Questions and Comments Received From Webinar Attendees Directed to Specific Speakers: Salil Pendse

Q: Can/should we always use the kinetic maximum dose (KMD) approach by applying it in relation to area under the curve (AUC), or is target organ concentration(s) (for parent and or metabolite) also important?

A: Target organ concentration ultimately rules the roost. However, in most studies, it is difficult to get a handle on target organ concentration. It may also be the case that the target organ itself is unknown as it relates to most sensitive adverse biological effect. With appropriate information, it may be possible to model target tissue concentration, but this presupposes that the target tissue is known. AUC of plasma concentration provides a good surrogate in most cases when information on target organs is lacking. It is also easier to measure plasma concentrations in animals. As such, KMD is often estimated based on AUC of plasma concentration. One should be cautious, however, because the interpretation of dose-response data requires information on the toxic moiety, in addition to dose proportionality.

Q: What is your guidance if you are testing a new chemical and you do not know whether the parent or the metabolite is the toxic chemical?

A: If metabolism itself is known and the parent metabolizes a small number of discrete chemical entities, then it's best to include both parent and metabolites in the determination of the KMD.

Q: In Dr. Boobis's plots of Michaelis-Menten kinetics, there was not a fixed inflection point, but a gradual change in slope with a limit of saturable rate. Your plots (on a log-log scale) seem to have a sharp inflection point. Can you explain that?

A: Dr. Boobis' plots of Michaelis-Menten kinetics showed rate of metabolism vs. concentration (e.g., liver concentration if describing liver metabolism). In my talk, the figures showed the relationship between internal dose (e.g. AUC of parent concentration) and external dose.

Q: Do you have a case study on a situation where flip-flop kinetics is occurring, or can you comment on a situation where the K_a (absorption rate constant) is slower than K_e (elimination rate constant)?

A: We do occasionally see flip-flop kinetics with pesticides, especially in dermal studies. A key thing with occupational exposure to pesticides is that the major routes of exposure are inhalation and dermal. Thus, dermal flip flop-kinetics become important, especially with some of the more lipophilic compounds. Flip-flop kinetics can reduce or increase the risk depending on the nature of the critical effect(s).

Q: We frequently only get three doses in absorption/distribution/metabolism/excretion (ADME) studies. What would be a better number of doses to better understand the kinetics of our test chemicals?

A: It is difficult to give an exact answer, but based on some of the mathematical descriptions we have looked at as a part of this symposium, five to six doses will give better confidence in the results.

Q: How do you know which dose metric from the model to focus on: AUC vs. maximum blood concentration (C_{max}) vs. average blood concentration (C_{avg})?

A: Any of those parameters can be used to determine dose proportionality and nonproportionality. AUC and C_{avg} are related (C_{avg} = AUC/time). If the mode of action (MOA) is known, the dose metric most related to the MOA should be used. However, in cases when MOA is unknown, AUC is more commonly used, since C_{max} doesn't reflect the entire ADME profile (e.g., the tail of the time course). The choice of C_{max} versus AUC may also depend on the toxicological nature of the key/critical effects. Toxicological effects that are pharmacological in nature (i.e. produce reversible effects due to a receptor-mediated process that does not result in tissue damage) tend to follow C_{max} (i.e., so-called "peak effects", which are often neurotoxic). Many other toxicological effects follow AUC. A knowledge of the toxic effects will help with this type of decision.

Q: Is some of your predicted data validated by *in vivo* experimental data?

A: We are not simulating the pharmacokinetic (PK) behaviors of a specific chemical, even though the parameters in these simulations are based on real chemicals. The purpose of this exercise is not to simulate PK for a specific chemical, but to understand the internal vs. external dose relationship based on basic PK concepts (e.g., Michaelis-Menten kinetics).