Pharmaceutical genotoxicity testing: regulatory testing and strategies for early candidate selection

Antonio Guzmán

Toxicology Department, Esteve. Parc Cientific de Barcelona. Baldiri i Reixac, 4. 08028 Barcelona, Spain.

Toxicology testing is a pivotal component of the drug discovery and development process, and allows to characterize the toxicological properties of the drug candidate and assess its potential to produce adverse effects in humans. Testing for genotoxicity aims at identifying the potential to cause DNA damage, which is considered essential for the induction of carcinogenesis and hereditary defects. Compounds that are positive for genotoxicity are considered to be potentially human carcinogens and/or mutagens. Because of its relevance for human safety, genotoxicity testing of pharmaceutical drug candidates is regulated by an extent of national and international guidelines. The ICH Guideline S2(R1) plays a central role in regulatory genotoxicity testing, as it establishes the requirement that pharmaceuticals are assessed for genotoxic potential in a "standard battery" of *in vitro* and *in vivo* assays, there being two options. Option 1, requires the conduct of (1) an *in vitro* test for gene mutation in bacteria (usually the Ames test), (2) an *in vitro* mammalian cell genotoxicity test (either a cytogenetic test for chromosomal damage or a mouse lymphoma *Tk* gene mutation assay, and (3) an *in vivo* test, generally for chromosomal damage in rodent hematopoietic cells. In Option 2, the *in vitro* mammalian cell assay is replaced by a second *in vivo* assay, or by including a second endpoint for assessment in the rodent micronucleus assay. ICH S2(R1) further establishes the minimum requirements for these studies to be acceptable to support the conduct of clinical studies and marketing authorization application. Genetic toxicology studies are conducted early in the safety evaluation program, in a generally accepted tiered approach, with *in vitro* studies preceding *in vivo* studies, and with ICH M3(R2) establishing when, in the context of the proposed clinical development programme, the different studies should be conducted. Within this battery, *in vivo* assays are considered to play a relevant role in the overall assessment of genotoxic potential, as they take fully into account the biological processes of absorption, distribution, metabolism and excretion of the test article. Recently, *in silico* prediction models have become an integral part of regulatory genotoxicity testing, with the computational prediction of the outcome of bacterial mutagenicity assay being used in the qualification process of potential genotoxic impurities. This aspect is reflected in the current draft ICH guideline M7, which is expected to be implemented within the first half of the current year 2014.