it is imperative that pharmaceutical scientists possess an understanding of the many grades of excipients that are accessible.

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Recognizing whether a new excipient will be needed for the formulation and how to get regulatory permission for these new excipients is also crucial. [8]

Pharmaceutical agencies and important stakeholders are increasingly focusing on excipient quality, traceability, and regulation as the regulatory control environment governing pharmaceutical excipients continues to change. [9] As with any substance given to a human, the components used as excipients must meet the necessary safety standards in addition to having the qualities required by their technological function[10]. Excipients must be used carefully because they can also affect the product's stability and use. Using the wrong excipient or in the wrong proportion will undoubtedly change the way medicinal products work. [11] There isn't a single, comprehensive international guideline that addresses the safety assessment of pharmaceutical excipients. [12]

Regulatory aspects of pharmaceutical excipients

Patients who receive medication manufactured with adulterated excipients will die. As a result, the International Pharmaceutical Excipients Council (IPEC), a regulatory body, is needed to oversee the functionality, safety, and quality of all pharmaceutical excipients. The International Pharmaceutical Excipients Council is referred to as IPEC. It establishes and controls requirements for pharmaceutical excipients, including those related to quality, safety, and functionality. IPEC has divided its regulations into chapters, such as IPEC-America, IPEC-Europe, IPEC-Japan, IPEC-China, and IPEC-India, based on geographical regions.

Control over pharmaceutical ingredients Pharmaceutical excipients are inert materials that create the intended pharmacological effects when employed as diluents, fillers, binders, or carriers in the creation of drug formulations. The regulatory requirements state that for the drug's safety and efficacy, every ingredient in the formulation must comply with and be tested in accordance with cGMP regulations.

The primary reason for the increased attention on excipients is the history of events in which pharmaceutical corporations' use of tainted excipients resulted in patient deaths. Therefore, it is now required by law to employ high-quality pharmaceutical ingredients when producing pharmaceuticals. Contaminated or adulterated excipients throughout the production process cause drug batches to fail and produce dangerous goods that put patients and manufacturers at risk. Excipients must be produced, processed, and packed in accordance with current good manufacturing practice (cGMP) in order to remove the aforementioned dangers. For pharmaceutical excipients used in bulk, the FDA does, however, support the IPEC GMP criteria. One crucial factor affecting the overall quality of pharmaceutical goods is the quality of the excipients. According to 21 CFR 211.84(d)(2), the producers of drug products must test each batch of drug excipients to ensure that it complies with stated requirements for purity, quality, and strength. [2]

Novel excipients

A comprehensive description of the excipient, its function, and its conditions of use should be provided; if the excipient is complex or consists of a mixture of compounds, the composition should be specified in qualitative and quantitative terms; documentation on the chemistry of excipients is required for all novel excipients, taking as its basis the CPMP Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96).

Full details of manufacture, characterisation, and controls with cross references to supporting safety data should be provided for novel excipients, under the drug substance format.

- The excipient's place of origin, including the manufacturer's name and address.
- A synopsis of the production and filtration processes.
- Organization. Tests for purity, identity, and physical and chemical characteristics.
- Analytical techniques validated with batch data shown.
- Unspecified data (microbiological testing, etc).
- Pollution, foreign material presence, solvent residue, etc.
- When an excipient is made from a combination of multiple components, it is important to indicate the quality of each component as well as the results of the mixture's physico-chemical testing.
- According to the Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99), stability data for the active ingredients must be included.
- The documentation provided in the dossier should serve as the foundation for establishing the regular test procedures and restrictions. [7]

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Regulatory filing process for new excipients

According to European Union (EU) directive 75/318/EEC, new chemical excipients will be handled the same way as new APIs. As a result, any new excipient must submit a regulatory dossier to the EU, meaning that thorough safety testing is necessary. The following procedures are used in the US to approve new excipients generally recognized as safe (GRAS) determination in accordance with 21 CFR 182, 184, and 186 (Code of Federal Regulations) consent to the petition for a food additive under 21 CFR 171 in a new drug application (NDA) that has been approved for a specific drug product and for a specified purpose or usage in that dosage form. In order to allow the excipient to be used in other products and eventually be included in the National Formulary, a DMF registration with the FDA will be necessary. Because the majority of pharmaceutical products are meant for global registration, these regulations' various evaluation schemes should be taken into consideration when choosing a new excipient. Different rules have consequently been provided by IPEC-Americans and IPEC-Europe.[8]

Qualification of excipients to use in pharmaceuticals

IPEC is a global enterprise that aids in the creation and unification of standards, such as excipient qualification. The certification of excipients to be utilized in the production of pharmaceuticals is a focus area for regulatory authorities more and more. Without the excipients in the formulation, the API cannot function as intended on its own. As a result, one could conclude that the excipients made up a sizable amount of the dosage form. Manufacturers of excipients are also known as providers, and the majority of these suppliers produce excipients that satisfy the fundamental requirements of ISO 9001 or food grade GMPs, but not pharmacopoeia cGMPs.

The use of these excipients in medications puts patients and pharmaceutical makers at serious danger. Although they still need to fulfill the highest standards, excipient vendors who adhere to the IPEC guideline give users a little more trust. The safety and quality of the excipients extend beyond the supply chain. [2] Excipients are deemed qualified when they meet the requirements set forth by IPEC and cGMP and are prepared in accordance with those rules. Along with APIs, the quality and dependability of excipients must also match the standards needed for the creation of pharmaceuticals. [3]

II. DOCUMENTATION RELATED TO EXCIPIENTS

Excipient Master Files and other filings

A collection of confidential technical information on the production of excipients is called an excipient drug master file (DMF). The format of the document follows the Common Technical Document (CTD) guidelines established by the ICH. The DMF may contain the following, depending on whether it covers compendial or non-compendial excipient proprietary data regarding test procedures and raw material specifications, an explanation of the manufacturing process, controls for the excipients both in-process and finished, information about packaging and labeling, stability data, and safety data. [3]

Excipient DMF

Manufacturers of excipients frequently submit DMFs to the relevant health authorities in order to divulge private information about excipients, safety, and compliance with relevant GMP regulations. The US, Canada, and Japan all have regulators that use an excipient DMF system. While the EU has a DMF system in place for pharmacological compounds, there isn't one for excipients.[3]

Certificate of Suitability (CEP)

The European Directorate for the Quality of Medicines issues Certificates of Suitability on a voluntary basis (EDQM). Two categories of CEPs exist. A Ph. Eur. monograph is complied with by one type. According to EMA410/01, the risk of spreading transmissible sporadic encephalopathies has been reduced to a manageable level, as evidenced by the other type of CEP. Drug compounds and excipients, even those without a Ph. Eur. monograph, are covered by these CEPs. They attest that the article satisfies Ph. Eur Chapter 1483's standards, meaning that there is an appropriate level of control over the danger of TSE transmission to humans through the pharmaceutical product.

In the EU, authorities support the following three categories of medication marketing authorization procedures with sensitive information by using a CEP:

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- centralized procedure
- mutual recognition procedure
- decentralized procedure

Excipient manufacturers should be willing to provide excipient information directly to the MAH for inclusion in the drug application, if no CEP is available. A confidentiality agreement can be used to facilitate disclosure of confidential information. Relevant data should be provided by excipient manufacturers to excipient users, marketing authorization holders (MAHs), or the relevant regulatory agency for inclusion in the medicinal product application, regardless of the drug marketing authorization procedure used [3].

Determination of appropriate GMP based on type and use of excipient

Principles and examples of quality risk management tools that can be applied to various aspects of pharmaceutical quality, including excipients, can be found in EudraLex Volume 4, Guidelines for Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part III: GMP related documents, and ICH guideline Q9 on Quality Risk Management (QRM) (ICH Q9). The risks to each excipient's quality, safety, and functionality should be evaluated using these quality risk management principles, and the excipient in issue should be categorized as low, medium, or high risk, for example. For this, it is best to employ quality risk management methods like those mentioned in EudraLex Volume 4, Part III, ICH Q9.

From the point of origin animal, mineral, vegetable, synthetic, etc. to the point of incorporation in the final pharmaceutical dose form, the manufacturing authorization holder for each excipient used from each manufacturer should determine the risks to that excipient's quality, safety, and function.

- Transmissible spongiform encephalopathy is one area that needs to be taken into account, among others.
- The possibility of infection by viruses
- Possibility of microbiological or endotoxin/pyrogen pollution
- Potentially, any impurity that comes from the raw materials itself or that is formed during the process and carries over.
- Assurance of sterility for excipients purported to be sterile.
- The possibility of contaminants from previous operations lingering if specialized tools and/or facilities aren't available.
- Control of the environment and, if necessary, cold chain management throughout storage and transit.
- Complexity of the supply chain, excipient stability and proof of packing integrity.

