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Letter to Editor

Potential Sunset of 2-Year Carcinogenicity Studies in Rodents for Small Molecule Pharma Compounds

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Toxicity/carcinogenicity studies in rodents have played a pivotal role in identifying chemicals that are potentially hazardous to humans. In fact, nearly all of the known human carcinogens are also carcinogenic in 1 or more rodent species. During the past 20 years, the quality and consistency of rodent studies has improved considerably, and much has been learned about mechanisms whereby chemicals initiate or promote the carcinogenic process in rats and mice. The process of identifying chemicals that cause toxicity or carcinogenicity in rodents is quite well established. However, there has been lot of debate among learned and concerned scientists both in the regulatory and the regulated community with respect to extrapolating these data for risk management decisions in the protection of human health.

While many would accept the assumptions that genotoxic chemicals that cause cancer in animals pose a cancer risk to humans and that genotoxic chemicals causing cancer at high doses pose a risk at lower doses, there is much less certainty with respect to nongenotoxic chemicals. The confusion about risk extrapolation for nongenotoxic chemicals has often leads to criticism of the hazard identification process for chemicals in general. There is increasing awareness of the complexity of the carcinogenic process that has made species extrapolation and dose extrapolation from rodent studies to humans more complex. Although, newer molecular biological techniques and cell kinetic measurements offer exciting possibilities for better risk assessment, it is the combination of well-designed rodent studies with appropriate mechanistic studies that offers the best hope for regulatory decisions based on sound scientific principles.

Datasets evaluated by the ICH S1 expert working group (S1 EWG) suggest that knowledge of pharmacologic targets and pathways together with toxicological and other data can, in certain cases, provide sufficient information to anticipate the outcome of 2-yr rat carcinogenicity studies and their potential value in predicting the risk of human carcinogenicity of a given pharmaceutical. Consideration of this information is hypothesized to provide sufficient information to conclude that a given pharmaceutical in certain cases presents a negligible risk or, conversely, a likely risk of human carcinogenicity without conducting a 2-yr rat carcinogenicity study.

The Pharmaceutical Research and Manufacturers of America (PhRMA) has conducted analysis of a dataset containing 182 compounds. Based on this analysis it was concluded that negative histopathology in a chronic rat study, together with a negative result in genotoxicity and negative evidence of a hormonal mechanism, could predict with 82% accuracy a negative outcome of the 2-yr rat carcinogenicity study for these compounds.

In addition to the PhRMA dataset analysis, the FDA conducted a similar study with 44 unique compounds, and the JPMA conducted a study with 64 compounds with minimal overlap of either dataset. These analyses confirmed the earlier conclusions from the PhRMA dataset with respect to negative predictivity. The EU Drug Regulatory Agencies (DRA's) has used the background data from these publications relating the pharmacology of the compounds and the outcome of the rat carcinogenicity studies. This analysis fully confirmed the conclusions reached earlier on the PhRMA database.

From the retrospective analysis of the various datasets (PhRMA, FDA, JPMA, and EU + FDA) it is fair to conclude that based on pharmacology, genotoxicity, and chronic toxicity data (usually present at the end of phase 2 in the development of a new pharmaceutical) the outcome of the 2-yr rat carcinogenicity study can be predicted with reasonable assurance at the two extremes of the spectrum. Negative predictions can be made when predictive carcinogenic signals are absent and positive predictions can be made when such signals are present. In between a category of compounds still remain for which the outcome of the carcinogenicity studies cannot be predicted with sufficient certainty.

However, recent molecular biochemistry techniques have evolved to the extent that many of the Adverse Outcome Pathways (AOP') in carcinogenesis can be studied in vitro. Such testing's with minimal animal studies accompanied with targeted mecha-

nistic and mutagenicity studies can obviate the need for actually conducting 2-year rat carcinogenicity studies for almost 90% of pharma low molecular compounds.

It is now a fairly common practice in the regulatory community to employ a Weight of Evidence (WOE) approach in predicting and extrapolating the carcinogenic potential of most compounds. Given sufficient scientific justification, many regulatory agencies are inclined to consider waiving the 2-year rat carcinogenicity studies. This is expected to improve pharmaceutical carcinogenicity evaluations, reduce use of animals in accordance with the 3Rs (reduce/refine/replace) principles, reduce the use of drug development resources, and reduce timelines to market authorization in some cases, all without compromise to patient safety.

These days nearly 50% of all drugs approved by the regulatory agencies and are marketed are large molecules (synthetic proteins and biological origin agents) which by and large do not need rodent carcinogenicity studies.

As a result, I suspect that by 2030, there may not be a need to conduct any 2-year rodent carcinogenicity studies with most small molecule pharma compounds which are used for extended period of time in humans. As a result, only companies who are sharp enough to tool themselves with Adverse Outcome Pathways (AOP'S) and in vitro molecular biochemical tests are going to succeed and offer services to the pharma industry.