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

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Formal GLP compliant genotoxicity studies are required by the Regulatory Authorities (such as EMA or FDA) to demonstrate the lack of gentoxic properties of a drug candidate during its safety assessment in the preclinical development process. Guidelines ICH S2(R1) and ICH M3(R2) recommend which package of studies should be performed and when they have to be conducted to support clinical trial administration. Due to the impact that these studies have in the *go/no go* decision of the compound research development, a general practice among the pharmaceutical companies is that the whole battery of GLP compliant genotoxicity studies is carried out as soon as possible, preferably in advance of the first administration in humans (phase I). However, before to initiate these formal regulatory studies and to avoid any potential undesired positive gentox result in already advanced phases of the preclinical drug development, pharmaceutical companies have implemented internal *in silico*, *in vitro* and *in vivo* High Throughput Screening assays (commonly known as HTS assays) to anticipate the identification of potential gentoxic properties of the research molecules. This approach is based on the philosophy: “Fail early, Fail cheap”. In other words: the faster the potential genotoxic properties of the research compound could be detected, the better (as this early identification implies a remarkable savings in resources and time). These screening assays are performed since the very initial steps of the drug discovery process using small quantities of compound in comparison with the full GLP studies obtaining limited, but at the same time, valuable information that could help to screening out those molecules showing undesired genotoxic properties. In this direction, the session will deal with the fundamentals of the different well know Medium-High Throughput Screening tools currently available (as DEREK, SOS-*umu*, Greenscreen, reduced versions of Ames, *in vitro* and *in vivo* Micronuclei assays, Comet assay, among others) and that the pharmaceutical industry employs to have a quick insight about the potential genotoxic characteristics of the molecules aimed to become future marketed drugs.