Regulatory genotoxicity: from the bench to the Dossier

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Genotoxicity assessment is a key point in the development of new substances in pharmaceutical, chemical, agrochemical and cosmetic industries. There are currently international regulations which establish how and when this assessment has to be done. Almost in all cases, positive results in genotoxicity assays mean a red flag and normally the compound does not continue in development.

As example, in the particular case of pharmaceutical industry, there are two main areas of genotoxic evaluation, 1) related to the active ingredient. This area is mainly regulated by ICH S2(R1) *Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use* and ICH M3(R2) *Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals*. These guidelines regulate the timing and the kind of assays to be performed. In a standard approach 2 *in vitro* studies (Ames + one with mammalian cells) prior to the first Phase I clinical trial and an *in vivo* study (usually a micronucleus test in rodent) prior entering in Phase II is the standard battery of assays. 2) related to the genotoxic assessment of impurities, this area is mainly regulated by ICH M7 *Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.* Impurities present in a pharmaceutical product may have pharmacological, toxicological or/and genotoxic potential even at very low doses as the majority of the impurities are generated in chemical synthesis processes, then are highly reactive. Not only the known impurities but also the putative ones should be evaluated in a step-by-step approach.

These guidelines also define follow up studies in case of contradictory results and allow, in the case of impurities, a cross assessment of the genotoxicity potential based on QSAR approaches. Similar guidelines regulate other industry sectors.

In summary, genotoxicity is an inherent property of a compound which has to be assessed. Overall, understanding the mechanisms behind the genotoxicity potential does not mean to lower the red flag from a regulatory point of view.