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FDA evaluation of excipients in generics Posted 23/10/2015

Generics may differ from their reference product in terms of inactive ingredients, e.g. excipients, provided this does not affect the safety and efficacy of the product. Authors from the Office of Generic Drugs at the US Food and Drug Administration (FDA) highlight general toxicology concerns caused by such formulation differences between generic and originator drugs [1].

An excipient is a natural or synthetic substance formulated alongside the active pharmaceutical ingredient (API) of a medication and included for the purpose of bulking up formulations that contain potent active ingredients (thus often referred to as 'bulking agents', 'fillers' or 'diluents').

Ideally, excipients do not have any significant effect in the human body at the maximal intended doses (of the API). They are therefore referred to as 'inactive ingredients'. Excipients may, however, play other important roles in a drug product, such as enhancing the solubility, stability, shelf life and palatability of the API. Like all chemicals, excipients are potential toxins and, historically, some have exerted toxic effects in humans.

Excipients are not independently evaluated during the review of originator or generic products. They are reviewed in the context of the drug product containing the particular excipient. Due to the lack of an independent approval process for specific excipients, FDA has published guidance on evaluating excipient safety in drug products:

Nonclinical studies for the safety evaluation of pharmaceutical excipients
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

With respect to generics, all applications undergo review from a Chemistry, Manufacturing and Controls, and Bio-equivalence perspective. Though a generic drug formulation may differ from the reference drug, not all formulation differences raise safety concerns.

The manufacturer can consult the inactive ingredient database (IID) for information on excipients used in FDA-approved drug products. The IID is publicly available and is maintained by FDA to provide information regarding excipients to pharmaceutical industry stakeholders. For a specific excipient in FDA-approved products, this database provides the highest amount (maximum potency) present per unit, route of administration and dosage form.

Many generics submissions do not undergo a non-clinical comparative safety assessment because they conform to FDA and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) standards and use excipients in contexts that are supported by previously approved products. Cases where a comparative safety evaluation is required include:

- an excipient that is not documented in the IID
- higher levels of excipients than the levels proposed in the IID
- an excipient is present in IID but is proposed for a different route of administration
- an excipient with a synergistic (or) an opposing effect compared with the API.

In such cases a 3-step approach is used:

Step 1: Evaluation of published non-clinical studies (*in vivo* animal studies and *in vitro* culture systems) performed using the excipient of interest.

Step 2: Analysis of the clinical precedence of the excipient in question. For this, the IID is consulted to determine if the excipient is being used in any currently marketed drug products. Products with the same route of administration are considered for reference.

Step 3: Assessment of the reference drug label to compare the risk associated with changing the formulation in the generic product.

Each proposed use of an excipient in a generic drug is considered on a case-by-case basis, with factors such as route of administration, duration of use and target population for the proposed indication considered when evaluating comparative risk.

Conflict of interest
The authors of the research paper [1] did not provide any conflict of interest statement.

Disclaimer: The ideas and views provided in the research paper [1] are the opinions of the authors and do not reflect any official policy of the FDA.

Related article
Formulation differences between generics and reference products

Reference
1. Rayavarapu S, et al. Comparative risk assessment of formulation changes in generic drug products: a pharmacology/toxicology perspective. Toxicol Sci. 2015;146(1):2-10.

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