Intersubject Variability in Pharmacokinectics and Subject Characteristics in Phase I Studies

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BACKGROUND:

- Pharmacokinetic (PK) and safety results of Phase I PK studies are assessed by pharmacokineticist and medical writer respectively with the statistician playing the supporting role, e.g., PK statistical modeling. Here examples are used to show a variety of statistical analyses and inputs that the statistician can provide to the pharmacokineticist and medical writer.
- When an individual subject's PK responses are repeatedly measured, mixed effects modeling can provide estimation of fixed-effects parameters, between-subject variability, and residual random effects (including within-subject variability). For example, a commonly used study design in Phase I PK studies is a crossover design in which the treatment sequence is randomly assigned to study subjects, and subjects are dosed during the course of the study according to the treatment sequence. The ANOVA model for crossover design is

  y = μ + treatment + sequence + period + subject (sequence) + e

  where μ is overall intercept; treatment, sequence, and period are fixed effects; subject (sequence) is the random effect; and e is the random error. The dependent variable y is log-transformed PK parameter, AUC or Cmax.

The crossover design is widely used in bioavailability/bioequivalence studies as well as drug-drug interaction and fed/fasted studies.

METHODS AND RESULTS:

Example 1:

- The statistical results from ANOVA modeling on crossover design are often summarized as follows:

Table 1.

Parameter	Geometric LS Means: Treatment A Test	Geometric LS Means: Treatment B Reference	% Geometric Mean Ratio	Confidence Intervals (90% Confidence)
AUC0-t (ng*hr/mL)	27.68	26.70	103.67	95.07 - 113.05
AUC0-inf (ng*hr/mL)	28.09	27.23	103.18	94.79 - 112.32
Cmax (ng/mL)	2.05	1.84	111.58	101.47 - 122.70

Parameters are ln-transformed prior to analysis.
Geometric LS Means are the exponentiated least-squares (LS) mean from the ANOVA.
Geometric Mean Ratio = 100*(test/reference)

- The primary focus is on whether the 90% geometric confidence interval for the ratio of treatment geometric means is entirely contained within the 80.00 – 125.00% equivalence range (Schuirmann's Two One-Sided Tests (TOST)) as is in Table 1. The statistician who works with the pharmacokineticist should also examine closely another set of statistical outputs from the ANOVA:

Table 2.

	ln AUC0-t (ng*hr/mL)	ln AUC0-inf (ng*hr/mL)	ln Cmax (ng/mL)
Fixed Effects			
Treatment (p-Value)	0.488	0.539	0.059
Sequence (p-Value)	0.622	0.625	0.667
Period (p-Value)	0.048	0.052	0.121
Random Effects			
Intrasubject CV (%)	25.93	25.38	28.51
Intersubject CV (%)	119.12	117.26	109.56

- A statistically significant sequence effect could indicate the carryover effect, treatment-by-period interaction, or failure of randomization. The cause of a statistically significant period effect is often unknown. This nevertheless should alert the statistician to further inspect the data. The intrasubject CV which indicates within-subject variability is derived from the residual error term, i.e., e in the above ANOVA model, using the formula, intrasubject CV (%) = 100 x sqrt[exp(residual)-1)]. Corresponding to intrasubject CV, there is intersubject CV which is derived from subject(sequence) as a random effect in the above ANOVA model.

  intersubject CV (%) = 100 x sqrt[exp(subject(sequence))-1)]

- Here, intersubject CV indicates between-subject variability after accounting for the fixed effects of treatment, sequence, and period. (If SAS Proc Mixed procedure is used, residual and subject (sequence) as well as their associated statistics are provided under Covariance Parameter Estimates.)
- In Table 1, the objective of demonstrating bioequivalence using TOST approach is attained. In Table 2, the intrasubject CV which determines the statistical power and confidence interval is not high (<30%). However, the high intersubject CV is quite noticeable and should be communicated to the pharmacokineticist for additional PK research. The statistician should also examine the assumptions of the statistical model. Normal probability plot of studentized residuals can be used to assess normality of residual error as well as identify outlier (there is one prominent outlier, Figure 1). Residual plot can assess model fitting and homogeneity of variance (Figure 2).

Figure 1.

