Michigan Society for Medical Research

BioFocus

A Newsletter Exploring Science & Biomedical Research Issues For School Educators

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Our Mission

The Michigan Society for Medical Research (MISMR) is a nonprofit educational organization that supports biomedical research and testing and the judicious use of animals in research, education and testing in the interests of human and animal welfare. Established in 1981, MISMR is made up of the state's leading research universities, teaching hospitals, pharmaceutical companies, voluntary health organizations and hundreds of scientists, educators and students who understand and support the importance of animal research and testing in advancing health care and treatment.

MISMR Educational Projects & Activities

ANNUAL ESSAY CONTEST

Every year MISMR sponsors an essay contest open to all Michigan high school students. Students from well over 500 schools in the state have annually participated in the contest to address the benefits of biomedical research. Prizes are awarded.

SPEAKERS BUREAU

MISMR volunteers visit K–12 schools and civic community groups through out Michigan each year to educate the public about biomedical research and to dispel commonly held myths.

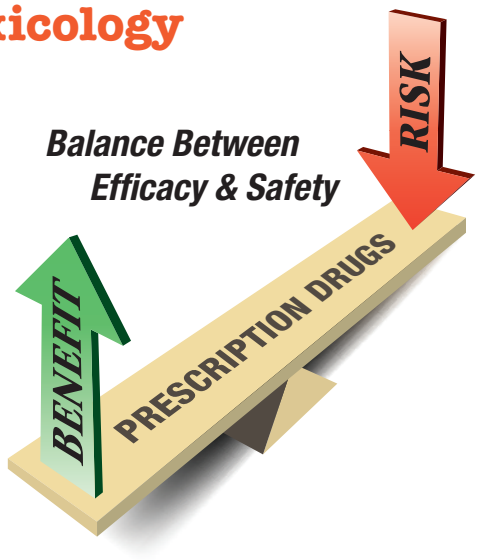
ANNUAL SYMPOSIUM

MISMR's popular annual meetings have often proved to be "standing room only," typically attracting local and national educators and researchers with interactive training workshops and presentations promoting biomedical research.

www.mismr.org

Study Directors in Toxicology

By Alan P. Brown, PhD, DABT



Advertisements for prescription drugs are frequently on television or in magazines, and oftentimes news reports of new drug discoveries or concerns regarding drug safety are in the media. Some drugs are commonly recognized and have become household names (e.g., aspirin, Tylenol, Lipitor, Viagra). But have you thought about the many and complex steps that need to occur for the discovery and development of a new drug? How are drugs determined to be safe enough to use and how are their potential side-effects identified? What types of studies are required by the government for conducting clinical trials or for granting marketing approval? This issue of *BioFocus* will attempt to provide one aspect of the complex journey of a new drug from discovery to the pharmacy.

In order for a company (the Sponsor) to initiate clinical trials of an experimental new drug, the Sponsor is required to submit an Investigational New Drug (IND) application to the United States Food and Drug Administration (US FDA). Prior to approval of an IND, laboratory studies need to be conducted in animals to assess the safety of the experimental drug (nonclinical studies). These studies are designed to identify risks and to determine whether the drug is safe enough to be tested in humans. The primary goals of the nonclinical studies are to: 1) characterize dose- and exposure-response relationships, 2) evaluate and identify potential effects of the drug, and 3) provide guidance for determining safe doses to test in humans. After a drug has been adequately studied in clinical trials, the Sponsor must submit a New Drug Application (NDA) to the US FDA to obtain approval to sell the drug. Additional nonclinical studies in animals are required for a NDA submission.

How are drugs determined to be safe enough to use and how are their potential side-effects identified?

What types of studies are required by the government for conducting clinical trials or for granting marketing approval?

The US FDA Good Laboratory Practice (GLP) regulations first became law in 1978 and are intended to provide rules and guidance regarding how nonclinical studies are to be conducted. These regulations are designed to assure quality, accountability, and reliability of the results, and provide guidelines for improving the quality of the science of the studies. A key element of the GLP regulations is with respect to the role of the

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Fast Facts...

What is Toxicology?

Toxicology is a multi-disciplinary endeavor in the biological sciences that studies the adverse effects of drugs, chemicals, medical devices, vaccines and biologics, food additives, natural products, pesticides, herbicides, etc. The science of toxicology involves diverse aspects of the biomedical sciences including physiology, biochemistry, pathology, pharmacology, medicine, and epidemiology.

