

A framework for estimation of area under the concentration versus time curves (AUC's) in complete and incomplete sampling designs

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Nonclinical in vivo animal studies have to be completed before starting clinical studies of the pharmacokinetic behavior of a drug in humans. These pharmacokinetic studies are commonly analyzed using a two-stage approach. The first stage involves estimation of pharmacokinetic parameters for each animal separately and the second stage uses the individual parameter estimates for statistical inference. This two-stage approach is only applicable in complete data designs where each animal is sampled for analysis once per time point. In the case of rats and mice, where blood sampling is restricted, the batch design or the serial sampling design need to be considered. In batch designs samples are taken more than once from each animal, but not at all time points while in serial sampling designs only one sample is taken from each animal across all time points.

In this talk we will present a uniform approach to estimate the area under the concentration versus time curve (AUC) that is applicable to all three designs. Based on the asymptotic distribution we construct confidence intervals that are then evaluated against commonly used resampling based intervals. We will then show an extension to test for linear combinations of AUC's and illustrate its use in an example to test for deviations of dose proportionality.