Strategies to Evaluate Over-the-Counter Drug Degradants

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1252
Workshop Session: Active Ingredient Degradation: Process and Challenges in Identification, Toxicological Limit Determination, and Regulatory Submission
Convention Center
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Abstract:
While the United States Food and Drug Administration (US FDA), United States Pharmacopeia (USP), and International Council on Harmonisation (ICH) have provided general guidance on the safety evaluation and qualification of drug degradants in prescription drugs, there is less guidance on how to set degradant specifications for older over-the-counter (OTC) drugs regulated under the FDA OTC monograph system. Considering that formal processes to qualify the safety of drug degradants and establish safety-driven drug degradant specification limits were not historically included in original OTC monograph submissions, a need to develop a weight of evidence (WOE) approach to qualify OTC degradants in support of the 3Rs was identified. Therefore, a framework integrating existing public and proprietary empirical data, in addition to NAMs-based data from in silico predictions and read-across, was developed to support safety of eight data-rich and data-poor degradants associated with five OTC cough and cold actives including phenylephrine, chlorpheniramine, dextromethorphan, doxylamine, and guaifenesin. Extending beyond typical animal-based approaches used to support degradant safety per ICH Q3A and Q3B, integration of in silico predictions and read-across strategies supported safety substantiation of data-poor degradants without the need to generate additional in vivo data. Based on upper-end degradant exposures (i.e., assuming degradant levels of 1-4% of the maximum daily doses of each case study drug and 10th percentile body weight data for pediatric patient groups per use described in 21 CFR), children were recognized as having the highest potential exposure relative to adults per body mass.

As part of the WOE, identified hazard data were considered in the context of anticipated exposure data for all intended patient populations to assess potential risk depending on data availability and relationship to the parent Active Pharmaceutical Ingredient (API) (i.e., known metabolite of API; close structural and anticipated mechanistic similarity), margins of safety (MOS) or exposure margins were calculated for each degradant. Overall, findings supported degradant safety, and indicated that this contemporary WOE approach could be utilized to assess historical OTC degradants with varying levels of empirical data.