What is a Nonclinical Laboratory Study?

According to the US FDA GLP Regulations: "Nonclinical laboratory study means *in vivo* (whole animal) or *in vitro* (e.g., cell culture) experiments in which test articles (e.g., experimental drugs) are studied prospectively in test systems (animals or cells) under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article." The primary purpose of these studies is to determine potential risks and toxicities of the test article.

BioFocus

WE WANT TO HEAR FROM YOU!

We want to include your stories, comments or questions relating to animals in your classroom in upcoming editions of *BioFocus.* Please email stories to: mismr@umich.edu

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Study Directors... *Continued from page 1*

Study Director, who is the individual assigned to have overall responsibility for the entire nonclinical study. Unless responsibility for conduct of a study is assigned to a single individual, the potential exists for individuals working on the study to receive conflicting instructions, and for study events to occur in an uncoordinated fashion. In addition, a single individual most familiar with the study is needed for evaluating all of the results and making final conclusions.

The US FDA GLP regulations state the following. "For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the Study Director. The Study Director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control.

The Study Director shall assure that:

- The protocol, including any change, is approved as provided in 58.120 (a section of the regulations) and is followed.
- All experimental data, including observations of unanticipated responses of the test system (animals or cells in which the study is being conducted) are accurately recorded and verified.
- Unforeseen circumstances (e.g., errors, mistakes, unplanned events, equipment failures) that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.
- Test systems are as specified in the protocol.
- All applicable Good Laboratory Practice regulations are followed.
- All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study."

The role of the Study Director is oftentimes challenging and dependent upon that individual's managerial, technical, and scientific capabilities. In addition to understanding the regulatory and scientific requirements for directing a study, the Study Director needs to successfully manage, communicate, and interact with numerous individuals who are involved with the design and conduct of the study. Individuals who serve as Study Directors typically have not received formal education in this endeavor, and many times have other responsibilities within a company. A degree in the biological sciences (e.g., BS, MS, DVM, PhD, MD) is generally required, although in certain circumstances an individual's professional experience may be sufficient for the absence of a degree in the biological sciences. Training and mentoring of Study Directors usually occurs "on the job" and is dependent upon the experience of the laboratory personnel interacting with that individual.

Types of Nonclinical Laboratory Studies

(See sidebar for the definition of a nonclinical laboratory study.)

Safety Pharmacology Studies evaluate the physiologic effects of drugs on the respiratory, cardiovascular, and nervous system in animals. These studies typically involve single doses of drugs in rats, dogs, or monkeys followed by evaluation

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Study Directors... *Continued from page 2*

of neuromuscular function, blood pressure, heart rate and rhythm, and pulmonary function.

Genetic Toxicology Studies evaluate whether a drug or chemical damages DNA or chromosomes, or produces mutations. These studies are conducted in various strains of bacteria, mammalian cell cultures, or rodents (mice and rats). Chemicals which are genotoxic may have the potential for causing cancer.

General Toxicology Studies comprise a wide range of study designs in various animal species (typically rats, rabbits, dogs, and monkeys). These studies are designed to determine the risks associated with drugs or chemicals following a relevant route of exposure (such as by oral dosing). Effects of the experimental chemicals or drugs on various organs and the relationship between dose, exposure, and effects are determined in these studies.

Carcinogenicity Studies are performed in mice and rats (typically following 2 years of daily dosing) to evaluate whether a drug or chemical can produce tumors, and therefore pose a risk as a potential carcinogen.

Sensitization Studies are conducted in guinea pigs (maximization study) or mice (local lymph node assay) to determine if a chemical can produce an allergenic response. Chemical allergies can result in skin changes such as hives and rashes (e.g., poison ivy).

References

Code of Federal Regulations Title 21, Volume 1, Parts 1 to 99, revised as of April 1, 1999. 21 CFR 58 Title 21 — Food and Drugs. Part 58 — Good Laboratory Practices for Nonclinical Laboratory Studies.

Brown, Alan P. "A practical guide to study directing." *Quality Assurance Journal,* 2009: 12, 40–50.

BioFocus is published by the Michigan Society for Medical Research. Please send your questions, comments, and suggestions to:

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