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REVIEW OF REGULATIONS FOR NOVEL PHARMACEUTICAL EXCIPIENTS

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ABSTRACT

Excipients form a bulk of the finished dosage forms. They affect various properties in the finished products like patient acceptability, dissolution, bioavailability, rate of release of active ingredients etc. Now a day's many new means of drug delivery systems are coming up which require new excipients to improve the characteristics of the dosage form. Further new excipients are being discovered which are replacing the older ones by having better desirable characteristics. The novel excipients are developed in such a way that they are more compatible with the active ingredients but there are several hurdles in their development. The establishment of safety of novel excipients is a major hindrance in their development. The evaluation of novel excipients requires huge investments of time and money. As a result, pharmaceutical manufacturers are not interested in evaluating novel excipients in terms of safety and efficacy because any discrepancies in their use may cause delays in the approval of the formulations causing a major loss to the manufacturers. Also there are no well defined laws for their evaluation in most of the countries. However, the regulatory agencies worldwide have been trying to draft guidelines for the safety evaluation of the novel excipients and establish a procedure to review the novel excipients. The article reviews the guidelines drafted by regulatory authorities of USFDA, EU and the IPEC for the safety evaluation of the novel excipients and lays emphasis to make these guidelines mandatory before any new excipient is used commercially. Further a uniform procedure of evaluation of these excipients should be followed throughout the world.

INTRODUCTION: Novel excipients are defined as the ingredients that have been used for the first time in a human drug product or by a new route of administration [1]. The US FDA defines a New excipients as any inactive ingredients that are intentionally added to the therapeutic and diagnostic products, but that: are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g. enhance absorption or control release of the drug substance); are not fully qualified by the existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration [2]. As per Japan, a substance qualifies to be a new excipient if; An approved food additive is used as an excipient in a product that will be administered orally, or if an approved cosmetic substance is used as an excipient in a pharmaceutical product that would be applied externally, then the substance must be treated as a new excipient if there is no prior instance of use as a pharmaceutical excipient. Even if there is no precedence of use in a pharmaceutical product overseas, if there are no prior instance of use in Japan, the substance is treated as a new excipient, and Even if there is a precedent for use

of a substance as a pharmaceutical excipient in the Japanese market, it will be treated as a new excipient when its route of administration differs from prior instance of use, or when its dose level exceeds that of prior instance of use [3].

The European Union drug regulatory authority, EMEA defines novel excipients as excipients which are being used for the first time in a drug product, or by a new route of administration. It may be a new chemical entity (NCE) or a well established one which has not been used for human administration and/or for particular human pathway in the EU or outside EU [4]. There are a number of conditions set out by the regulatory authorities to allow for the use of an excipient that has not previously been used before.

One of the primary requirements for the new excipients to be used in drug products is the establishment of its safety. The excipients used for the first time should be safe for use in drug products for human use .All excipients are not inert in nature; some have been shown to be toxic. It is important to perform risk-benefit assessments on proposed new excipients in drug products and to establish permissible and safe limits for these substances. The Federal Food, Drug, and Cosmetic Act of 1938 was enacted after the tragedy of the elixir of sulfanilamide in 1937 in which an untested excipient was responsible for the death of many children who consumed the pharmaceutical [5].

The Act required manufacturers to perform safety testing of pharmaceuticals and submit new drug applications (NDAs) demonstrating safety before marketing. Since that time, the USFDA has become aware that certain other excipients used in commerce can cause serious toxicities in consumers of prescription and over-the-counter (OTC) drug products in the United States and other countries.

United States of America: The US FDA has issued guidance on non-clinical studies for new excipients to establish the safety of the new excipients to be used in dosage forms entitled “Non Clinical Studies for the Safety Evaluation of Pharmaceutical Excipients”. The guidance helps in assessing the safety of a chemical for use as an excipient. The manufacturer of a new or novel excipient should develop the safety information recommended in these guidelines appropriate to their intended use. The guidance is concerned with the development of safety profiles to support use of new excipients as components of drug or biological products.

1. **OTC Products:** For the OTC products, 21 CFR 330.1(e) requires the following condition to be fulfilled: “The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 721 of the act and subchapter A of this chapter.”

2. **Generic Products:** The USFDA requires that the generic drug products intended for parenteral, ophthalmic, or otic use should contain the same excipients in the same concentrations as the reference listed drug product, with the exception of buffers, antioxidants, and preservatives, provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product. For other routes of administration (e.g., topical dermal, oral), there is no requirement that the excipients in the final formulations be the same as those in the reference listed drug product, although the applicant must demonstrate that the inactive ingredients do not affect the safety or efficacy of the proposed drug product.

3. **New Drug or Biological Product Application:** For new products, the required supporting data can be placed in application directly or in a drug master file (DMF) [6].

