Challenges in the Assessment of ANDAs with IVPT Studies - Bioequivalence Perspective

Modernizing Bioequivalence Approaches for Topical & Transdermal Products - September 10, 2026

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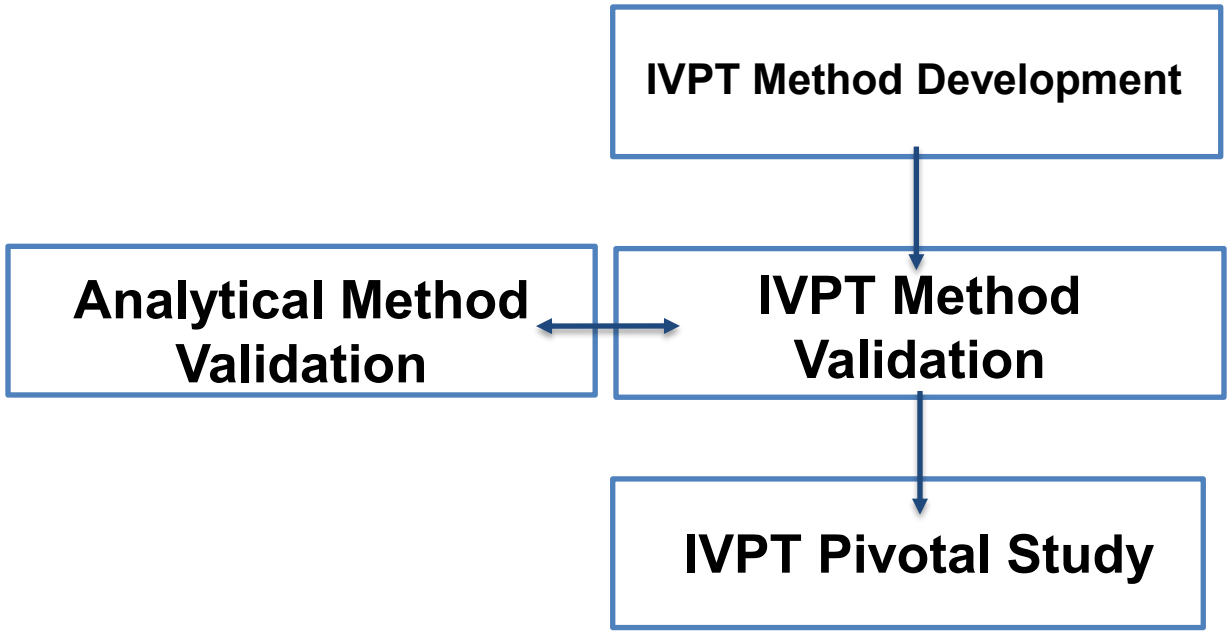
Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objective

- Highlight continuing challenges observed in the conduct and analysis of in-vitro permeation test (IVPT) studies in ANDA submissions for topical drug products
- Provide general recommendations on critical aspects of study conduct and analysis to improve submission and data quality

IVPT Methodology



IVPT Method Validation Framework

Qualification

- Equipment
- Skin
- Receptor Solution & its sampling

Environmental Control

Sensitivity ⭐

Pilot Study

- Selectivity ⭐
- Permeation Profile & Range
- Precision & Reproducibility
- Dose Depletion

➢ Supported by method development, validated analytical method and a quality management system

IVPT Method Validation Foundation

Sensitivity

- Key purpose is to establish the suitability of final IVPT method parameters
- Detect changes due to dose modulation
- Same product at different dose amounts or dose durations

Selectivity

- Performed as a part of pilot study
  - Reference Standard, Test and Altered product
- Provides evidence that the developed IVPT method can discriminate between RS and an altered formulation, designed to be different from the RS

Designing an IVPT Sensitivity Study

- Uses **4 to 6 skin donors** and minimum **4 replicate skin sections** per donor per treatment group
- Consistent method parameters across sensitivity, pilot and pivotal studies
- Treatments run in parallel on a given skin donor, including non-dosed cell
- In general, start using 3-fold difference amongst dose amounts

