Abstract: (Q)SAR: Introduction to Methodology and Regulatory Application in Drug Development

(Quantitative) structure-activity relationship [(Q)SAR] modeling has a long history of use in drug development. However, the International Council for Harmonization (ICH) M7 guideline for assessing the mutagenic potential of drug impurities stands as a milestone in the regulatory acceptance of (Q)SAR. The guideline describes how complementary modeling methodologies can be used in combination with expert knowledge to support classifying an impurity as mutagenic or non-mutagenic, which in turn determines acceptable levels of the impurity during synthesis and degradation. The selection of appropriate (Q)SAR models for ICH M7 impurity qualification requires knowledge of how models are constructed and how predictions are generated. Technical considerations such as the molecular descriptors used to interpret chemical structure, the type of algorithm used to extract structure-activity relationships, or the way the model confirms it can make a reliable prediction are critical for the user to understand so that the model output is interpreted correctly.

Part one of this seminar will provide an introduction to the basic concepts and technical considerations of (Q)SAR modeling. Key concepts, such as reconciling conflicting predictions or applying the OECD Validation Principles to assess model suitability will be covered, as well as the limitations of the methodology. An introduction to expert knowledge and strategies for structural analog searching will be provided along with best practices for the comprehensive reporting of results in regulatory submissions.

Part two of this seminar will provide a pharmaceutical industry perspective on the regulatory use of (Q)SAR. A general process for evaluating mutagenic potential with an emphasis on impurities will be discussed. This process covers the generation of predictions, application of expert knowledge, and final classification. The utility of read-across will be highlighted. Finally, case studies will be presented to emphasize key concepts and demonstrate best practices.