

Panel Discussion

IVPT Data Challenges and Statistical Analysis

In-vitro Release Test (IVRT) and *In-vitro* Permeation Test (IVPT) Methods
Best Practices and Scientific Considerations for ANDA Submissions
Virtual Public Workshop
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Priyanka Ghosh, Ph.D.

Acting Team Lead/ Co-chair of the Bioequivalence Standards for Topicals Committee
Office of Research and Standards (ORS), Office of Generic Drugs (OGD)
CDER | U.S. FDA

Introduction

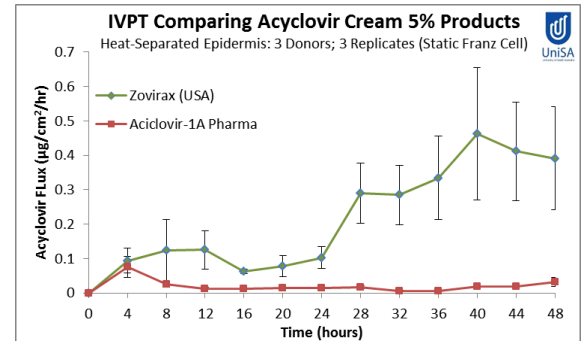
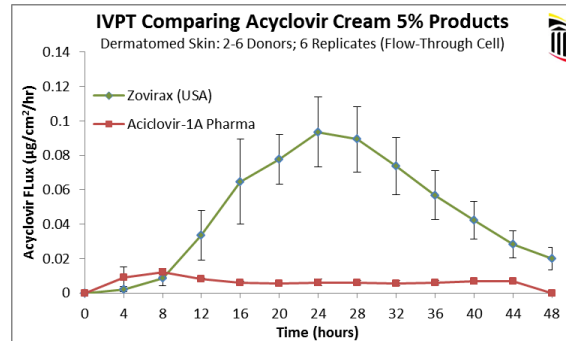
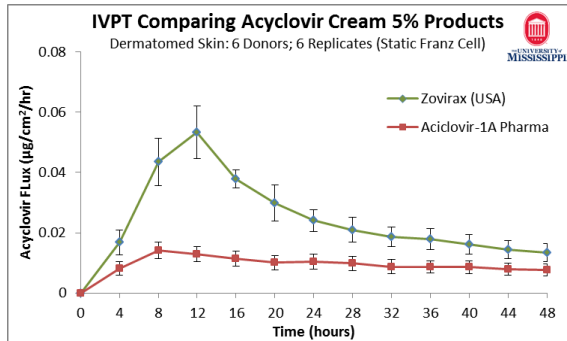


- **Charles Bon, MS** President, Biostudy Solutions LLC
- **Elena Rantou, PhD** Lead Mathematical Statistician (DB8), Office of Biostatistics, OTS, FDA
- **Hiren Patel, PhD** Staff Fellow, Office of Bioequivalence, OGD, FDA
- **Paul Lehman, MS** Vice President and Head of Dermal and Transdermal Research, QPS, LLC
- **Pina D'Angelo, MSc** Vice President, Biometrics, Innovaderm Research Inc.
- **Sam Raney, PhD** Associate Director for Science, ORS, OGD, FDA
- **Stella Grosser, PhD** Director (DB8), Office of Biostatistics, OTS, FDA
- **Yuzhuo Pan, PhD** Pharmacologist, Office of Bioequivalence, OGD, FDA

IVPT Study Results



	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm ²		
Dosing technique	Dispensed-Spatula Dispersed-glass rod	Dispensed and dispersed- Positive displacement pipette	Dispensed- Pipette Dispersed- Syringe plunger
Skin type	Torso	Abdomen	Abdomen
Thickness	Dermatomed	Dermatomed	Heat separated epidermis
Instrument	Franz diffusion cell (2 cm ²)	In-Line Flow through cell (0.95 cm ²)	Franz diffusion cell (1.3 cm ²)
Skin Integrity	Electrical Resistance	Trans Epidermal Water Loss	Electrical resistance