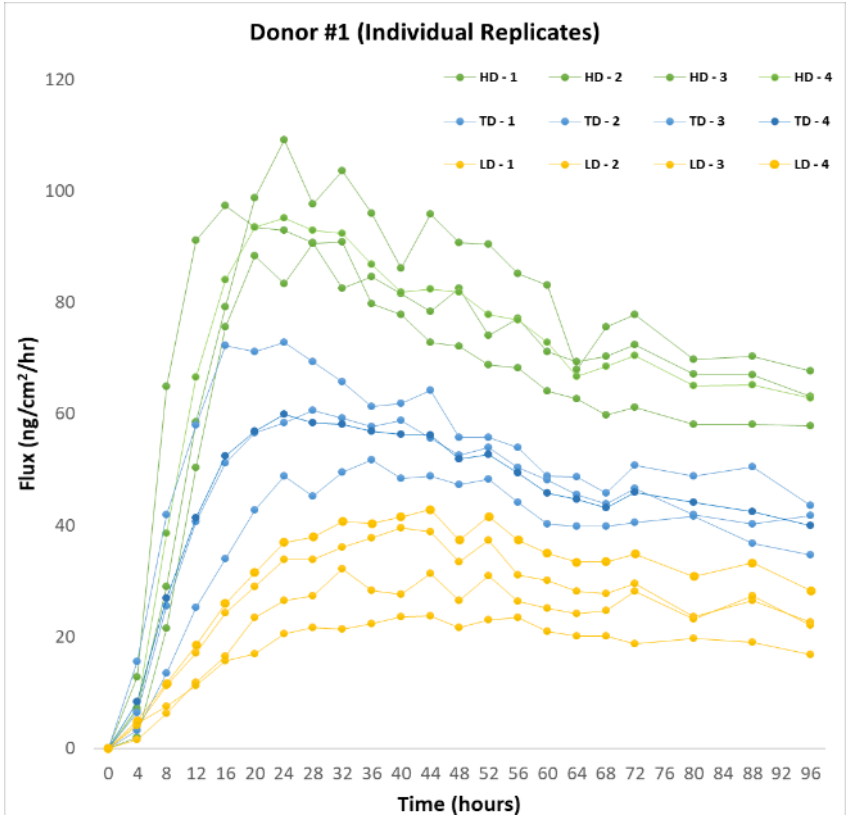
Special Considerations for Dose Duration Modulation study design:

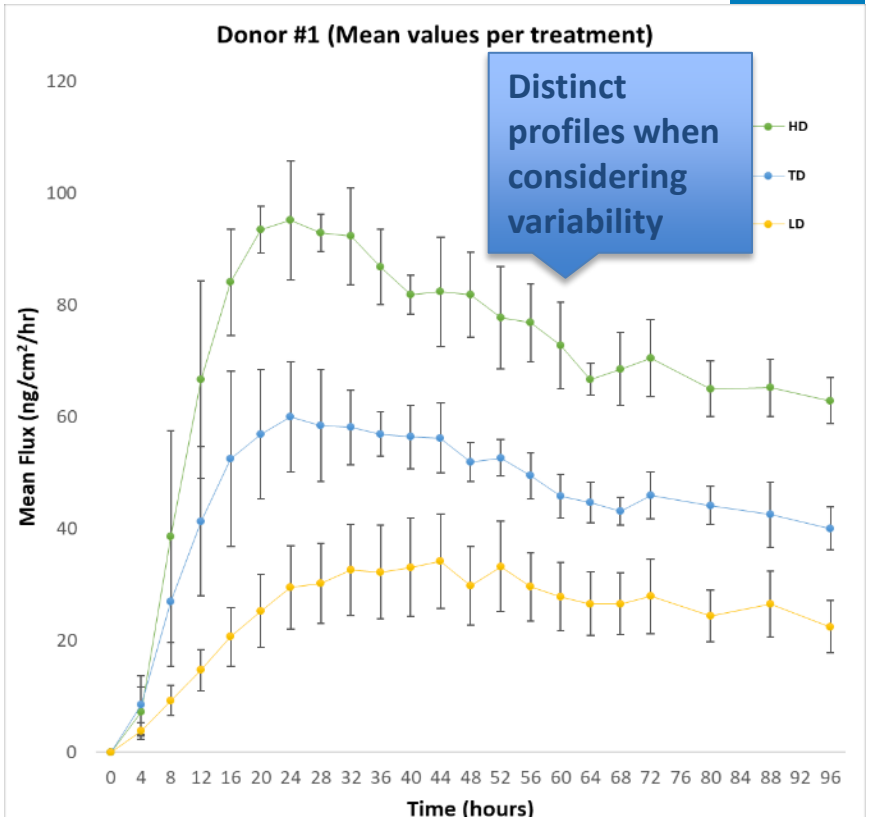
- Sufficiently characterize the flux profile shape and use this to select appropriate dose durations for the study
- The dose removal procedure should be consistently applied; it should be developed, optimized, and demonstrated to be precise and reproducible

IVPT Sensitivity

- The IVPT method may be considered sensitive if it consistently demonstrates higher and lower flux profiles in response to increased and decreased drug delivery for the **majority of donors**
- Assessment: across multiple donors, evaluate method sensitivity using a qualitative approach
  - Mean permeation profile and individual replicate profiles for each donor and each treatment

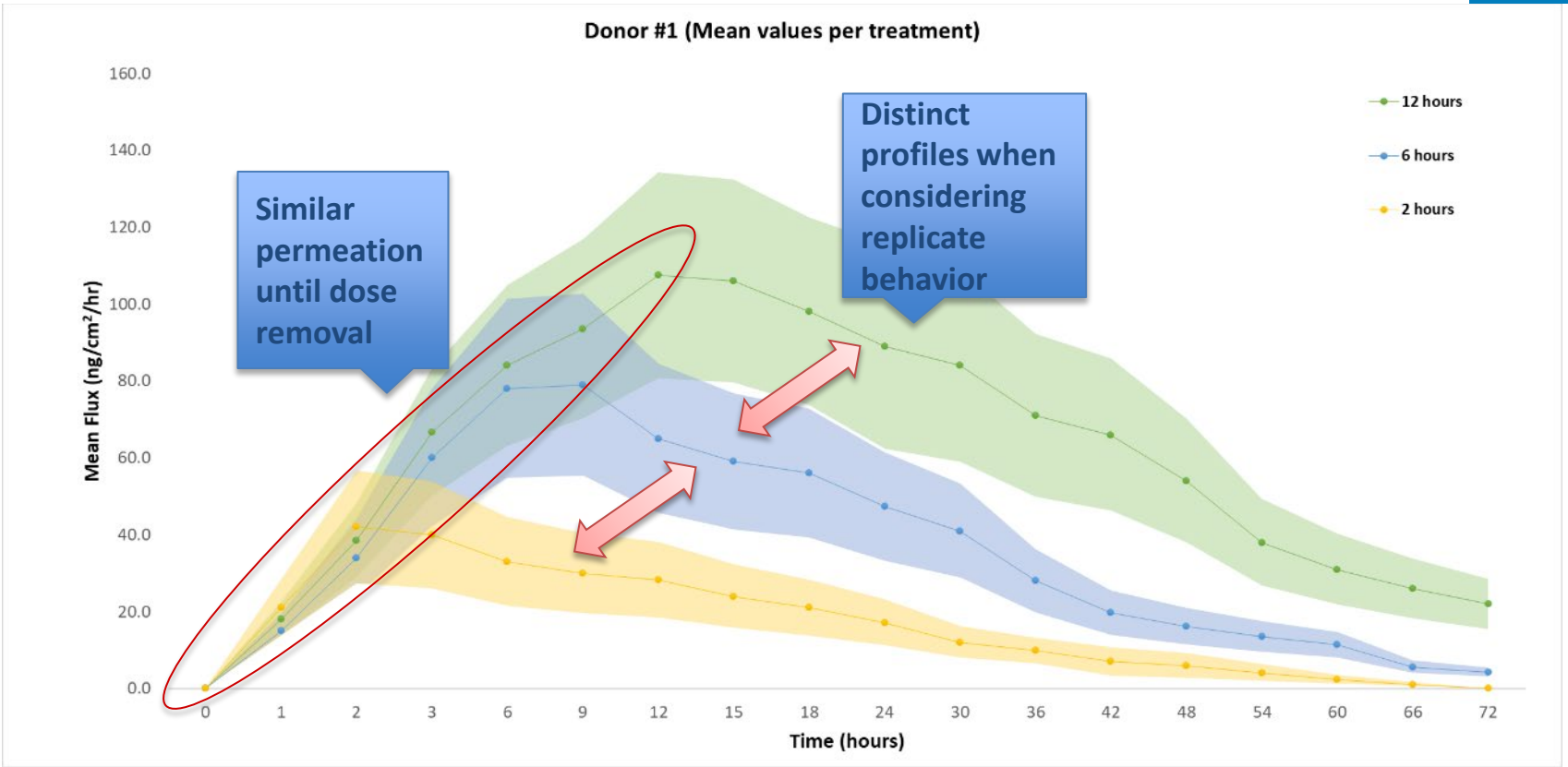
Hypothetical Case Study





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

Sensitivity: Modulation of Dose Duration



slide courtesy of Dr. Hiren H. Patel (OGD/FDA)

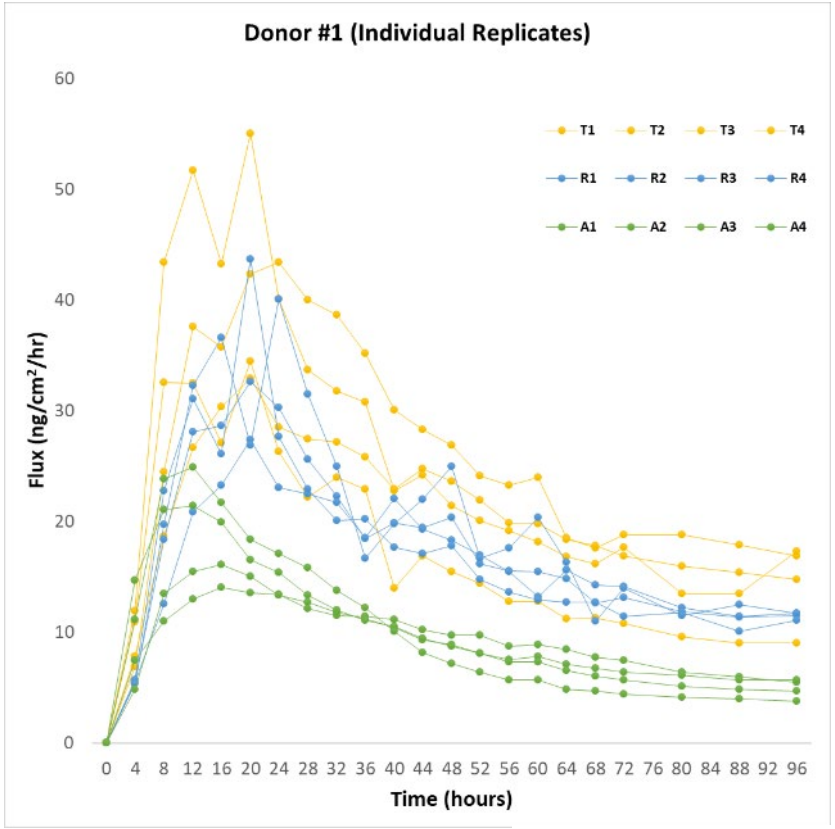
Designing an IVPT Selectivity Study

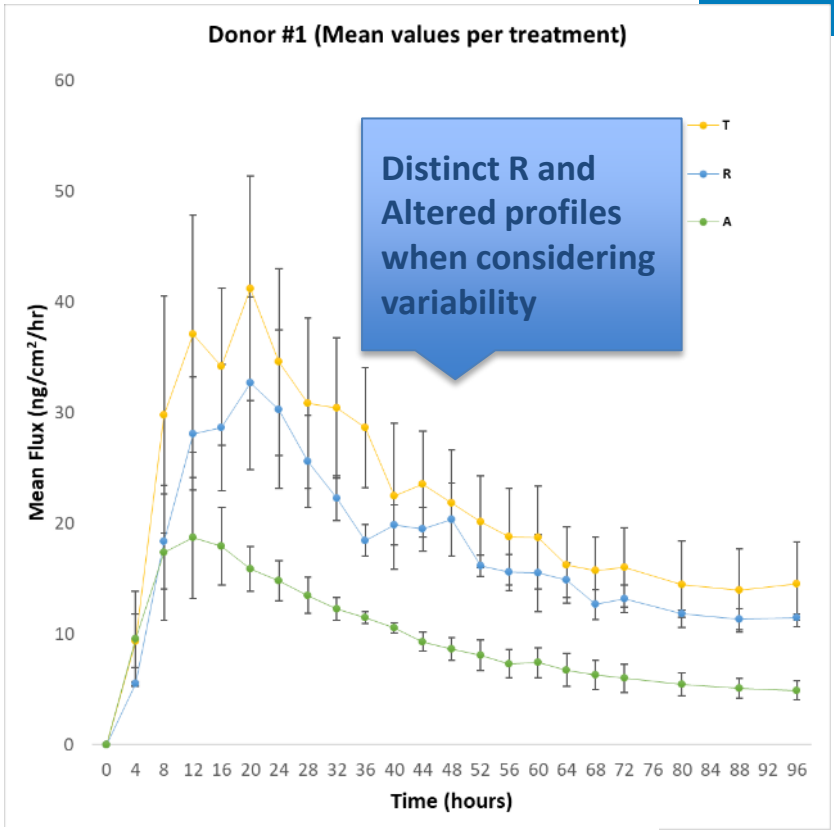
- Uses **4 to 6 skin donors** and minimum **4 replicate skin sections** per donor per treatment group
- Consistent method parameters across IVPT studies (sensitivity, pilot, pivotal)
- Treatments run in parallel on a given skin donor, including non-dosed cell
- Select altered product which is expected to have different permeation from the Reference Standard (e.g., different Q3 characteristics, solution vs. cream)
    - Include batch information for altered formulation (batch formula, manufacturing date, manufacturing process, batch size, potency/content uniformity, etc.)

