Qualitative Analysis of Generic and Reference LAI Drug PK Profiles Using Multivariate Score Space

Prokash Paul[a], Garry Handelman[b], Jaeyeon Kim[c], Seongkyu Yoon[a]
[a]Department of Chemical Engineering; [b]Pharmacology, Clinical Bioanalytical Chemistry, University of Massachusetts, Lowell, MA 01854, USA
[c]Novartis Pharmaceuticals, Cambridge, MA

Motivation

- The active pharmaceutical ingredient (API) in long acting injectable (LAI) products is usually encapsulated in microspheres that extends the release of API into the systemic circulation.
- LAI has long apparent half-life and a unique PK profile.
- The PK profile of these products usually consists of three phase:
  (a) **An initial release phase**: surface API absorbed systematically
  (b) **A lag phase with minimal API release**
  (c) **A main release phase**: the ingredients in the formulation degrade allowing the API to be absorbed into the systemic circulation completely.
- The current BE guidance in regards to LAIs is that the generic formulations are required to be qualitatively (Q1) and quantitatively (Q2) the same as the reference-listed drug.
- In general, the FDA recommends are *in vivo* single-dose, randomized, parallel BE study in healthy volunteers. However, parallel BE studies with LAI products are very challenging due to high inter-subject variability, complex PKPD profiles, study length and expenditure.
- The focus of this project is to utilize pharmacometric modeling and simulation and develop a methodology to assist development of generic LAI products

Scores and Loadings

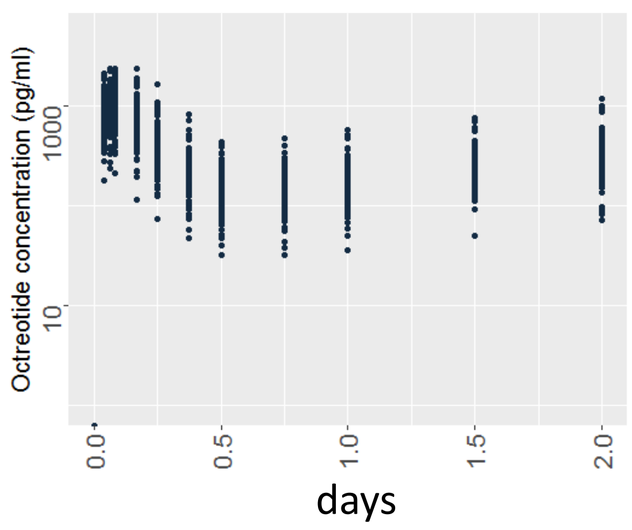
The ***score space*** is one of the most important metric in MVDA approach and is defined as the plane/space created by more than one principle components. The aim is to examine similarities/dissimilarities among drug formulations in terms of time trajectory of PK profiles.

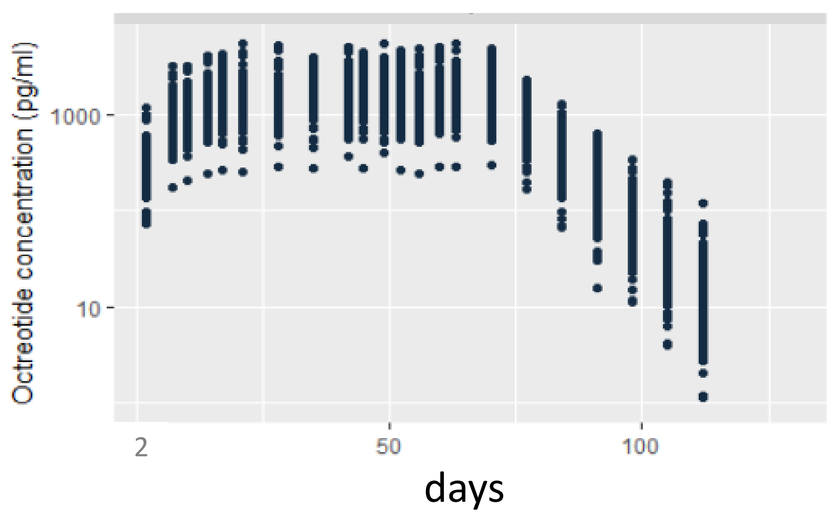
The ***loadings*** define the orientation of PC plane with respect to the original X-variables. In this work, loading plot displays the relationship among sampling instants.

Conventional Method
BE acceptance criterion 80% - 125%

LAI PK Simulation

- Study title: A single dose, sequentially assigned, open-label, one-period, two-treatment, parallel, comparative bioavailability study
- 200 subjects ; healthy non-smoking male volunteers
- 30mg octreotide acetate