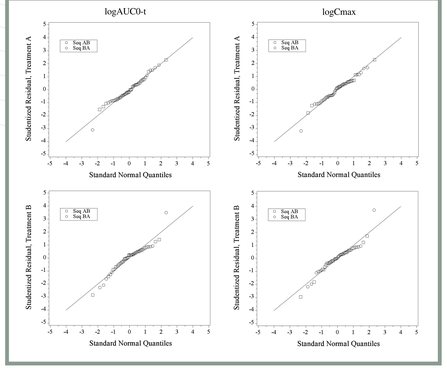


Figure 2.

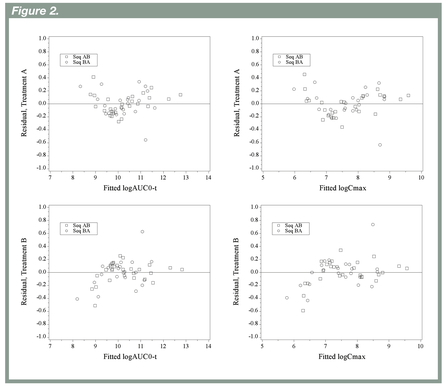
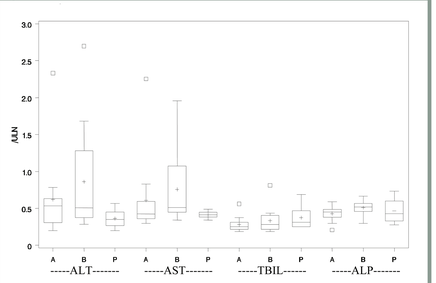
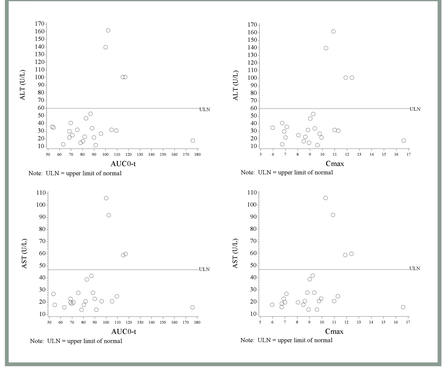


Figure 3.



ULN = upper limit of normal (/ULN = lab value divided by ULN); A and B = active treatments; P = placebo

Figure 4.



Example 2:

- It is beneficial to understand the relationship between subject characteristics and variability in PK among subjects, especially when high intersubject CV is noticed. A multitude of demographic, physiological, and therapeutic factors can influence the PK of a drug. It is then necessary to explore collected subject covariates such as gender, age, weight, liver and renal function that can relate to PK behavior. Box plot which graphically summarizes distributions of multiple datasets can be useful to compare different lab tests by treatment groups as in Figure 3. Lab values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and alkaline phosphatase (ALP) are divided by the upper limit of normal range (ULN). The purpose is to screen for subjects with a test value exceeding 3xULN for ALT or AST or 2xULN for TBIL and ALP (Hy's Law for detecting potential liver toxicity). In Figure 3, no subject exceeds 3xULN for ALT or AST. However, for ALT and AST, the active treatments A and B are different from placebo. Using simple scatter plots relating ALT and AST to PK parameters, Figure 4 further indicates that 4 active subjects who showed high ALT/AST values also had high AUC0-t and Cmax values (however, the subject who had the highest AUC0-t and Cmax values did not exhibit this pattern).

DISCUSSION AND CONCLUSION:

- Crossover design uses a within-subject comparison between treatments (the subject serves as his/her own control) by separating out the between-subject variability component. For this reason, the statistician wants to focus on intrasubject CV to ensure sufficient power and sample size because failing bioequivalence can be due to high within-subject variability resulting in too wide a confidence interval. Here we suggest that the statistician should also inspect intersubject CV. A high intersubject CV indicates variation in absorption, distribution, or elimination of the drug across subjects. High intersubject PK variability can especially be problematic for drug with narrow target concentration window. Although understanding the actual causes of within- and between-subject variability belongs to the realm of PK, it's the statistical modeling that actually quantifies the magnitude of these two types of variability for the pharmacokineticist.
- Most Phase I studies use healthy subjects with restrictive inclusion and exclusion criteria. The sample size of such studies is also small. The results from these exploratory analyses are suggestive for direction of future research work. For example, a high intrasubject CV (>30%) can lead to replicate design to better quantify within-subject variations for the test and reference products whereas a high intersubject CV should prompt closer examinations of subject covariates.