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Regulatory Aspects of Pharmaceutical Excipients in India and their Qualification to Use in Pharmaceuticals

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Abstract

Excipients are an inactive substances formulated along with the active pharmaceutical ingredient(s) (APIs) of medication for bulking up of formulations or to give a therapeutic enhancement of API in the final dosage form. Almost of all the marketed products contain excipients thereby the excipients play a crucial role in the manufacture of medications by helping to preserve the efficacy, safety and functionality of the APIs. Excipients categorized as compendial excipients (official in pharmacopoeia) and non compendial excipients (non official in pharmacopoeia). The main objective of excipient in formulation is, they can deliver a drug from its dosage form in desired path. This paper deals with the challenges, regulatory aspects of excipients and role of International Pharmaceutical Excipients Council (IPEC) in regulating the quality of excipients.

Key words: Regulatory affairs, Excipients, IPEC, Challenges, Qualification.

1. Introduction

Currently Regulatory agencies are becoming increasingly concerned about the quality and safety of excipients and are enacting new regulations requiring drug makers to ensure the quality of their ingredients. Active pharmaceutical ingredients (APIs) would not perform as desired without the optimal functionality of the excipients in the formulation. Since excipients generally comprise a significant portion of a dosage form, the quality and reliability of the excipients should match the quality expected for APIs. Excipient quality, if not adequately controlled, could

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compromise the quality, stability or efficacy of the drug, leading to product recall, worse and patient safety issues [1].

2. Trends in excipients

Recently, co-processed excipients technology is most preferred, where two or more excipients are combined to form a one product and it also supported by the research works / studies, where it was found that the medications developed with co-processed excipients showed good results than the medications developed with individual excipients [2]. Another trend in excipients usage is Quality by Design (QbQ), that provides closer working relationship for both drug manufacturers and excipients manufacturers. QbD allows drug manufacturers to better understand every component during the formulation development. It is an important place to the excipient manufacturers to concentrate on the development of multifunctional excipients [3].

3. Challenges

It is a risky business to develop innovative pharmaceutical excipients because of there is no specific approval process for novel excipients. Currently, excipients will be approved only for specific function as a part of the pharmaceutical product and if the product is failed to gain an approval, the excipient also would remain unapproved. Another challenge for excipient manufacturers is, usually it will take 7-10 years of time to develop novel excipients. Due to the large number of excipients, it is also one more challenge for regulatory bodies to audit all the excipients and if want to audit, it will take 10 audits per day [4].

4. Overcoming challenges

It is requested to facilitate the proper approval process for innovative excipients. According to guidelines of the regulatory bodies, drug manufacturers should conduct the physical audits of the excipient manufacturers and suppliers in order to ensure a secure supply chain [5].

5. Regulatory aspects of pharmaceutical excipients

Adultered excipients for manufacture of medication lead to death of the patients. Hence, there is a requirement of regulatory body which is known as International Pharmaceutical Excipients Council (IPEC) to control the quality, safety and functionality of all the pharmaceutical excipients [5].

6. What is IPEC?

IPEC stands for International Pharmaceutical Excipients Council. It regulates and frames the standards such as quality, safety and functionality for pharmaceutical excipients [6].

7. What do you meant by chapter in IPEC ?

According to geographical region, IPEC has framed its regulations called chapters such as IPEC-America, IPEC-Europe, IPEC-Japan, IPEC-China and IPEC-India [7].

8. Objectives of IPEC

It is a global organization that promotes quality and safety in pharmaceutical excipients. Some of its objectives are promoting supply chain security, harmonization of standards and development of third party certifications. Let us study about the IPEC-India chapter [8].

9. Regulatory aspects of pharmaceutical excipients in India

9.1. *IPEC-India*

9.1.1. *Why IPEC-India ?*

India is a one of the biggest pharmaceutical manufacturers. Hence, it is an important aspect to control the quality and safety of the excipients in India [9-10].

