Questions and Comments Received From Webinar Attendees Directed to Specific Speakers: Fiona Sewell

Q: Is low power to detect low incidence of chronic effects also a weakness of the kinetic maximum dose (KMD) approach? Some findings at a maximum tolerated dose (MTD) might be irrelevant to human exposure, but other might still be relevant from that perspective.

A: Yes, low power is an issue only if you are looking for hazard and not risk in a normal expected use pattern. For accidental and/or intentional exposure, acute study results should guide the physicians treating the patients. And, sometimes KMD and MTD will be the same.

Q: Do we need to conduct toxicokinetics (TK) in all the repeat-dose studies?

A: Incorporation of TK into all repeat-dose studies would be useful, both to provide more information to improve interpretation of the results from that same study (e.g. to link observed toxicity to circulating levels) and also to inform dose selection in any further studies (e.g. information on the dose response curve, to identify saturation, departure from linearity, etc.). Use of microsampling avoids the need for additional animals through satellite groups.

Q: Nonlinearity in absorption/distribution/metabolism/excretion (ADME) is sometimes important for chemicals in consumer products. For example, chemicals such as skin care actives or oral care actives may have a benefit in a product when used at a concentration where absorption is saturated, and that is a benefit for the human safety profile since low systemic absorption is anticipated. However, if hazard testing is stopped at the point of nonlinearity, how do we get to doses/concentrations that support human usage once uncertainty factors (sometimes as large as 1000 or more) are applied to the hazard data? Does the current risk assessment paradigm need to rethink how to determine margins of safety using animal toxicity data?

A: Risk analysis starts with problem formulation. For example, what is the intended use of the product? Toxicity testing should not be conducted in a vacuum and hence issues such with this product should be considered when designing the testing strategy.

Q: Microsampling is common in human clinical trials (particularly Phase I trials with healthy human participants) for the reasons you noted. And I believe there are also national guidelines, which can be shared when you send out the survey.

A: Yes, there are guidelines on microsampling, including the U.S. Food and Drug Administration's "Questions and Answers" guidance on International Conference on Harmonization S3A (FDA 2018).

Q: What are your thoughts on using adaptive study designs, such as those commonly used in human clinical trials? I'm thinking Bayesian adaptive study designs would be a great fit for guideline toxicity studies and would be interested in what your thoughts are.

A: I think a case-by-case approach would work well, based on all available information, which means that it may be appropriate to adapt study designs for future studies as new information becomes available.