IVPT Data Challenges

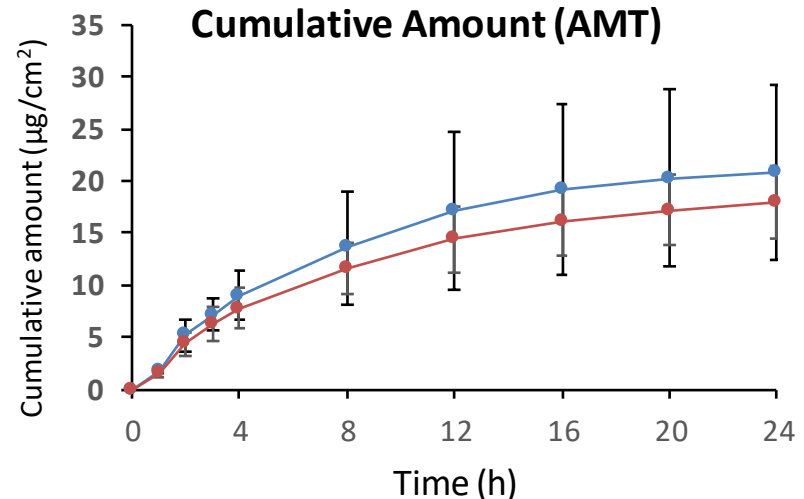
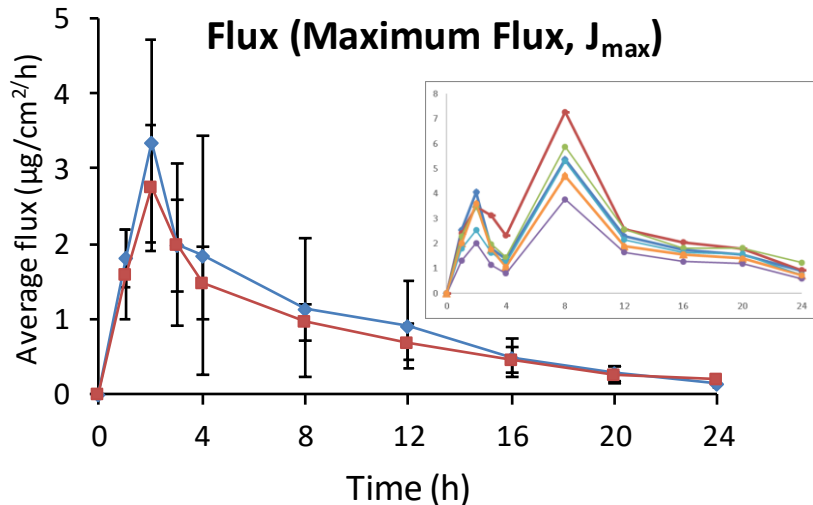
- *Challenges related to data analysis*
 - due to inconsistency of study conditions across method validation and pivotal studies
 - due to frequency of sampling and sampling technique, e.g., full receptor replacement vs. aliquot sampling
 - related to duration of the IVPT study as it relates to maximum flux (J_{\max})

IVPT Data Challenges

- *IVPT Sensitivity and Selectivity studies*
 - Number of donors and replicates for method validation studies
 - Qualitative vs. Quantitative assessment of data
- *IVPT pivotal study*
 - Number of donors (N) and replicates for pivotal study
 - Alternate options for identifying N, compared to utilizing a pilot study
- *Challenges related to data analysis for formulations with multiple active pharmaceutical ingredients*

Statistical Analysis

- *Challenges related to calculation of flux and cumulative permeation*
- *Challenges related to utilization of statistical approach*
- *Challenges related to handling “zero” values*

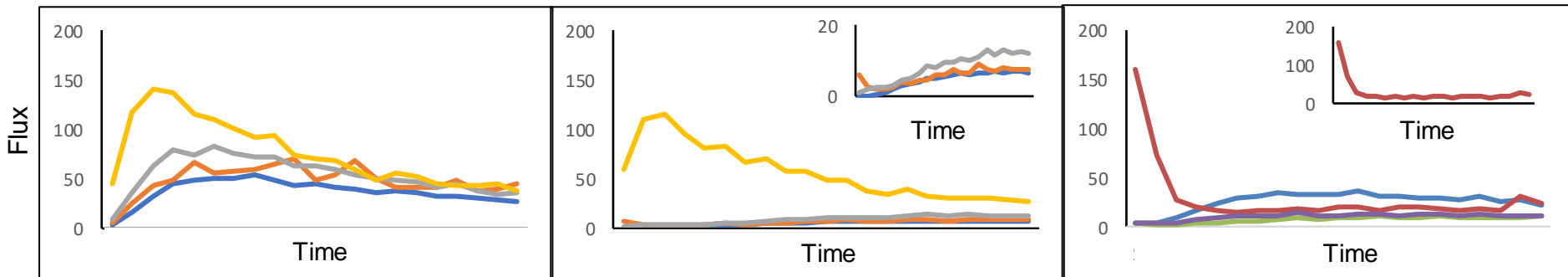


Data from 1 donor, represented as mean \pm std. deviation

Statistical Analysis



- *Challenges related “aberrant” data*



- Documentation related to exclusion of data with documented protocol violations or experimental errors
- Handling of “aberrant” data without documented protocol violations or experimental errors



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