CE 6 Methodologies in Human Health Risk Assessment

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This course provides an overview of more advanced aspects of chemical risk assessment, following up from a successful CE course on basic principles offered at the Annual Meeting in 2013. This new course will focus on methodologies, which incorporate increased use of biological and chemical specific data as a basis to provide more accurate estimates of risk. In addition, it will address evolving areas such as problem formulation as a basis to better target toxicity testing and tailor assessments to the needs of risk management. The course will feature presentations and discussions focusing on the value of mode of action analysis for characterization of hazard, the fundamental tenets of physiologically based pharmacokinetic (PBPK) model development and implementation, use of benchmark dose (BMD) models to identify points of departure, and use of chemical specific adjustment factors to address inter- and intraspecies uncertainty and variability. The principles and key components of these methodologies will be illustrated with applied case examples from the regulatory risk assessment arena.

CE 7 Nonclinical Animal Models Enabling Biopharmaceutical Advances in Translational Medicine

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A fundamental theme in drug discovery and nonclinical development is the utilization of appropriate animal models that are predictive for efficacy or adverse events in humans administered a novel biopharmaceutical. The accurate prediction of human adverse effects using nonclinical animal toxicology studies remains a major goal in drug development and relies on appropriate animal models. Essential attributes for an appropriate animal model include similar target distribution, target pharmacology, systemic pharmacokinetics, metabolism, and distribution to those of humans. Utilization of the most appropriate animal model aligns with the 2011 US FDA Strategic Plan to advance regulatory science and modernize toxicology in order to enhance product safety and develop better models of human adverse responses. The Preclinical Safety Leadership Group (PSLG) of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is creating a contemporary industry-wide database to determine accuracy with which the interpretation of nonclinical safety assessments in animal models correctly predicts human risk. The course will present considerations for the selection of an appropriate animal model for nonclinical safety, the use of animal models of disease in safety testing, emerging use of the minipig in safety testing, data from an industry-wide nonclinical to clinical translational database, and the use of animal safety data in the design and conduct of clinical trials. Output from the course will help identify advances and remaining gaps in the utilization of animal models in biopharmaceutical development.

CE 8 Nanotoxicology: Past Achievements, Future Challenges, and Potential Solutions

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Nanomaterials (NM) possess tremendous promise to advance consumer, military, and medical applications due to their unique physicochemical properties, such as enhanced surface area, tunable size, modifiable surface chemistry, and particle reactivity. However, these same properties have made NMs a potential health hazard, thus giving rise to the field of nanotoxicology (NT), which has become a prominent player in toxicological advancement and research over the past decade. Initial NT studies were limited by a lack of both available materials and characterization tools. Through advances in material science, enhanced capabilities have been developed that allow for the synthesis of distinctive NMs and the ability to accurately evaluate their characteristics. Taking advantage of these developments, NT has made remarkable progress in evaluating the hazards of NMs and correlating specific properties, such as size, shape, coating, and composition, to observe cytotoxicity. However, even with these numerous advances, there are still a number of constraints plaguing the field of NT. One principal area of concern is the development of procedures that account for new NT facets; including NM behavior in a physiological environment, varied aggregate structure, role of ionic dissolution, and realistic modes of exposure. Another limitation is the need for new and more powerful characterization tools. Recently, the question of dosimetry has become a forefront topic and whether a universal, conceptual standard should be adopted, such as mass, surface area, or particle number. Arriving at a consensus on this issue is critical for the establishment of NM exposure limits and risk assessment metrics, which are significantly lacking. To accomplish accurate risk assessment and regulatory evaluations, NT will have to develop a means to improve the correlation of *in vitro* data to *in vivo* predictions, via enhanced cell models, relevant dosages (low vs. high), and realistic exposure scenarios. This CE course will evaluate where NT stands, by highlighting key research successes, identifying challenges facing the field today, and exploring solutions to overcome current limitations.

CE 9 Epidemiology for Toxicologists: What the Numbers Really Mean

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21st Century risk assessment relies on data from multiple lines of evidence. High quality human epidemiology data are generally preferred for regulatory decision-making, but the body of evidence often includes animal toxicity, *in vitro, in silico,* animal dosimetry, and human exposure data. The quality of individual epidemiology studies can be highly variable and dependent on study design as well as other critical factors that sometimes cannot be controlled for. For risk assessors to fully understand the implications of epidemiology evidence, they must understand how the overall integration of toxicity and mechanistic data with human epidemiology findings facilitates science-informed decision-making. A sufficient understanding of the epidemiology data is a necessary starting point for appropriately integrating all the available information. The course is geared towards the toxicologist who is trying to determine how to appropriately evaluate, use, and integrate epidemiology data in a weight-of-evidence evaluation or risk assessment. Attendees first will be given a basic overview of epidemiology, with a focus on different epidemiology study designs and their strengths and weaknesses. Attendees will also gain an understanding of exposure assessment and biomonitoring, and how this information is used and evaluated in epidemiology studies. Additional learning objectives of the course: How to determine when an association may be supportive of a causal relationship and what confidence intervals mean; how to use trend information; how to evaluate and understand adjustments that are made for potential confounding factors; and how to evaluate several epidemiology studies on the same topic, particularly in light of available toxicity and mechanistic data. Finally, attendees will learn to integrate all types of data streams with a real example. Attendees will leave the course with a stronger understanding of how to interpret and use epidemiology data in their weight-of-evidence analyses and risk assessments, and how epidemiology can help inform regulatory decision-making.

CE 10 Innovations in Methodologies for Inhalation Exposure and Interpretations of *In Vivo* Toxicity

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The respiratory system presents most diverse structural and cellular heterogeneity suited to handle complicated aspects of air liquid interface such as the direct exposure of the delicate cellular and capillary surfaces to the atmosphere and the encounter of lung epithelial cells to complex mixtures of particles and gases. Not only the respiratory depositions of inhaled substances vary regionally but also the regional responses generated by the respiratory tract. Recently the field of inhalation technology and respiratory toxicology has seen revolutionary growth because of the emergence of the use of nanomaterials and renewable energy sources creating new environmental challenges. Moreover, the paradigm shift of toxicology testing to high throughput screening has led to the development of novel inhalational approaches for cells. Speakers will cover the recent advances in inhalation methodologies for various types of emerging inhalants and focus on generation of atmospheres for *in vivo* and *in vitro* toxicity assessment. These aerosols will include gas and particulate emissions from vehicles using old and new energy sources, forest fires, coal combustion, manufactured nanomaterials and mixtures formed from atmospheric aging. The dynamic of physicochemical composition of such mixed aerosols will be discussed to allow for identification of causative constituents and lung site-specific injuries. Structural differences in the respiratory tract of rodents and large mammals, including humans, impacting dosimetry will be discussed. Respiratory system heterogeneity between humans and animals, and their differential neurohumoral mechanisms will be discussed to aid in interpretation of inhalational hazard for

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