



Opportunities to Modify Current Regulatory Testing Guidelines and Advance the Assessment of Carcinogenicity Risk in the 21st Century

Background

The Federal Food, Drug and Cosmetic Act (FDCA) of 1938 was passed some 70 years ago requiring manufacturers to prove the safety of any product that would be marketed over state lines. The legislation also banned the use of misleading labels on food, drugs, and medical devices. In 1962, additional legislation was passed to require manufacturers to establish the safety and effectiveness of all drugs on the market. The measure, the Kefauver-Harris Act, also stipulated that the Food and Drug Administration (FDA) oversee the drug industry. Today, FDA must approve all new drugs before they can enter the marketplace.

New drugs are developed by a variety of sources including independent researchers, university medical centers, government research centers, and private organizations. Some of the actions of drugs that are developed are measured using laboratory tests, called assays. This process of making and selecting chemicals, and measuring their effects in numerous assays can take a significant amount of time, but more often, the process is accelerated using computers and other automated technologies. The goal of animal tests is to learn how the blood absorbs the drug, how the drug is broken down chemically in the body, if the drug does what it is expected, how quickly the drug is excreted from the body, and the toxicities of the drug. After short-term animal toxicology studies are completed, the sponsor of the drug applies for approval from the Center for Drug Evaluation and Research (CDER) to allow testing of safety and effectiveness of the drug in human clinical trials. The members of the CDER who specialize in medical, chemistry, pharmacology, toxicology, and other fields, to determine whether there are flaws in the initial

studies and whether the overall plan is viable, and carefully review these applications.

After short-term animal toxicology tests are complete, one of the many studies that must then be run is to dose approximately 1,000 rats and mice every day for two years to determine if a drug may cause cancer in humans. Predicting the ability of drugs to cause cancer has remained a challenge to the scientific community for decades owing to the lack of predictability of animal models. In order to understand the risk that drugs pose to humans, improved methods are needed to more accurately predict the ability of compounds to induce cancer and to understand their mechanism of action.

Research

The ability of drug candidates to induce cancer has historically been evaluated in two-year rodent bioassays, where mice and rats are dosed with compounds for their lifetime and the number and type of tumors are enumerated. This bioassay takes up to three years to complete and costs \$2 to \$3 million. Representatives from 13 pharmaceutical companies have been sharing with each other, with the FDA, and with the European Medicines Agency, all the data they have been collecting on almost 200 compounds over the past 20–30 years from these two-year rat cancer studies along with the results of shorter rat toxicology studies that are run for six-months to support clinical trial safety. These data indicate that the six-month studies appear to be sufficient to conclude which drugs will not result in tumors in a two-year rat cancer study and so may not require such additional testing in the future. The data indicate that approximately 40% of drugs will fall into this category. The FDA and the Japanese Pharmaceutical Manufacturers Association (JPMA) are also inspecting their separate

data files on different sets of drugs to determine if they come to the same conclusion looking at the same endpoints in the same types of studies. The data are also helpful in defining a research strategy that will deliver further improved testing and accurate early prediction. In addition, advances are being made through collaborative research initiatives that point to anticipated growth in qualified biomarkers for monitoring in both animal models, and *in vitro* test systems that will permit faster resource sparing approaches to improved cancer risk identification. These approaches may also provide better understandings into mode-of-action and relevance to humans.

Gaps in Knowledge

Gene expression profiling has been proposed as an approach to identify those qualified biomarkers that could be used to improve cancer risk identification and understanding. Changes in gene expression have been shown to precede the onset of pathology, and can reveal mechanisms of drug toxicity, thereby allowing the prediction of carcinogenic potential and an understanding of the mechanisms to facilitate human risk assessment from shorter-term animal studies and *in vitro* test systems. In the near term, the justification may be established based on careful inspection of decades of existing test data, to reduce the conduct of two-year rodent bioassays by 40%. But even further reductions are anticipated following continued laboratory research in new technologies including gene expression profiling.