9.1.2. *Objectives of the IPEC-India*

The major objective is providing voluntary guidance and conducting programs to meet the appropriate highest standards for quality, safety and functionality of excipients throughout the manufacturing process and supply chain [9-10].

9.1.3. *Regulation of pharmaceutical excipients*

Pharmaceutical excipients are inert substances which are used as diluents or fillers or binders or vehicles for the development of drug formulations and are responsible for desired pharmacological actions. According to the regulatory guidelines that all the constituents of drug formulation should be complied and tested as per the cGMP regulations for safety and efficacy of the drug. The increasing focus on excipients is mainly due to the past incidents, where patients expired due to the contaminated excipients used by pharma companies (Table 1). Hence, the regulations have made that, it is the responsibility to use quality pharmaceutical ingredients in the manufacture of medications [11].

During manufacturing, contaminated or adultered excipients leads to failure of drug batches and it results in hazardous products, which are risky for patients and manufacturers. To eliminate the above risks, excipients must be manufactured, processed and packaged as per Current Good Manufacturing Practice (cGMP). Actually regulatory bodies have not developed regulations on cGMP conformance for excipients but developed for APIs i.e. ICH Q7A GMP. However, FDA is supporting the IPEC GMP guidelines for bulk pharmaceutical excipients. The quality of the excipients is important characteristic to the overall quality of the drug products. The drug product manufacturers are required to test every batch of the drug excipients as per 21 CFR 211.84(d)(2) for conformity with written specifications such as purity, quality and strength [11].

IPEC-India chapter was started in the month of April, 2014 as an associate member along with the IPEC-China [9-10].

10. Qualification of excipients to use in pharmaceuticals

IPEC is an international industry that contribute to the development and harmonization of standards i.e. qualification for the excipients (Figure 1). Regulatory bodies are increasingly focusing on qualification of excipients to be used in the manufacture of medications. The API itself can not perform as it desired without the excipients in the formulation. Hence, it could say that the excipients occupied a significant portion of the dosage form. Excipient manufacturers can also called as suppliers and most of the suppliers manufacturing the excipients to meet the basic requirements of food grade GMPs or ISO 9001 requirements but not compliant with the pharmacopoeia cGMPs. These excipients use in pharmaceuticals leads to high risk to pharmaceutical manufacturers and patients. Excipient suppliers who meet the IPEC specification add a little bit confidence for users but still require highest standards [Figure 2].

Excipients quality and safety goes beyond the of supply chain [12].

cGMP requirements for manufacturing and control

Table 1. Contamination cases leads to death.

Year	Country	Product	Contamination with	No. of deaths
1986-1996	India & Bangladesh	Paracetamol syrup	Diethylene glycol from propylene glycol origin	236
1990	Nigeria	Cough syrup	Solvents	47
1996	Haiti	Glycerine	Diethylene glycol	88
2008	Nigeria	Toothing formula	Diethylene glycol	84

