Follow-up to a positive genotoxicity study result: when science meets regulation criteria. Case study

D. López Ribas

Innoqua Toxicology Consultants, S.L., Barcelona, Spain
E-mail: dlopezribas@innoqua.net

Genotoxicity assessment is a key point in the development of new substances in within the pharmaceutical industry. There are currently international regulations which establish how and when this assessment has to be done. Almost in all cases, positive results in a genotoxicity assays mean a red flag and "stop the engine". ICH S2(R1) *Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use* defines several follow-up scenarios after a positive result in order to rule out (or confirm) its relevance to humans.

This case study describes the strategy followed after obtaining a positive result in an *in vitro* Mouse Lymphoma Assay which showed an increase in mutation frequencies at several concentrations after 24 hours of exposure in the absence of S-9 mix. Other genotoxic studies (*in vivo* and *in vitro*) performed with this pharmaceutical within the standard battery defined by ICHS2(R1) were negative.

Similar positive findings in *in vitro* studies and positive results in an *in vivo* comet assay performed as part of a 2-week repeated dose toxicity study are described in the literature for other members of this chemical/pharmacological family. This family is also a known group of substances which can induce reactive oxygen species (ROS), known to responsible for damaging DNA and inducing cytotoxicity.

The information from the literature and the regulatory requirements were combined to define a customized *in vivo* comet assay where 1) toxicokinetic samples were also collected to state an exposure threshold of action, 2) the assessment for oxidative damage to DNA was incorporated by measuring 8-OH-dG adducts, and 3) genotoxicity assessment was performed on liver and GI.

Fortunately this study showed negative results, the "drug development engine" was restarted and this pharmaceutical has been allowed to progress in clinics with no comments on the genotoxicity from FDA or EMA.

S1.01