Strategies recommended supporting marketing of new Excipients in Drug Products:

1. **Safety Pharmacology:** The pharmacological activity of all potential new excipients is evaluated using a battery of standard tests according to ICH guidance for industry, S7A

Safety Pharmacology Studies for Human Pharmaceuticals. These evaluations can be performed during the course of toxicology studies or as independent safety pharmacology studies. It is useful to obtain these data at an early point during the safety evaluation of an excipient, since, if the excipient is found to be pharmacologically active, this information can influence subsequent development.

2. **Potential Excipients intended for Short-Term Use:** New excipients intended for use in products that are limited by labeling to clinical use of 14 or fewer consecutive days per treatment episode and are infrequently used include the following types of studies;

   Acute toxicology studies, Toxicokinetics & Pharmacokinetics of an excipient, Standard battery of genetic toxicology, 1-month repeat-dose toxicology studies are performed in both a rodent species and a mammalian non-rodent species by the route of administration intended for clinical use. It includes complete clinical pathology, histopathology, and toxicokinetic analysis and Reproductive toxicology

3. **Potential Excipients intended for Intermediate use:** New excipients intended for use in drug products that are labeled for clinical use of more than 2 weeks but less than or equal to 3 months per treatment episode include at least the following;

   All tests of safety pharmacology & intermediate use except of 1-month repeat-dose toxicity studies, 3-month repeat-dose toxicology studies are performed in both a rodent species and a mammalian non-rodent species by the appropriate route of administration. It is important that the studies include complete clinical pathology, histopathology, and toxicokinetic analysis and Additional studies like studies involving parenteral administration

4. **Potential Excipients intended for long-term use:** New excipients that are intended for use in drug products labeled for clinical use of more than 3 months in a given patient (either as a single treatment episode or as a result of multiple courses of therapy to treat a chronic or recurrent condition) include at least the following tests;

   All tests of safety pharmacology, short term and intermediate use. 1-month and 3-month toxicology studies are not essential, but may provide useful dosage selection data, 6-month repeat-dose toxicology study is performed in a rodent species by the appropriate route. It includes complete clinical pathology, histopathology, and toxicokinetic analysis. FDA recommend that studies that involve excipients of low toxicity in general use the limit dose as the highest dose for testing.

   If toxicity and pharmacologic effect were absent in state-of-the-art sub chronic studies, a 6-month study may be sufficient. When toxicity is detected in shorter duration studies, or in rodents, a chronic study in non-rodent of 9 to12 months may be appropriate, Carcinogenicity studies according to ICH.

5. **Potential Excipients for use in Pulmonary, Injectable, or Topical Products:** Safety Pharmacology, Short term use, Intermediate use, and Long term use as appropriate, using the appropriate route of administration studies should be conducted. Studies of the to-be-marketed formulation of the drug product are preferred, if this information is available at the time of excipient evaluation, Sensitization study (e.g., guinea pig maximization study or murine local lymph node assay).

   For excipients intended for injectable use, the following considerations may be appropriate:

a) An *in vitro* hemolysis study could be performed at the intended concentration for I.V. administration (bolus and/or infusion) to determine the hemolytic potential.

b) The plasma concentrations of creatinine kinase determined at the intended excipient concentration for I.M. or S.C. administration can provide information on potential muscle damage.

c) Protein binding evaluation in relation to local site tolerability could be done.

- Excipients intended for topical use may require data support from toxicology studies by both the intended clinical route and the oral or Parenteral route if clinical pharmacokinetic studies conducted under conditions of maximum exposure show patients would experience systemic exposure to the excipient or its metabolite, particularly if limited systemic exposure were observed in nonclinical studies conducted by the clinical route of administration.

- For topical dermal products and ophthalmic products, an ocular irritation study can be conducted.

6. **Photo Stability Testing:** FDA recommends that excipients be evaluated regarding the need for photo safety testing as described in the CDER guidance for industry Photo safety Testing. Either the excipient or the complete drug product could be tested [6].

The European Union: The IPEC Europe Safety Committee has published a similar guideline for the evaluation of safety of the potential novel excipients. In the Europe, the information about the novel excipient to be used in the dosage form is to be provided in the application for marketing authorization application by the applicant. The information to be included by the applicant is according to the guidance entitled "guideline on excipients in the dossier for application for marketing authorization of a medicinal product".

Following information is to be submitted:

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

a. A detailed description of the excipient, its function and its conditions of use is to be provided. If the excipient is complex or consists of a mixture of compounds, the composition should be specified in qualitative and quantitative terms.

b. For novel excipients and for excipients presented as a mixture of compounds the following should be taken into consideration:

- Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.

- The Community provisions concerning additives in foodstuffs: any criteria which are based on the toxicological data, with cross-references to these data. The quality specifications which have been laid down in the directives are satisfactory as long as the routine control tests used are validated.

