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Call for stricter regulatory oversight of excipients

OUR BUREAU, MUMBAI

PHARMACEUTICAL experts have called for stricter regulatory oversight of excipients with a view to avoid unwanted side effects and interactions with the medicines.

Excipients in pharmacological dosage forms have well-defined functional activities. Modulating active pharmaceutical ingredients' (APIs) solubility and bioavailability, improving active ingredient's stability in finished dosage forms, maintaining pH and osmolarity of liquid formulations, acting as an antioxidant, emulsifying agent, aerosols, tablet binders, disintegrates, lubricants and diluents are among their many functions.

In the past the adverse drug reaction of excipients was overlooked. Now the system has changed entirely. The selection of excipients has become an important part of deciding drug formulations. Excipients' intercompatibility may alter physical, chemical, microbiological, therapeutic properties of drugs in its dosage forms.

For instance, Cofset-AT, a cough syrup manufactured by Kala Amb-based Digital Vision pharma company which has the presence of excipient diethylene glycol caused renal failure to a two-year-old girl. Similarly, there are reports of cardiotoxicity induced by excipient propylene glycol.

"Excipients are crucial partners in a dosage form and impact the formulation's qualities. Excipients were once thought to be inactive components; however, it has now been discovered that they can have substantial adverse effects. However, compared to APIs, the regulatory supervision over the use of excipients is still unclear. Excipients require strict regulation and laws to avoid side effects," said Dr Sanjay Agrawal, a leading pharmaceutical consultant.

Excipients should undergo numerous evaluations before being included in a formulation, such as toxicity tests, preclinical studies, compatibility studies, and so on, said Dr Agrawal.

He called on regulatory agencies and industries to evaluate excipients in the same way that APIs are considered.

Excipients which have a vital role in ensuring the active principle's dose, stability, and bioavailability are the essential portion of a drug in terms of its weight. The components used as excipients must have the properties required by this technical purpose, and must also meet appropriate safety requirements, as with any substance delivered to humans. The importance of assessing the excipient's potential adverse effects was overlooked in the past, he stated.

Excipients are now more than just fillers in a dosage form; they can also be actual partners of APIs, with the ability to improve or degrade performance. Excipients must meet regulatory standards before being utilized in a particular dosage form. Several organizations have issued exclusive development, manufacturing, and control guidelines. Some of the studies looked at safety testing for new excipients and existing excipients with a new application, Dr Agrawal added.

Pharmaceutical companies are increasingly focusing on developing excipient ingredients in challenging medication formulation. The growing demand for more complex excipients and new applications for existing ones has fuelled these advancements. The first consideration is the material's safety. It is because pharmaceutical excipients are no longer considered inert chemicals, it is critical to understand their safety and efficacy, said Anshu Yadav, another pharmaceutical expert.

The use and safety of current and new excipients are now a priority in developing new drugs. Chemical, manufacturing and preclinical data are critical considerations in excipient's development. Substances emerging from a structural alteration of an 'authorized' excipient, a recognized food additive, a structurally modified food additive, or a constituent of an over-the-counter (OTC) drug are examples of new excipients from the intermediate category, he added. ❍

Eight year high

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registered for the year 2017-18, at $17.28 billion. The year 2018-19 has seen a growth of 10.72 per cent to $19.13 billion compared to the previous year, 2019-20 with a growth of 7.37 per cent to $20.58 billion, before hitting an eight year high or 18.19 per cent growth to $24.47 billion in the year 2020-21.

However, the country has been facing challenges in terms of availability of APIs, intermediates and key starting materials (KSMs), and depended on China for many of the key ingredients. In the wake of Covid-19 pandemic impacting global supply chain for various materials including the key raw materials for essential medicines and the resultant price increase, the Government of India has decided to increase the domestic production of APIs, drug intermediates and KSMs, also to reduce India's dependency on other countries for critical inputs and bulk drugs in the long run

This include the scheme on promotion of bulk drug parks for financing common infrastructure facilities in three bulk drug parks with financial implication of Rs. 3,000 crore for next five years, production linked incentive (PLI) scheme for promotion of domestic manufacturing of critical KSMs/drug intermediates and APIs and for domestic manufacturing of pharmaceuticals, among others, said the Minister in Lok Sabha. ❍

Much needed flexibility

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amendments for the API and intermediates as single category instead of individual products in order to provide flexibility to the industry to change the raw material mix and product mix within the sanctioned pollution load.

The memorandum stated that henceforth all the Expert Appraisal Committees (EACs) or State Expert Appraisal Committees (SEACs) shall appraise the proposals for prior environmental clearance under the provisions of EIA Notification, 2006 and subsequent amendments under the category of the schedule of EIA Notification, 2006 for the API and intermediates as single category instead of individual products. Accordingly, the EAC/SEAC shall clearly recommend the permissible pollution load i.e. quantity, quality and composition of emissions, discharges and solid waste generation from such activity for inclusion in the prior environmental clearance.

"Similar amendments are needed in case of Consent to Establish (CE) and Consent to Operate (CO), both of which are issued by the states. EC is just the first stage in the prior requirements before a manufacturer is able to make any "changes" in the unit. Unless similar exemptions are also forthcoming as regards to CTE & CTO, the intended benefit of providing flexibility to manufacturers to quickly adapt to the changing needs of the market will remain only on paper, stated IDMA.

The industry body has recently made a representation to GSPB appealing to it to make appropriate changes to CE and CO so the consents can also be issued in the same way as EC in the common terminology of "API & intermediates" so as to provide Gujarat API manufacturers much needed flexibility once again.

"EC is just the first step in the various permissions needed for a unit to operate and discharge treated effluent. Without back up of similar legislation allowing consents to be issued as "API & intermediates", at the state level the concept of immediate change over will remain only on paper, as the consents will still continue to be issued in names of individual products. For change of product mix, the laborious task of amendment to the consents will defeat the purpose of allowing just the EC to be issued in the general name of API & intermediates," it stated.

India has been overly dependent on China for bulk drugs (APIs) and key intermediates, which has been rightly identified by the central government as a threat to national medicine security. ❍