The manufacturing authorization holder should also take into account the following when determining the purpose and usage of each excipient:

- the pharmaceutical form and use of the medicinal product that contains the excipient.
- the purpose of the excipient in the formulation, such as the preservative in a liquid formulation or the lubricant in a tablet product;
- the excipient's percentage in the composition of the medicinal product;
- the excipient's daily patient intake;
- any known fraud or quality defects, both locally and globally, related to the excipient;
- whether the excipient is a composite;
- the excipient's known or potential impact on the critical quality attributes of the medicinal product; other factors as determined or known to be pertinent to ensuring patient safety.
- After determining and recording the excipient's risk profile, the holder of the manufacturing authorization should determine and record the components of EudraLex Volume 4 that, in his opinion, must be in place to regulate and preserve the excipient's quality [3].

Trends in excipients:

As of late, co-processed excipient technology which combines two or more excipients to create a single product has become the most popular. This trend is further validated by research studies, which have shown that drugs created using co-processed excipients perform better than those created using individual excipients. Quality by Design (QbQ), which fosters tighter collaboration between excipient and medicine producers, is another trend in the use of excipients. Drug producers can gain a deeper understanding of each component during the

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formulation development process thanks to QbD. Focusing on the creation of multifunctional excipients is crucial for excipient makers.[2]

Challenges

Creating novel pharmaceutical excipients is a dangerous business since there is no special approval procedure for such excipients. Excipients are now only permitted to serve a certain purpose in pharmaceutical products; if the product is not approved, the excipient will likewise stay unapproved. The fact that developing novel excipients typically takes seven to ten years is another difficulty for excipient manufacturers. Owing to the vast quantity of excipients, regulatory agencies face an additional issue of having to audit each and every one of them, which would require ten audits every day.[2]

Complaints, returns, recalls

The recording and investigation of complaints, recalls, and withdrawals related to pharmaceutical use should be outlined in a formal system that is kept on file. Every choice made and action performed in response to a complaint needs to be documented.

At the very least, complaint records ought to contain the following:

- The date the complaint was received
- The complainant's name, address, and other pertinent information
- The complaint's specifics, including the batch number and excipient's name
- The investigation's findings and actions taken
- A copy of the response given and final judgment based on the investigation's findings. The recall protocol should specify who is responsible for what, how to start the recall, who should be notified, and how to manage the recalled material. It should also outline the obligations of the persons involved.

The recall method should specify who is responsible for what, how to start the recall, who should be notified, and how to handle the recalled material. It should also outline the duties of the persons involved. The quality unit should authorize how the returned goods is to be handled. When determining what should happen to the returned product, consideration should be given to the circumstances in which the excipient intended for pharmaceutical use had been delivered and stored. Unless there is a scientific explanation that demonstrates the product satisfies the relevant predetermined quality requirements, the product should be disposed of if the state of the container itself raises questions about the safety, quality, or purity of the excipient [6].

Current regulatory situation

The regulatory framework in Europe includes testing of excipients because new excipients must be assessed as new chemical entities (e.g., Notice to Applicants, 1998) and because marketing authorization applications (MAAs) for new drugs are expected to include information on excipients (CPMP/DGIII, 1992). Therefore, approved excipients are included to MAAs with the presumption that their pharmacopoeia characterization and presence won't cause problems for European authorities.

Excipients are not mentioned in the guidelines for preclinical data for a new drug application (NDA) in the United States (CDER, 1987). However, just like in Europe, it is considered that using a "approved" excipient guarantees its acceptability in the new drug formulation. Submissions of NDAs ought to cross-reference to a drug master file (DMF) that has all pertinent excipient data. The Food and Drug Administration (FDA) supports the use of "generally recognized as safe" (GRAS) compounds, established food additives, and commercially available excipients.

III. CONCLUSION

Pharmaceutical excipients must adhere to the rules and regulations set forth by regulatory organizations including ICH, IPEC, and cGMP. Excipients have a significant role in a dosage form and have an impact on a formulation's characteristics. When it comes to excipients, the regulatory regulation is still unclear compared to active pharmaceutical ingredients. Excipients require strict control and legal protection in order to prevent unwanted side effects and drug interactions. Therefore, before being added to a formulation, excipients should undergo a variety of evaluations, such as toxicity tests, preclinical studies, compatibility studies, etc. Thus, regulatory agencies and industry groups need to standardize the assessment of excipients in the same way that they do for APIs. The main markets' approaches to regulating novel excipients differ greatly from one another. For example, the FDA will evaluate a new excipient in combination with an NDA, but in Europe, it is regarded as

a new drug application. A significant number of research publications in this area of excipient safety emphasize the importance of the growing concern to make safe and non-toxic excipients available. The regulatory bodies should take into account the research findings when formulating the guidelines with the goal of developing safe pharmaceutical products. It may be challenging to extend and apply the regulations that apply to APIs and finished products to the excipients, but it should be recognized that the concerns of the formulators who employ these additives are taken into consideration.

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