EDITORIAL

Evaluating mutagenic impurities of pharmaceuticals

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The genotoxicity screening during non-clinical development of pharmaceutical products mandates a rigorous drug testing approach in accordance to ICH M3 (R2) and S2 (R1). Prominently these harmonization guidelines points for the bacterial reverse mutation assay (Ames test) as initial requirement for every new drug submitted for approval. In addition to the novel drug or active pharmaceutical ingredient including their impurities, intermediates or residues generated during the process must also be characterized and evaluated for their mutagenic potential (1). It is evident that Ames test holds the key to impurity qualification of suspected genotoxic impurities. The outcomes of Ames test compilations have significantly contributed to knowledge databases for *in silico* genotoxicity prediction and depend on its positivity for sensitivity since those findings enjoy a good correlation with carcinogenicity data for genotoxic carcinogens and non-carcinogens. Currently there are several *in silico* computational toxicity prediction tools available which have abundant proprietary and non-proprietary information of various compounds from previous gene mutation experiments.

Usually evaluation of genotoxicity is routinely considered for impurities above the qualification limits in accordance to ICH Q3 harmonized guidelines. Owing to this European Medicines Agency (EMA) had come up with a FAQ type list of Question and Answers in the year 2007 that covers issues such as TTC (Threshold of Toxicological Concern) approach; ALARP (as low as reasonably practicable) and limitations of genotoxic impurities. Meanwhile the need was genuinely felt for a comprehensive recommendation aimed at testing approaches during impurity assessments of drug substance and compounds related to drug substance. Not after much speculations, a prospective guideline was rolled out as ICH M7, a draft consensus document (Step 2) in the year 2013. Finally this ICH M7 guideline "Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Carcinogenic Risk" was adopted in 2014 which now provides basis for assessment and control of DNA reactive impurities in pharmaceuticals. This took a step forward in defining the regulatory application of in-silico predictions in order to minimize the risk of human exposure to DNA reactive chemicals and replace or reduce in-vitro studies. The basic purpose of this guidance is to provide a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. Besides that it is also intended to complement ICH Q3A, Q3B and M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. Nevertheless structural alerts to support prediction of genotoxicity have been available for more than 30 years (2). In particular when no adequate experimental mutagenicity or carcinogenicity data is available computational toxicology or QSAR (Quantitative Structure Activity Relationship) techniques can utilize the structure of a chemical for alert predictions. QSAR have become a high-throughput alternative for assessment of potentially mutagenic impurities and emphases on probability of DNA reactivity.

The ICH M7 guideline basically describes the need for two predictive systems, one as expert rule-based and the other statistical based simultaneously by applying two different methods. The analysis of mutagenic hazard identification leads to assignment of each impurity to one of the five classes described in Table 1 of the guideline along its controlling strategies. If a structural alert is predicted, an Ames testing is required as follow up action for Class 1 to 3 assigned impurities, conversely if no positive alerts are fired the impurity falls within Class 4 or 5 demanding no further action. The combination of more than one system in tandem increases the sensitivity and minimizes false negative predictions, with an expert system, which are stored as knowledge, based on rules or facts then after retrieved by reasoning. Whereas the statistical based system is driven by the data having final output from a statistical-based system which is derived from database from training sets available to them (3). ICH M7 have enabled the development of predictive *in silico* models with sufficient accuracy and transparency to support expert review which is frequently performed to further strengthen or over-rule keeping in view any additional data or simulations. The ICH M7 guideline is currently being implemented throughout the pharmaceutical industry to fulfill regulatory requirements (4).

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