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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
August 18, 2021

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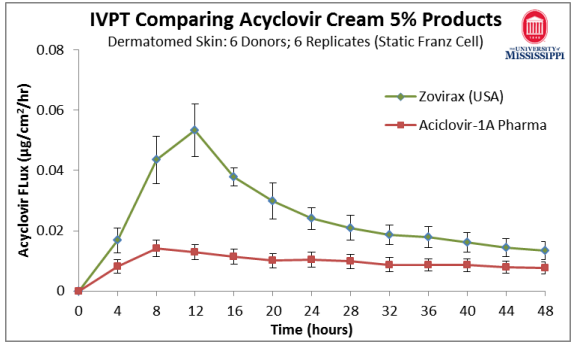
CDER | U.S. FDA

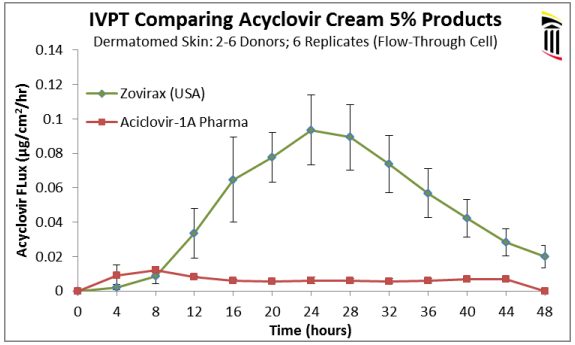
Introduction

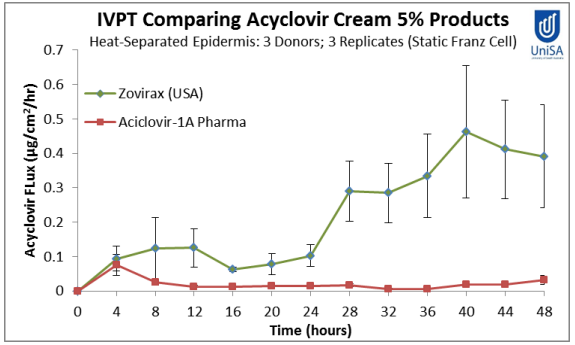
- ***Charles Bon, MS*** *President, Biostudy Solutions LLC*
- ***Elena Rantou, PhD*** *Lead Mathematical Statistician (DB8), Office of Biostatistics, OTS, FDA*
- ***Hiren Patel, PhD*** *Staff Fellow, Office of Bioequivalence, OGD, FDA*
- ***Paul Lehman, MS*** *Vice President and Head of Dermal and Transdermal 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

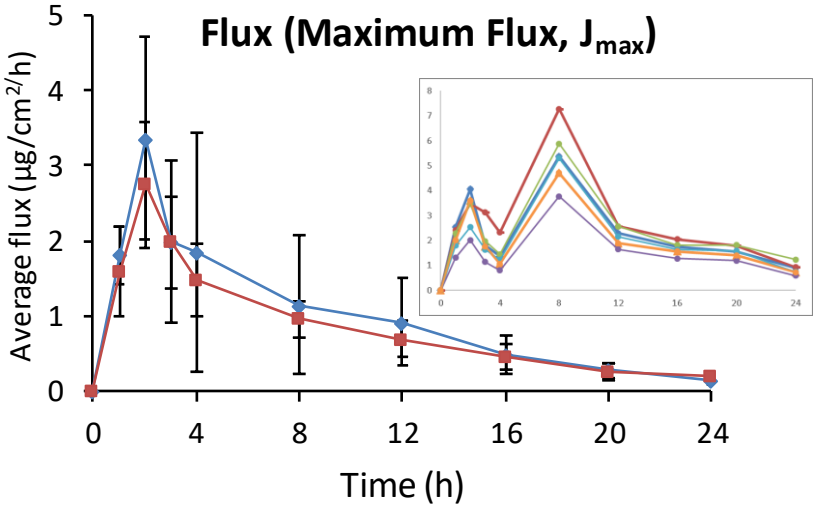
- *Challenges related to data analysis*
  - due to inconsistency of study conditions across method validation and pivotal studies
  - due to frequency of sampling and sampling technique, e.g., full receptor replacement vs. aliquot sampling
  - related to duration of the IVPT study as it relates to maximum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

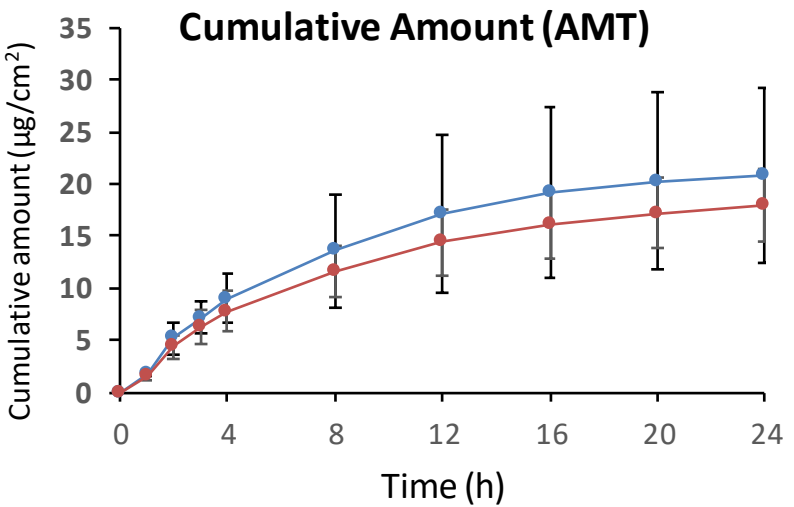
IVPT Data Challenges

- *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*

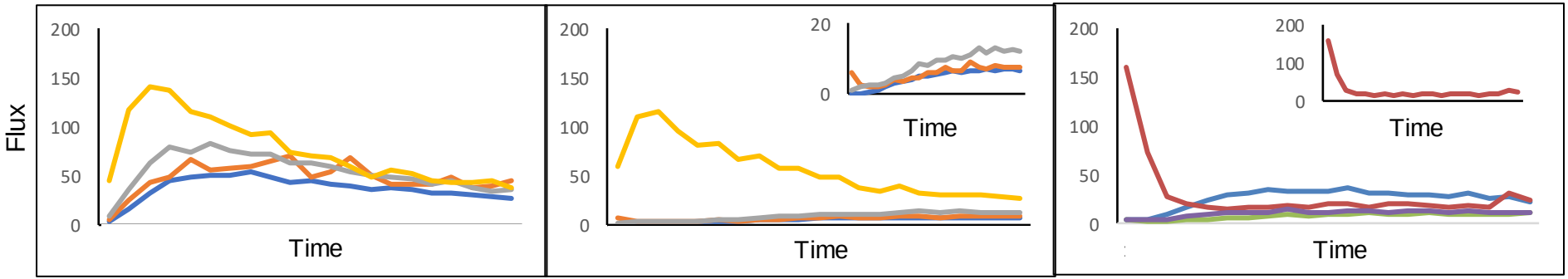




Data from 1 donor, represented as mean ± std. deviation

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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