- The international specifications (FAO/WHO/JECFA), and other publications, such as the Food Chemical Codex.

- For medicinal products for cutaneous use, data on the ingredient used in cosmetic products.

- Data concerning the toxicology of the novel excipient according to the dosage form and the route of administration of the medicinal product in Module 4, the safety section of the dossier.

c. Documentation on chemistry of excipients is required for all novel excipients, taking as its basis the CPMP Guideline on the Chemistry of New Active Substances and should include:

- The origin of the excipient, including the name and address of manufacturer.

- A general outline of the manufacturing and purification procedures.

- Structure.

- Physical, chemical properties, identification and purity tests.

- Validated methods of analysis with a presentation of batch results.

- Miscellaneous information (microbiological tests, etc).

- Contamination, presence of foreign substances, residual solvents, etc.
- In the case of an excipient obtained from a mixture of several components, the quality of each component and the Physico-chemical tests for the mixture should be described.
- Stability data should be provided as required for the active substances [4].

Novel Excipient Evaluation Procedure: A big investment is required to bring a novel excipient to the market, thus they novel are not finding their way into drug products. Most of the drug manufacturers rely on using excipients already approved in their drug products for their formulation needs. Under current drug approval processes, novel excipients are only reviewed as a part of the drug application containing the excipient. There is no regulatory approval process specifically for a new excipient as an individual molecule. In 2007, the IPEC- Americas Safety Committee proposed and developed the IPEC Novel Excipient Safety Evaluation Procedure.

This is an independent excipient review procedure which was anticipated to reduce the cost and uncertainty related to the use of novel excipients in pharmaceutical formulations and encouraging their use in drug-development programs and providing a needed boost to drug formulation innovation. The Aclairo Pharmaceutical Development Group (Aclairo PDG, Vienna, VA) manages the Novel Excipient Evaluation Committee (NEEC), an independent expert group of IPEC charged with conducting the safety evaluations of new excipients. Solutol HS 15 has been successfully evaluated by the review group and is in the process of reviewing others [7].

Review Procedure: The primary function of NEEC is to evaluate compliance of excipient data with the FDA guidance on safety evaluation and to make recommendations to the excipient manufacturer. The expert committee is independent of the IPEC Americas Safety Committee. It is comprised of three experts in general toxicology and members having experience in industrial, academic, or regulatory toxicology, including experience in toxicology laboratories.

An excipient safety dossier in the format of common technical document (CTD) is submitted to Aclairo PDG. The PDG sends it to the expert committee chairperson, who in turn distributes it to other committee members. Review takes about one to three months. The chairperson after receiving the comments of the committee members writes a draft report that is sent to each member for further discussion.

Once agreement is reached, the final draft is sent to the excipient sponsor for review and comment. If the expert committee cannot reach agreement on one or more points in the final draft, the sponsor is told about the disagreements and the reasons for them. The sponsor may discuss the final draft with the expert committee, request clarifications or explanations and when satisfied, the final report is signed by the chairperson and sent to the sponsor who is the sole owner of the committee report.

The committee report contains at a minimum:

1. A discussion of chemical and toxicological data and human safety concerns based upon intended use of the excipient.
2. Opinions on conformance with data needs according to the FDA guidance on safety evaluation for excipients.
3. Identification of any data gaps.
4. Points of reviewer disagreement if not resolved with the reasons identified in the final draft.

The panel's activities are managed by a consultant on a fee- for- service basis. The interested excipient manufacturer, through direct discussions with the consultant, provides the consultants with a table of contents and summary of the expected studies needed for a review. The consultants then provide a cost proposal and time frame based on expected time of review and the expert's hourly fee. The consultant provides the manufacturer with the report after the evaluation. The report can be included in the sponsor's DMF or given directly to the product applicant.

IPEC plays no role in the process but only tracks the number of reviews. The evaluation procedure is kept confidential between the sponsor and the panel. Till date, one submission has been received by the IPEC

procedure for the review and several others are in planning stages. This procedure may prove to be a remedy to the regulatory problem for the development of the new excipients [8].

CONCLUSION: Novel excipients have not been able to find a suitable position in the pharmaceutical industry till today. These cannot use the established procedures like Pharmacopoeial monographs and certificates of suitability for their review as more detailed information about these novel materials is required by the reviewers to establish their safe use. The current system for novel excipients review is inadequate. There are only a few regulations for establishing their safety so that they can be easily used in the drug products. The lack of regulatory mechanisms for reviewing new excipients is a hindrance to the development of innovative, new pharmaceutical products. There is a need to overcome this situation and develop measures to facilitate and standardize excipient review so that the advantages of novel materials can be utilized. Thus, regulatory mechanism and harmonized global standards are required for the development of the novel excipients to bring revolution in the pharmaceutical industry.

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