Toward Best Practices for Read-Across in Evaluation of Drug Impurities, Extractable, and Leachable Compounds

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Abstract:
Formal read-across (RA) guidance and approaches have been implemented by the ECHA Read-Across Assessment Framework (RAAF), U.S. EPA Generalized Read-Across (GenRA), and others for use in the assessment of data-poor industrial chemicals, waste compounds, consumer products, cosmetics, and pesticides. Throughout the drug development process, scenarios for which RA might be implemented have also been identified, including endpoint-specific evaluation of drug impurities and assessment of extractable/leachable compounds for which adequate toxicity data may not exist. However, current frameworks and tools are not tailored explicitly for purposes relevant to analysis of these compounds, and publicly available, fit-for-purpose RA guidance is lacking from major regulatory agencies including U.S. FDA and EMA. Therefore, a need exists to implement robust formalized processes to use RA in pharmaceutical risk assessments. To address this gap, we describe implementation of existing RA frameworks and tools for drug impurities and leachable/extractable compounds in a series of case studies. The first describes the overall approach used to evaluate the carcinogenic and genotoxic potential of a drug impurity based on identification and assessment of potentially reactive substructural features present in the impurity, and related analogs, using the OECD QSAR Toolbox. The second case study focuses on tools used to identify an appropriate analog for oxidized Irgafos 168 derived from a drug container closure system for the purpose of deriving a safe daily exposure limit. In addition to RA framework implementation, the following topics are considered: