Practical Considerations Related to *In-vitro* Permeation Test Studies for Topical Products Submitted in ANDAs

SBIA 2022: Best Practices for Topical Generic Product Development and ANDA Submission
Virtual Public Webinar
August 11, 2022

Hiren H. Patel, Ph.D.
Staff Fellow, Division of Bioequivalence II
Office of Bioequivalence, Office of Generic Drugs
CDER | U.S. FDA

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Bioequivalence of Topical Products

- Traditional methods to establish bioequivalence (BE)
  - *In-vivo* Pharmacokinetic Studies
  - *In-vivo* Pharmacodynamic Studies
  - *In-vivo* Comparative Clinical Endpoint Studies
- Alternative methods to establish BE
  - *In-vitro* Characterization Based Approaches:
    - No difference in inactive ingredient components and the quantitative composition. E.g., Qualitative (Q1) and Quantitative (Q2) Sameness
    - Physical and Structural (Q3) Sameness
    - *In-vitro* Release Test (IVRT)
    - *In-vitro* Permeation Test (IVPT)

IVPT Method Development Parameters

Parameters	Description/Details
Equipment*	Vertical Diffusion Cell (VDC) or Flow-Through Cell Types
Dose Amount	Finite Dose
Stirring Rate	Can often be standard
Sampling Amount	Larger sample volumes may reduce errors
Sampling Schedule	Suitable resolution for the flux profile
Receptor Solution	Suitable solubility for the drug without altering skin barrier
Skin Source	Cadaver or harvested from patients undergoing a surgical procedure
Skin Type	Anatomical location (e.g., posterior torso, abdomen, etc.)
Skin Preparation	Dermatomed, Heat-separated epidermis, etc.
Skin Barrier Integrity Test	Trans-Epidermal Water Loss (TEWL), Tritiated Water, Electrical based

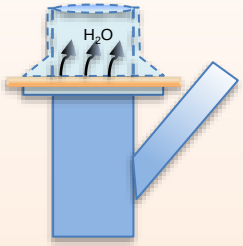
* termed as “Apparatus” in the draft product-specific guidance (PSG) of Acyclovir Cream

Skin Barrier Integrity Testing: Basics

- Identifies (for exclusion) skin sections with compromised barrier integrity
- May not correlate with permeation of most topically applied drugs
- The technical procedures do not irreversibly alter the skin barrier
  - If the test involves hydrating the stratum corneum, sufficient time is afforded for the stratum corneum to return to a normal state of hydration before dosing.

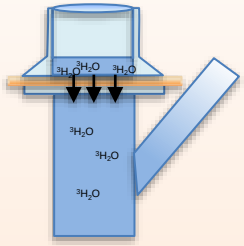
Skin Barrier Integrity Testing

Trans-Epidermal Water Loss (TEWL)



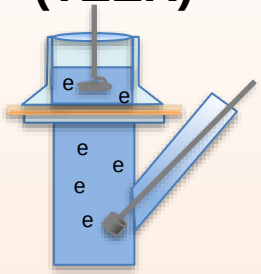
Test results reported as TEWL ($g/m^2/hr$)

Tritiated Water (^3H_2O)



Test results reported as permeated amount of tritiated water per skin area (eq. $\mu L/cm^2$)

Trans-Epidermal Electrical Resistance (TEER)



Test results reported as resistance (kΩ) or conductance (1/kΩ or mS). Units may also involve normalization of skin area.

Skin Barrier Integrity Testing

- Acceptance criterion is a pre-defined inclusion/exclusion cutoff to pass/fail the test
  - Based on the distribution of results (from multiple donors and replicates) when using the specific test procedures with the specific type and preparation of skin
- Acceptance criterion discriminates skin sections with a normal barrier integrity from those with a compromised barrier integrity
  - Verified by assessing the ability of the barrier integrity test method to correctly identify skin sections with a deliberately compromised skin barrier

Receptor Solution Qualification

- The receptor solution should be qualified in relation to:
  - Stability of the drug in the receptor solution
  - The use of an anti-microbial agent in the receptor solution (e.g., ~0.1% sodium azide or ~ 0.01% gentamicin sulfate)
  - Solubility of the drug in the receptor solution
    - 0.1% or 0.2% polyoxyethylene[20]oleyl ether (also known as Oleth-20, Volpo-20, or Brij-20) is commonly used as a solubility enhancer for hydrophobic drugs
  - Compatibility with the skin (i.e., no alteration to skin barrier function).
    - Inclusion of organic solvents and alcohols in the receptor solution may alter the skin barrier function

IVPT Method Validation: The Foundation

Sensitivity

- Typically performed toward the end of the IVPT method development phase
- Key purpose is to establish IVPT method parameters such as dose amount, dose duration, study duration, etc.

Selectivity

- Performed once the IVPT method parameters are established
- Typically performed as a part of IVPT pilot study which supports multiple IVPT method validation parameters

IVPT Sensitivity

- IVPT sensitivity is the ability of the IVPT method to detect changes in the cutaneous pharmacokinetics of the drug as a function of differences in drug delivery.

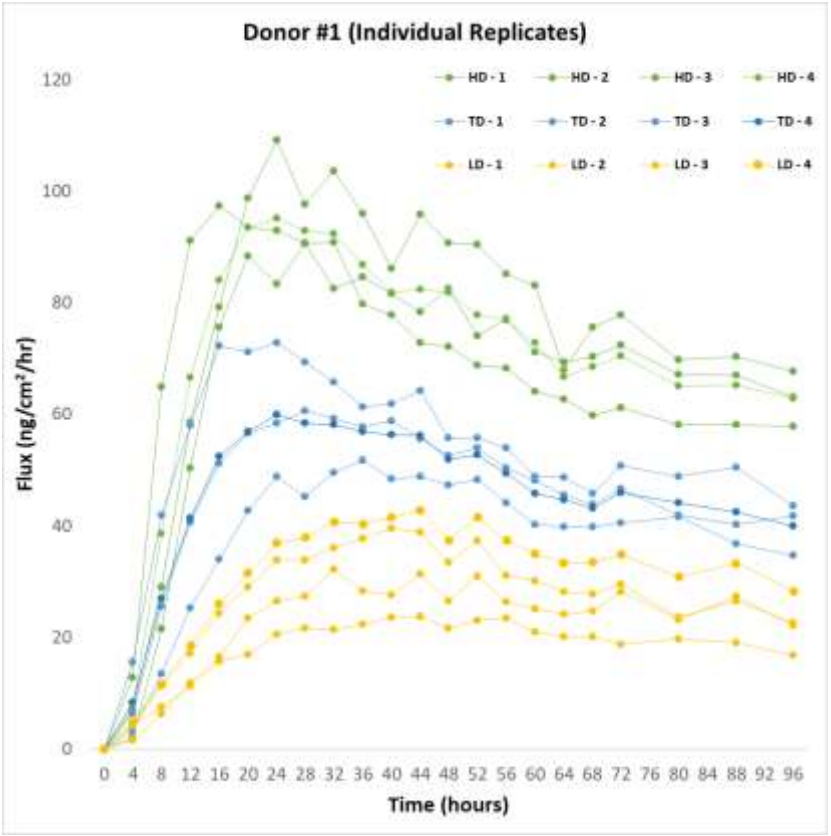
- The IVPT method may be considered sensitive if it consistently demonstrates higher and lower flux profiles in response to increased and decreased drug delivery.

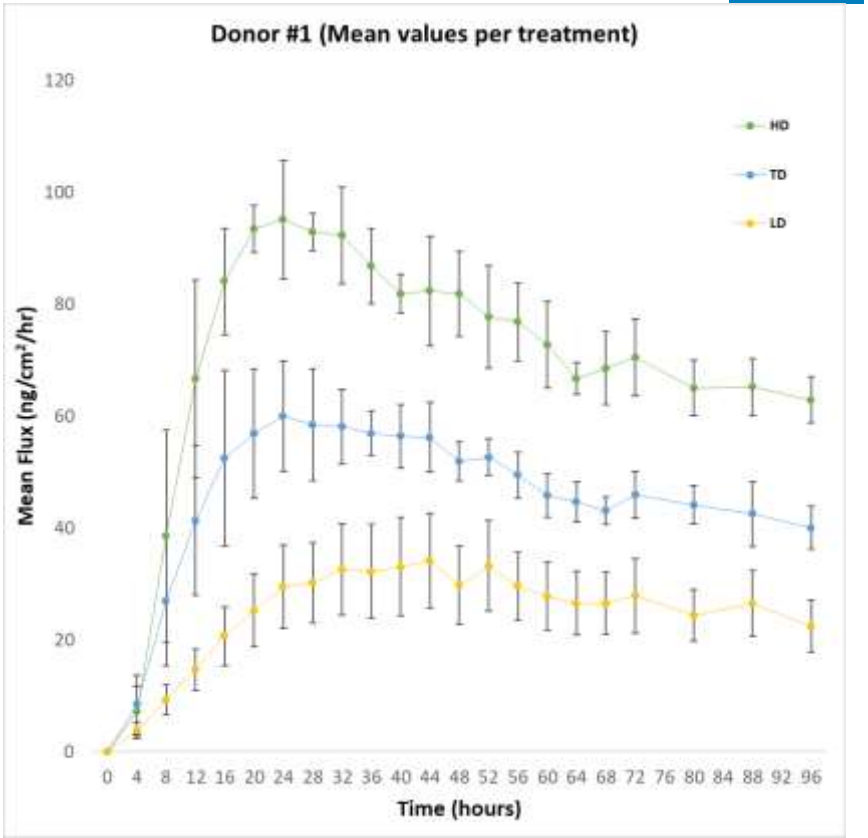
- The differences in the IVPT permeation profiles are not expected to be specifically proportional to the differences in the dose amount, dose duration, or product strength.

Sensitivity using Dose Amount

- This approach is well suited to topical products that contain volatile components that evaporate from the formulation following dose application to the skin.
  - For example, a thinner dose will tend to evaporate more rapidly and tend to deliver less drug into the skin (and/or for a shorter duration) compared to a thicker dose.
- Modulating the dose amount may not necessarily produce perceptible differences in drug delivery for certain topical drug products, e.g.,
  - Petrolatum-based ointments
  - The topical products that do not evaporate on the skin
  - The products that may not experience dose-dependent differences in metamorphosis

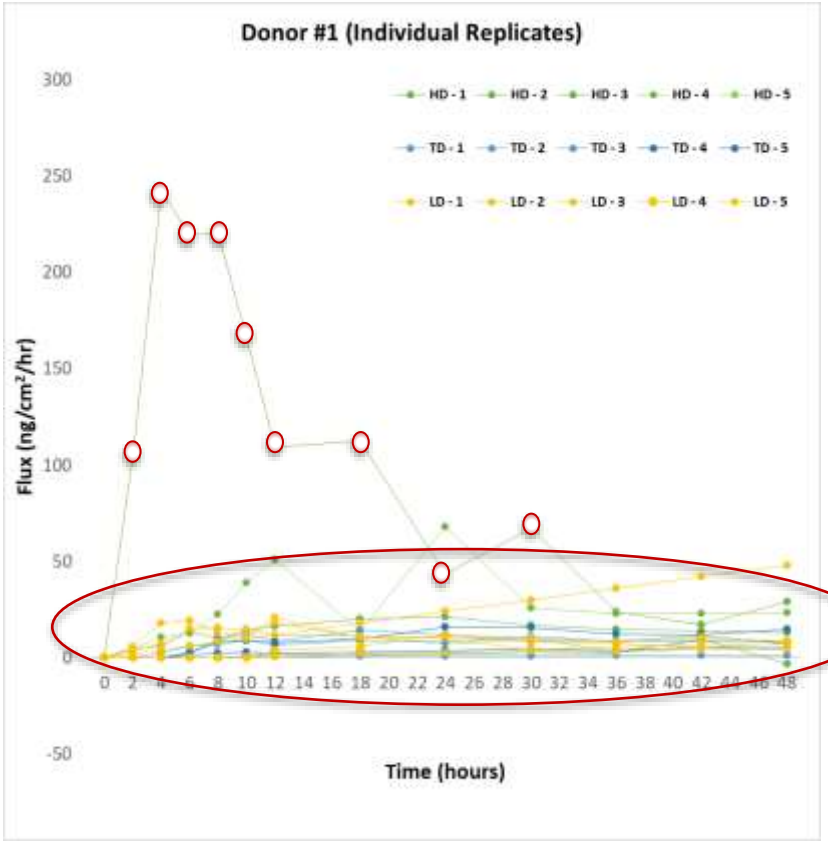
Case Study #1

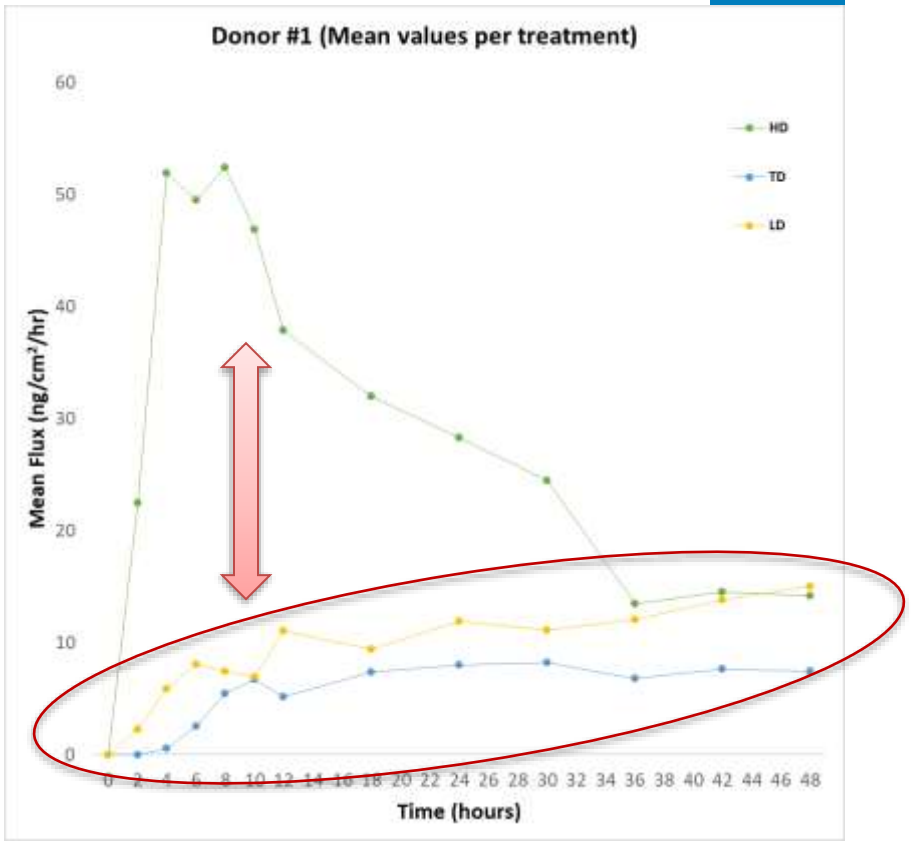




HD: Higher Dose Amount; TD: Target Dose Amount; LD: Lower Dose Amount

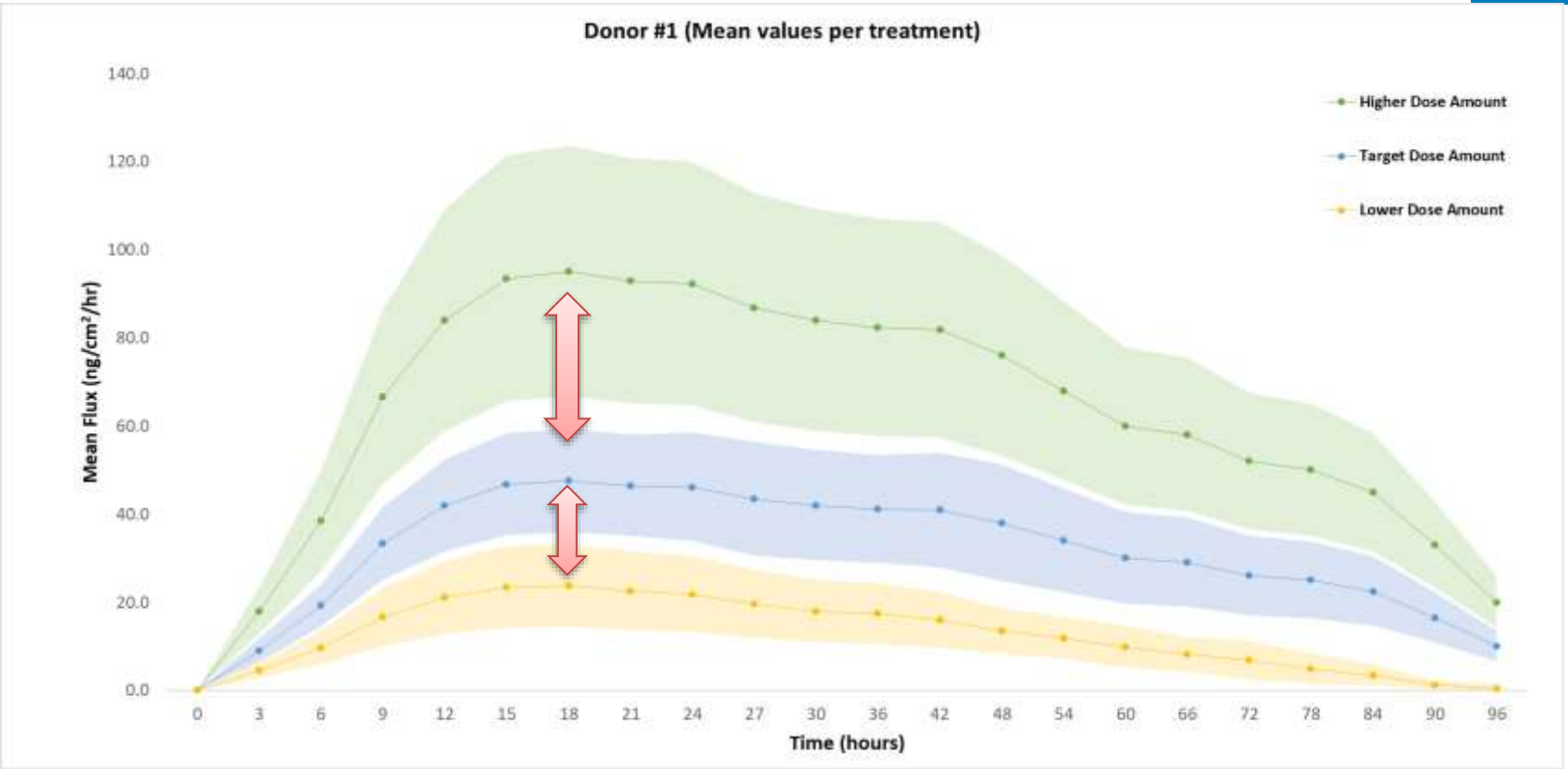
Case Study #2





HD: Higher Dose Amount; TD: Target Dose Amount; LD: Lower Dose Amount

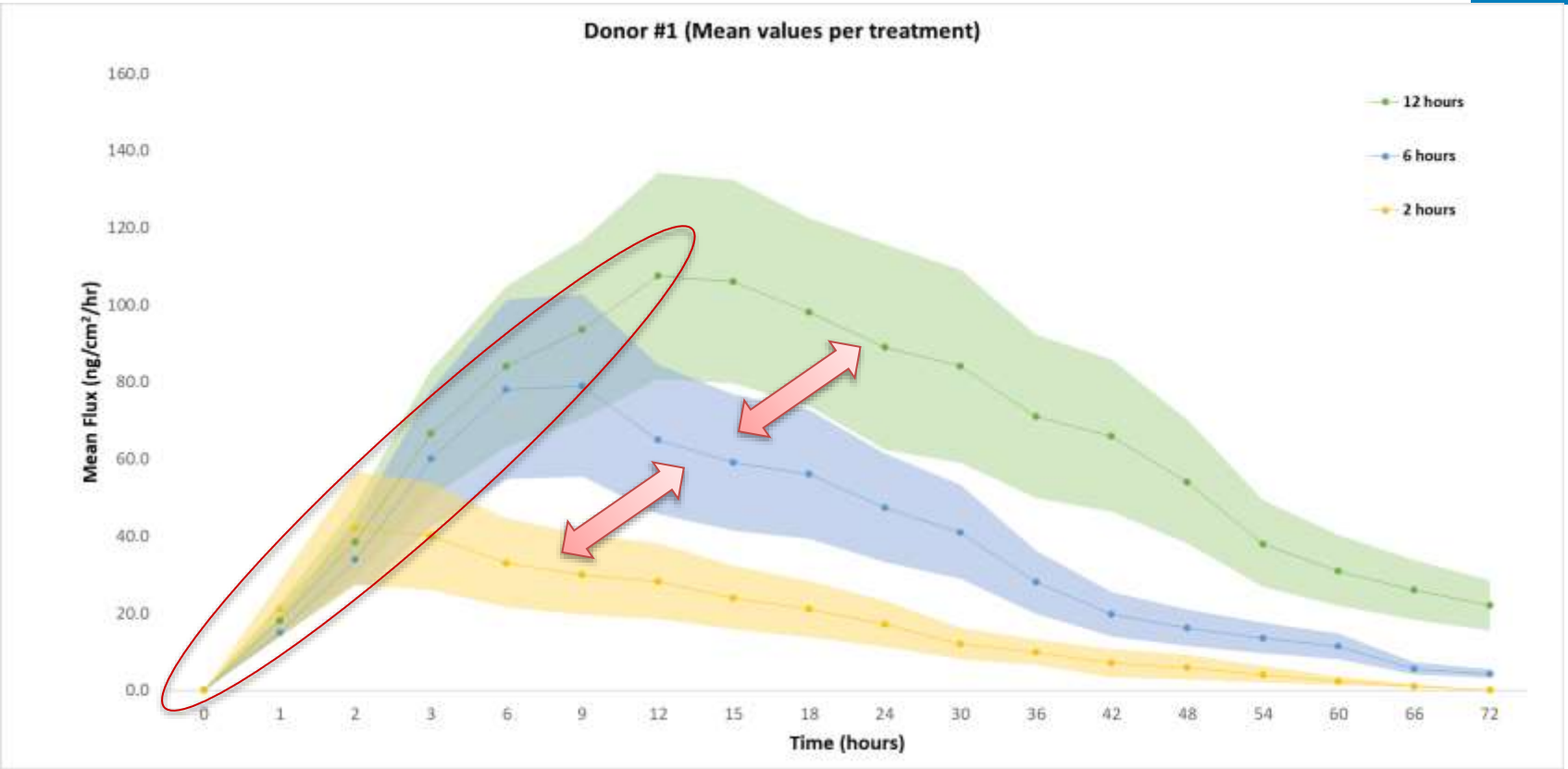
Sensitivity: Modulation of Dose Amount



Sensitivity using Dose Duration

- An IVPT study with a controlled dose amount applied for different dose durations may be well suited to provide supportive evidence that the IVPT methodology is sensitive.
- An important feature of the results from such an IVPT study is the duration of the initial phase of the permeation profile, when the flux is increasing at a relatively rapid rate.
- Considerations for the selection of dose duration
  - Target dose duration: Sensitivity of sample analytical method, and/or the labeled use of the topical product (which may indicate that the topical product should be re-applied every 4–6 hours).
  - Shortest dose duration: Sensitivity of the sample analytical method and its ability to produce a permeation profile that can be perceptibly discriminated from that produced by the target dose duration (e.g., 6 hours)

Sensitivity: Modulation of Dose Duration



Sensitivity using Product Strength

- Altered strength formulations are routinely used to validate the sensitivity, specificity, and selectivity of an ***in-vitro* release test (IVRT)** method.
- It may seem convenient to use these altered strength formulations in an attempt to demonstrate the sensitivity of an IVPT method; however, doing so may not produce the desired outcomes.
- In general, the modulation of product strength to support a demonstration of IVPT sensitivity is not recommended because it may not consistently produce the expected increase or decrease in drug delivery.
  - In certain situations, there may be exceptions.

IVPT Pilot Study

- Performed with skin sections from multiple donors (e.g., 4 – 6 donors) with minimum 4 replicates per donor per treatment
- Conducted with three parallel treatments of
  - Test product
  - Reference product
  - A topical product or formulation that is known or designed to be different from the reference topical product
- Supports a validation of IVPT method parameters like permeation profile, range, precision, reproducibility, and selectivity
- May be useful to estimate the number of donors (and replicates) needed to power the pivotal IVPT study

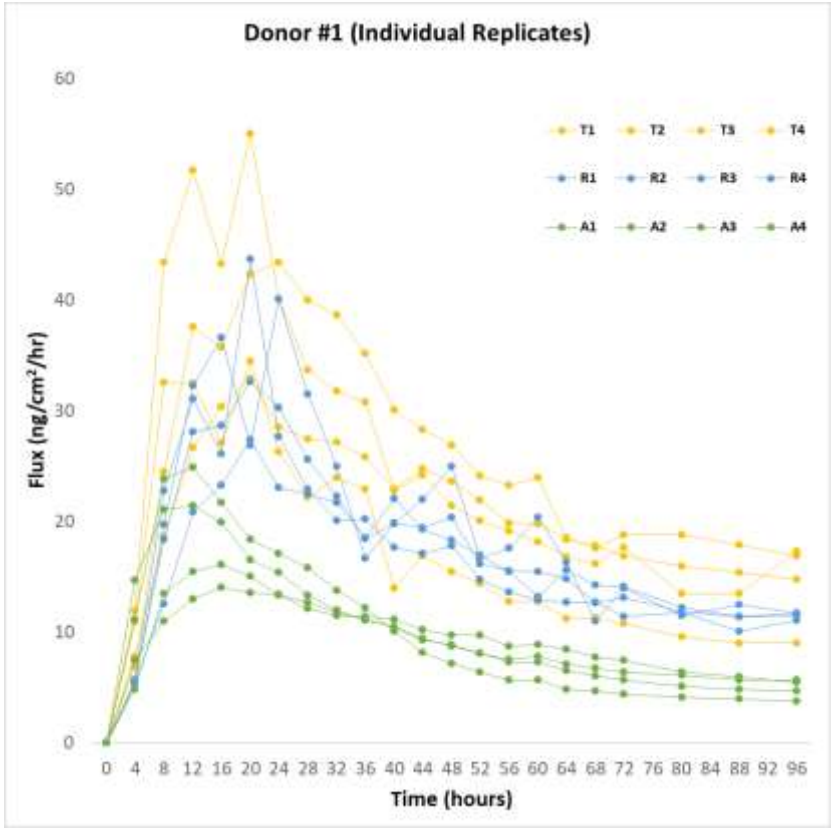
IVPT Selectivity

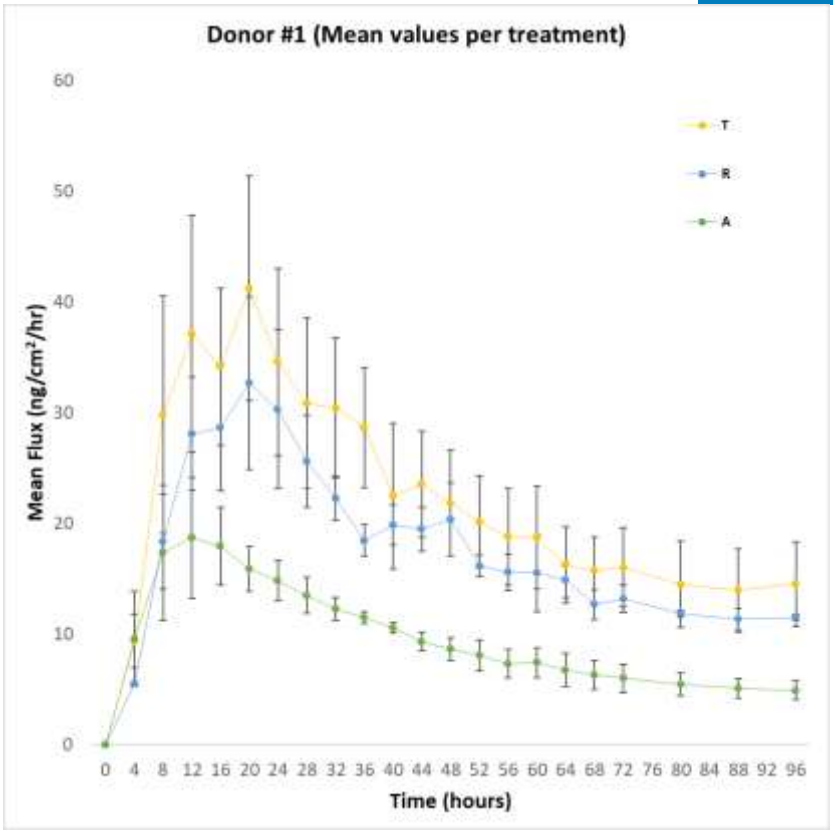
- IVPT Selectivity is the ability of the IVPT method to discriminate the cutaneous pharmacokinetics of a drug between products or formulations that exhibit differences in drug delivery.

- Parallel assessment in the IVPT pilot study of the reference product, the test product, and a third product or formulation (that is known or designed to be different from the reference product) provides supportive evidence that the IVPT methodology is selective.

- This IVPT selectivity study is performed as part of the IVPT pilot study.

Case Study





T= Test Product; R= Reference Product; A= Altered Formulation/Product

Control of Study Procedures

- Control of procedures related to the skin include the consistent control across the study about the skin preparation (e.g., dermatoming of skin sections) and the thickness of skin sections mounted on diffusion cells, as well as the skin storage conditions, including the duration for which the skin was frozen and the number of freeze-thaw cycles to which the skin was exposed.

- Skin from the same anatomical site should be used from all donors, and the demographics (age, race, sex) should be reported and used for all donors for IVPT sensitivity, pilot, and pivotal studies.

Control of Study Procedures

- Control of procedures related to the dose include the control of the area of dose application, the dose amount, the dosing technique, the dose duration, and the blinding and randomization procedures for dosing.
  - The test and reference topical products should be dosed in an identical and consistent manner for all diffusion cells in the study.
  - Differences in dosing technique may alter the metamorphosis of the dosage form on the skin, and inconsistencies in the diameter of the area dosed on each diffusion cell may significantly influence the dosed area and contribute to errors in the calculation of flux.

Control of Study Procedures

- Control of procedures related to sampling include the control of sampling time, the sampling technique, the duration of sampling and replacement of receptor solution, the sample volume or flow rate, and sample handling and storage.
- Control of procedures related to the IVPT study should include a non-dosed control skin section from each skin donor and should be treated identically to the dosed skin sections.
  - This procedure ensure that there is no drug contamination across the duration of the study.
- A pre-dose “zero” sample collected from each diffusion cell is also recommended, which may identify potential contamination associated with each skin section and/or each diffusion cell.

IVPT Endpoints

- Maximum flux (J_{max})
  - The flux (rate of drug permeation) profile should be plotted as the flux (e.g., ng/cm^2/hr) on the Y-axis versus time on the X-axis.
- Total cumulative amount (AMT)* permeated into the receptor solution across the study duration
  - The extent of drug permeation should be plotted, as the total cumulative amount of drug permeated (e.g., ng/cm^2) on the Y-axis versus time on the X-axis.

* termed as “AUC” in the draft PSG of Acyclovir Cream

Statistical Analysis

- If $S_{WR} \geq 0.294$, use the reference-scaled average BE approach to determine BE for the individual IVPT endpoint(s)
- If $S_{WR} < 0.294$, use the regular average BE approach through the two one-sided tests (TOST) procedure to determine BE for the individual IVPT endpoint(s)
- At the completion of the study*,
  - If the number of skin replicates are the same for all donors in the test and reference topical product treatment groups in the IVPT study, use a balanced design statistical analysis
  - If skin sections or diffusion cells are excluded from the final statistical analysis because of experimental loss/issues, and the resulting data set is unbalanced, use an unbalanced design statistical analysis

* Excerpted from Dr. Elena Rantou's presentation on "Statistical Considerations in Assessing BE of IVPT Data" from virtual public workshop hosted by FDA and the Center for Research on Complex Generics (CRCG)

Resources to Refer…

- The recordings and meeting materials from virtual public workshop hosted by FDA and the Center for Research on Complex Generics (CRCG) on August 18-20, 2021, *In Vitro* Release Test (IVRT) and *In Vitro* Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Available at http://www.complexgenerics.org/IVRTIVPT/.

Acknowledgements

- Anil K. Nair, PhD
- Diana Vivian, PhD
- Xiaojian Jiang, PhD
- Hongling Zhang, PhD
- Bing Li, PhD
- Partha Roy, PhD
- Ying Jiang, PhD
- Tannaz Ramezanli, PhD
- Priyanka Ghosh, PhD
- Sam Raney, PhD
- Bioequivalence Assessors

Thank you!

Questions?

Hiren H. Patel, Ph.D.
Staff Fellow, Division of Bioequivalence II
Office of Bioequivalence, Office of Generic Drugs
CDER | U.S. FDA


FDA
U.S. FOOD & DRUG
ADMINISTRATION