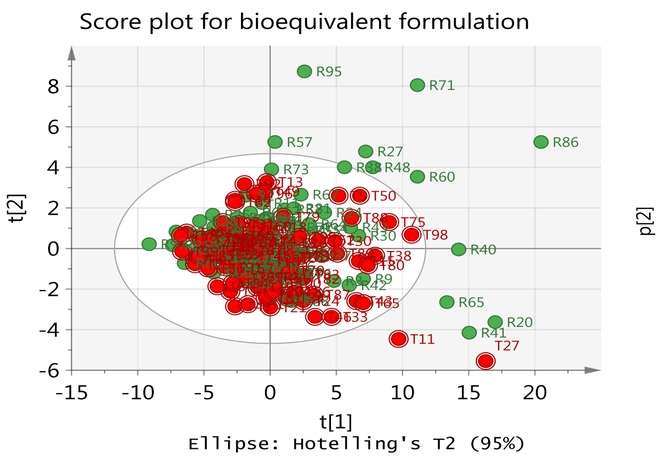


Baseline Demographic and Clinical Characteristics of Study Population

Demographic Variable	Statistic	Value
Age(year)	Mean [SD] Range	43.5[10.2] 19-55
Sex	Male Female	7 (11.9%) 52 (88.1%)
Race	Caucasian Black Hispanic	51 (86.4%) 6 (10.2%) 2 (3.4%)
Height (*cm*)	Mean [SD] Range	166.5 [9.2] 149.5-188
Weight (*kg*)	Mean [SD] Range	77.7 [13.9] 51.1-103
BMI (kg/m^2)	Mean [SD] Range	28.1 [4.8] 17.4-35.5

Multivariate Data Analysis

Case study 1: Bioequivalent – test and reference drug data simulated by small variation in fast absorption rate constant KA_f



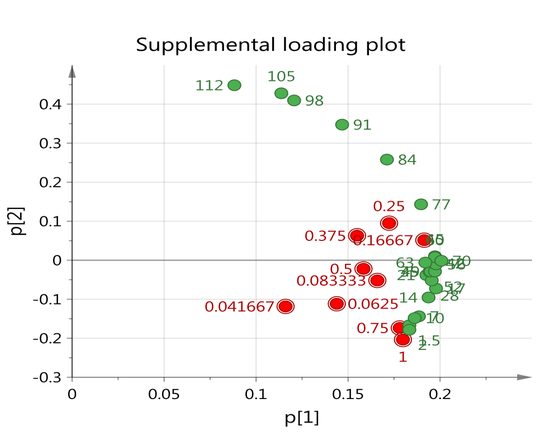
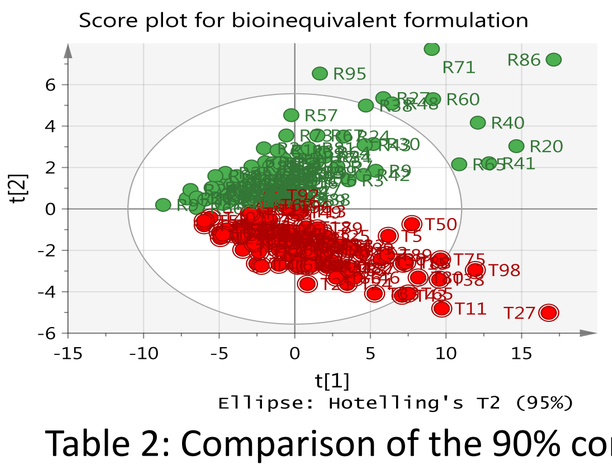


Table 1: Comparison of the 90% confidence intervals of natural log transformed pharmacokinetic parameters of octreotide following administration of two formulations (test/reference) of octreotide.

Parameters	Point estimate (%) [squared root of (lower 90%CI * upper 90%CI)]	Lower 90%CI	Upper 90%CI
$ln\ C_{max}$	104.60	95.28	114.84
$ln\ AUC_t$	100.79	91.70	110.79
$ln\ AUC_\infty$	100.78	91.69	110.78

- C_{max} maximum concentration
- *AUC* area under the serum octreotide concentration-time curve
- AUC_t from time 0 to time t and AUC_∞ from 0 to infinity.

Case study 2: Nonequivalent – test and reference data simulated by varying the fraction available for immediate release



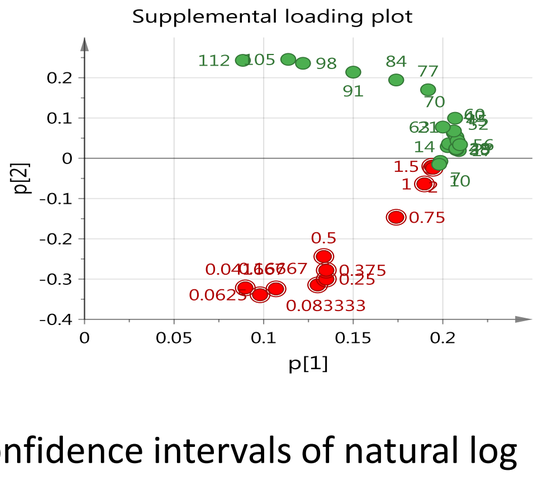


Table 2: Comparison of the 90% confidence intervals of natural log transformed pharmacokinetic parameters of octreotide following administration of two formulations (test/reference) of octreotide.

Parameters	Point estimate (%) [squared root of (lower 90%CI * upper 90%CI)]	Lower 90%CI	Upper 90%CI
$ln\ C_{max}$	274.43	249.91	301.358
$ln\ AUC_t$	100.50	91.43	110.473
$ln\ AUC_\infty$	100.48	91.41	110.452

Acknowledgement

Funded by U.S. Food and Drug Administration (FDA). This technical effort was performed under the RFA-FD-15-008 of Center for Drug Evaluation and Research.

Future Work

- Quantitative analysis of score space
- Sensitivity analysis due to variation in drug formulation and fraction of drug for immediate release