Allowable levels of excipients in drug products

Medicinal products typically cannot be manufactured without using excipients. Here, Dave Elder and Fabio Faïs discuss factors for excipient selection and the importance of defined allowable limits to ensure continued product safety.

According to the US Food and Drug Administration's (FDA's) 21 CFR 210.3(b)(8) guidance, an excipient or inactive ingredient is any component of a drug product other than the active ingredient. However, this view is almost certainly outdated and limited.

Excipients typically influence a variety of critical quality attributes and process parameters of a drug product and can often be used to enhance oral bioavailability, modifying both drug solubility and permeability; particularly for BCS (Biopharmaceutical Classification System) class III or IV compounds. Excipients can also have multiple functions in a formulation or in different delivery systems. For example, hydroxypropylmethylcellulose (HPMC or hypomellose) can be used as a coating agent or binder in solid oral dosage forms; as a suspending agent in oral suspension products; as an intra-nasal products.

Excipients endow formulations with stability or else allow a more effective and safe delivery option and are typically classified into functional categories, which are dependent on the medicinal product. For example, in tablets they are classified as diluents/fillers, binders, lubricants, glidants, etc. Excipients can also have multiple functions in a formulation or in different delivery systems. For example, hydroxypropylmethylcellulose (HPMC or hypomellose) can be used as a coating agent or binder in solid oral dosage forms; as a suspending agent in oral suspension products; and as a viscosity-enhancing, mucoadhesive in intra-nasal products. Innovation in drug products can also be driven by formulations with atypical levels of known excipients or established oral excipients via a different delivery route or novel excipients. Regulators regard novel excipients as new substances and this constitutes an important barrier to development of innovative drug products. No general well-defined principles exist for selection of the most appropriate excipient, or its most appropriate grade or supplier. Commonly, these decisions are based on “institutional preconceptions” or personal experience. Having selected the excipient, grade and supplier, the formulator must decide the level of the excipient within the formulation. Selecting the optimal amount requires experience, pharmaceutics textbooks – including the Handbook of Pharmaceutical Excipients – which are both useful and relevant; but often the only true way is through Design of Experiments (DoE). Additionally, other important factors for excipient selection include the existence of regulatory dossiers or master files (MFs) and previous use of the excipient via the intended route of delivery, duration and allowable levels. The FDA’s Inactive Ingredient Database (IID) provides information on excipients that are present in FDA-approved drug products, and this information is clearly an aid in drug development. If a particular excipient was approved in a certain dosage form at a certain level, a sponsor could consider it safe for use for a similar type of product. Unfortunately, there are known issues with this database: “Incomplete and inaccurate information as well as discrepancies in nomenclature related to inactive ingredients have impacted the ability of Abbreviated New Drug Application (ANDA) applicants to make timely and high-quality submissions”. In an effort to address these shortcomings, “by 1 October 2020, the FDA will complete enhancements to the IID so users can perform electronic queries to obtain accurate Maximum Daily Intake and Maximum Daily Exposure information for each route of administration for which data is available. The FDA will update the IID on an ongoing basis and post quarterly notice of updates made. Such notices will include each change made and, for each change, the information replaced”. From a European perspective, it is a concern that the European Medicines Agency (EMA) has not developed a similar system, as this would help innovator companies and specifically formulators immensely. An excipient database that also covered drug products in development and classified the safety data available for each excipient based on what regulators might reasonably expect at the time of submission, which covered the highest allowable levels of established excipients or defined allowable limits for established excipients via new administration routes, would be invaluable.

References

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Dave has nearly 40 years of service within the pharmaceutical industry at Sterling, Syntex and GlaxoSmithKline. He is now an independent GMC consultant. He is a visiting professor at King’s College, London and is a member of the British Pharmacopoeia. He is a member of the Joint Pharmaceutical Analysis Group (JPAG) and the Analytical Division Council of the Royal Society of Chemistry.

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