IVPT Selectivity

- Discrimination in permeation profiles between the reference standard and altered formulations should be apparent to demonstrate method selectivity
- Assessment: across multiple donors, evaluate method selectivity using a qualitative approach
  - Mean permeation profile and individual replicate profiles for each donor and each treatment

Hypothetical Case Study





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

IVPT Receptor Solution Qualification

- Verifies **compatibility** with skin and **stability** of drug in receptor solution at testing conditions
- Drug **solubility determined in triplicate** — must exceed the highest expected sample concentration
  - consider expected higher concentrations generated under increased drug delivery conditions (e.g., sensitivity study)
- Utilization of an anti-microbial agent is recommended
- May use solubility enhancer
  - 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

IVPT Skin Qualification

- Each skin section should be qualified using a barrier integrity test procedure as described in the guidance with proposed acceptance criteria supported by experimental data
- Consistency is key
  - Skin source, storage temperature, preparation and handling
- Avoid handling the skin in a way which may damage the skin barrier

IVPT Skin Qualification

Best practice

- Provide replicate and mean data
- Provide manufacturer, instrument and other information as applicable e.g., adapter used
- Include integrity measurement before IVPT run
- Standardize procedures for measuring skin barrier integrity

Avoid

- Prolonged submersion of the skin in aqueous media prior to mounting
- Creating imbalances in skin thickness across treatment groups
- Measuring barrier integrity after completion of the IVPT run

IVPT Dosing and Sampling

- Dosing procedures are critical step in the IVPT method
  - ensure consistent dosing application, dose amount and dosed area
- IVPT diffusion cells should not be occluded
- A non-dosed skin section should be run and sampled at all sampling points
- Ensure consistent durations between dosing and sample collection across all diffusion cells
  - provide sampling details and supporting evidence demonstrating the suitability of the respective sampling method, whether manual or automated

Perspective: Aberrant Data

- Well-controlled procedures should be in place during the conduct of the IVPT study
  - if protocol deviations arise for any reason, they should be appropriately documented (e.g., real time observations of the cells and equipment)
- It may be possible to observe aberrant data that cannot be explained by any documented protocol deviation
- Outlier criteria should be defined prospectively in the study protocol (e.g., statistical test and alpha level).
  - Evaluate the impact of aberrant data on BE analysis; provide appropriate justification if impacted
  - The acceptability will be evaluated on case-by-case basis considering totality of the data

Concluding Remarks

- IVPT method validation studies, especially sensitivity and selectivity studies, present persistent challenges in the ANDA assessment
- By following established guidance and best practices, applicants can meaningfully improve submission quality, reduce review cycles, and support the timely availability of safe and effective generic topical drug products for patients.
- Provide supporting justification in the submission if deviating from guidance recommendations

Resources to Refer…

- Draft Guidance for Industry: In-vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs

- The recordings and meeting materials from two public workshops hosted by the FDA and the Center for Research on Complex Generics (CRCG)

  - 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/.

  - April 29-30, 2025, Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration. Available at https://www.complexgenerics.org/education-training/implementing-fdas-ivpt-guidance-recommendations-a-step-by-step-ilustration/

- USP Chapter <1724>: Semisolid Drug Products- Performance Tests

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Thank you!