Tom Lewandowski, Ph.D., DABT, ERT, ATS
Joel M. Cohen, Sc.D., DABT

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Known Unknowns: Challenges and Approaches for Handling Chemical, Hazard and Regulatory Uncertainty in Medical Device Safety Assessments

The regulatory landscape for the safety evaluation, clinical testing and commercial development of medical devices is undergoing considerable changes, including new requirements for material characterization and chemical risk assessment early on in the development process. In this dynamic environment, extractables and leachables analysis is becoming a key tool in biocompatibility assessments and establishing regulatory compliance. The first speaker will begin the discussion on medical device chemical characterization strategies, a necessary step for understanding potential chemical exposures from medical device components. This presentation will discuss current "best practice" strategies for extractables experimental design and analytical testing. Specific discussion will include how information concerning material chemistry and the manufacturing process can reduce the cost and effort associated in resolving "unidentified" extractable compounds. The next presentation will focus on predictive toxicology methods for evaluating potential risks from extractable compounds. Chemical analysis often identifies unique or complex extractable chemical structures that lack complete toxicological data packages. Best practices for using new approach methodology (NAM) predictive tools to evaluate these detected chemicals have yet to be formally established. This presentation will provide an overview of predictive toxicology tools currently available for evaluating risks to human health (e.g. computational toxicology programs, read across, threshold of toxicological concern), along with a discussion of potential pitfalls and best practices. Case studies will be presented to demonstrate the importance of expert judgement when interpreting in silico hazard predictions, as well as approaches for justifying a read across approach for risk assessment of extractable compounds. The third speaker will then discuss the FDA perspective on the issues raised in the preceding talks. Agency experience with unique non-targeted analytical methods that generate data adequate for toxicological risk assessment will be presented, which includes but is not limited to, extraction method design, analytical instrument/tool selection, sample manipulation, system suitability, calibration, identification/semi-qualification, and data reporting. The selection and application of the analytical evaluation threshold (AET) will also be discussed. Unique chemical/toxicological considerations that aid the analytical chemist and toxicological risk assessor in prioritizing non-targeted extractables for toxicological risk assessment will also be discussed. The final speaker will present a broader overview of the changing global regulatory landscape for medical device safety evaluation. Notable activity includes the revision of ISO 10993-1, implementation of the European Union's revised Medical Devices Regulation, and amendments to California Proposition 65. This presentation will provide an overview of the recent regulatory changes and how new requirements for extractables and leachables analysis will affect manufacturer's ability to justify the safety of hazardous substances within devices, verify warning label exemption, evaluate biological equivalence of predicate/proposed devices and also support supply chain controls, ensure efficient change management.