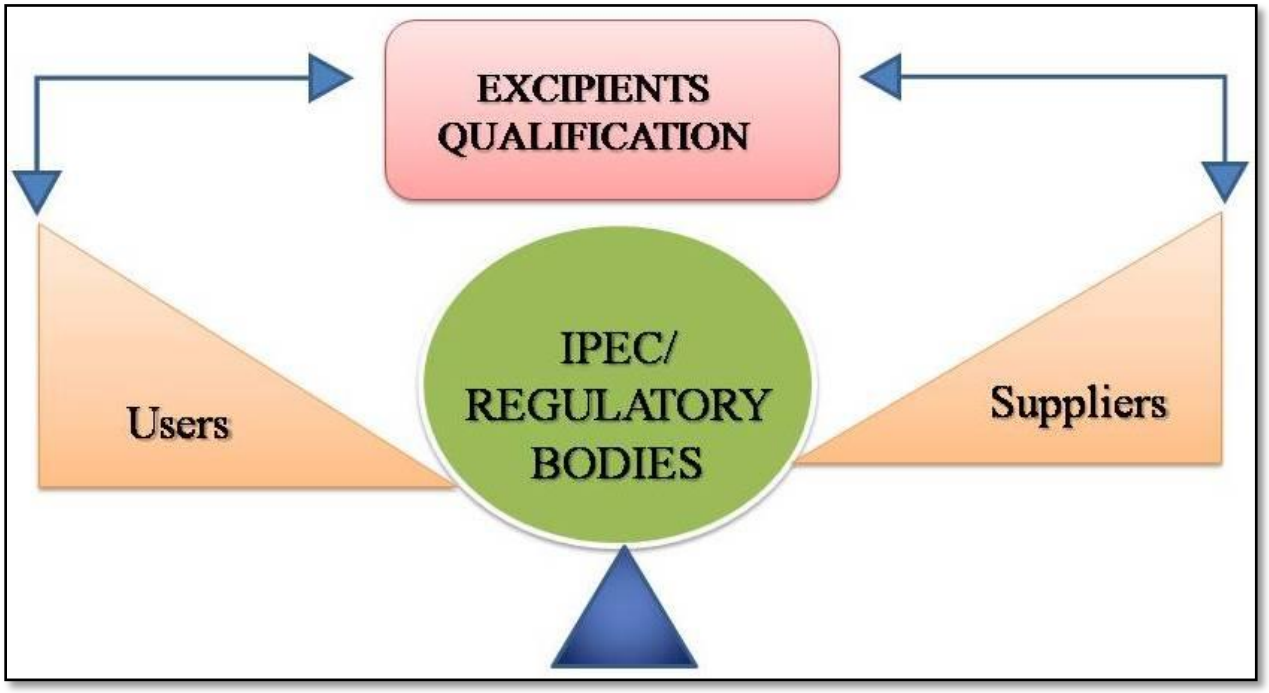

Figure 1. Process of excipients qualification and role of IPEC/Regulatory bodies.

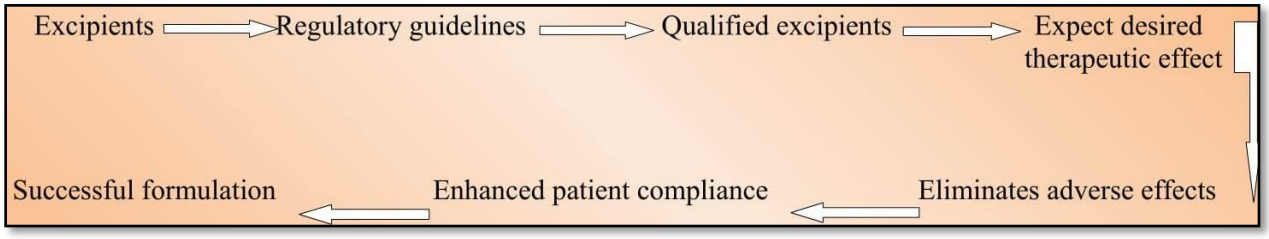

Figure 2. Process of making successful formulation with qualified excipients.

11. Excipients to be qualified

When the excipients manufactured according to the cGMP guidelines and complied with the specifications laid down by cGMP and IPEC, the excipients considered as qualified. It is also must that the quality and reliability of excipients should meet the expected quality required for the development of medication along with APIs [12].

12. Excipients to be disqualified

When the excipients compromised with the quality, efficacy and stability of the drug leading to product failure and patient risks, then those considered as disqualified excipients [12].

13. Global market

The market of global pharmaceutical excipients is a multimillion market. According to the Markets and Markets analysis, it is projected that the global pharmaceutical market will expand at 6.7% annually in the next 5 years and reaches USD 8.4 billion by 2019. It is also expected to reach 8.1 billion by 2021 and 8.23 billion by 2023 [13-14].

14. Conclusion

Excipients to be used in pharmaceuticals should follow the guidelines and specifications laid down by the regulatory bodies such as ICH, IPEC and cGMP. Hence, those will be considered as qualified excipients for effective use in the manufacturing of medications.

15. Conflict of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

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