

Current Regulatory Requirements and Trends for Developmental, Reproductive, and Neonatal Non-Clinical Safety Testing and Risk Communication

Abstracts

Risk Communication: A Clinical Perspective – Anthony Scialli

One of the ultimate consumers of the information generated in toxicology studies is the clinician and patient who are making health care decisions. The way toxicology information is presented has a significant impact on the response of the clinician and patient and on the decisions they will make. Word choice can be critical; use of a highly charged word like "teratogen" may have important consequences in spite of not having a clear definition. The FDA Pregnancy Categories are examples of ill-defined communication devices that can lead to poorly-informed decision-making. There are more accurate ways of presenting toxicology information.

Current Regulatory Requirements in Developmental and Reproductive Toxicity Testing: Segmental Design versus the Biologic Continuum – Joseph Holson

The current international regulatory guidelines for developmental and reproductive toxicology of pharmaceutical products will be reviewed and contrasted with the U.S. Federal guidelines for developmental and reproductive studies of environmental agents and agricultural chemicals. The benefits and deficiencies of each will be explained through the use of case study examples, and recommendations for when and when not to employ certain "standard" designs will be offered. These various guideline-type designs (segmented) will be discussed relative to how they violate or accommodate developmental and reproductive processes, which are temporally continuous and intimately connected physiologically and anatomically.

Use of Primates in Teratology Studies – Gary Chellman

Non-human primates are frequently used for reproductive toxicology testing of biological therapeutics, due to antigenicity or lack of pharmacologic response in conventional models (rodents, rabbits). Cynomolgus monkeys are most often used, based either on use in the general toxicology program or on impracticality of using other primate species. Depending upon the intended clinical use, developmental toxicity (teratology) testing may be indicated. Such studies typically involve dosing of pregnant females during organogenesis, followed by c-section for teratologic evaluations. In addition to endpoints

that are standard for general toxicity studies, a number of specialized endpoints may also be incorporated into the study design: ultrasound fetal evaluations, pharmacodynamics, toxicokinetics and antigenicity. Each study should be designed purposefully and based on scientific rationale, and each endpoint should be carefully considered in terms of practicality, cost, and interpretability of data generated (including availability of historical control data). Non-human primates present both advantages and disadvantages in conducting these studies, which will be discussed. Numerous technical challenges exist, which need to be understood and anticipated at the outset. To demonstrate key points, sample data sets will be presented. The presentation is intended not only for those experienced with the complex challenges of teratology studies in non-human primates, but also for those who may be considering such studies for the first time.

Developmental Immunotoxicology and Later Life Immune Dysfunction – Rod Dietert

Given the unique nature of immune development, it is not surprising that the fully matured and dispersed immune system of an adult is an ineffective surrogate for predicting developmental immunotoxicity (DIT) risk. This presentation will consider the critical developmental windows for DIT, the nature of the errors associated with adult exposure-assessment, the spectrum of later-life immune dysfunction resulting from DIT and the keys to an effective DIT assessment program.

Current Neonatal Testing Requirements – John DeSesso

Development of mammalian organisms begins in the uterus and ends after birth. Birth occurs at a point during the developmental timeline, but the stage of development of an organism at the time of parturition is not the same for different species. The recognition that significant development occurs after birth and of the differences in stages of maturity of the offspring of different species at the time of birth has caused not only challenges for the testing of drugs and chemicals but also complexity in extrapolating findings among species. This presentation will review the current requirements for testing of animals in the perinatal and juvenile periods in conjunction with a discussion of contemporary science regarding interspecies similarities/differences and how these affect the safety assessment process. The presentation will conclude with the author's appraisal of the likely future for this type of safety evaluation, and how basic science can influence the appropriate design and interpretation of these studies.