

# Theoretical Principles and Best Practices In Vitro Permeation Testing (IVPT)

**SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval**  
**Day 2, Session 3: (Topical Products Pt. 2)**

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CDER | U.S. FDA

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# Learning Objectives

- *Discuss how an IVPT can be utilized as a component of characterization-based bioequivalence (BE) approaches*
- *Discuss Challenges and Current Thinking Related to IVPT*
  - IVPT method development (MD) studies
  - IVPT method validation (MV) studies
  - IVPT pivotal study and data analysis

# IVPT Studies

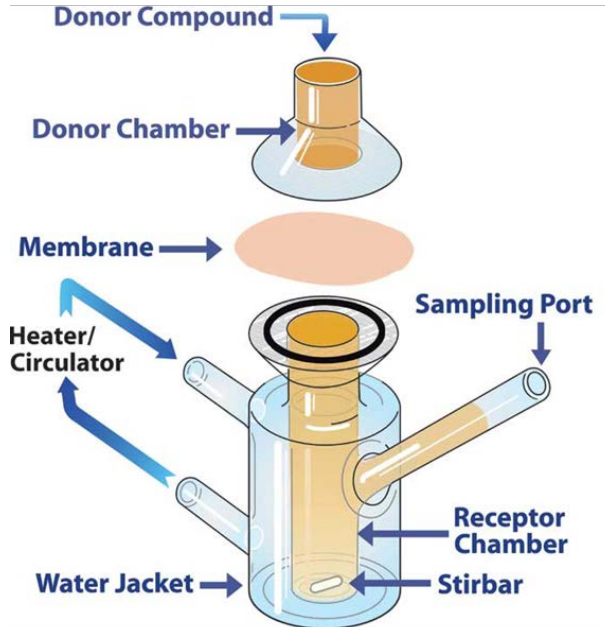
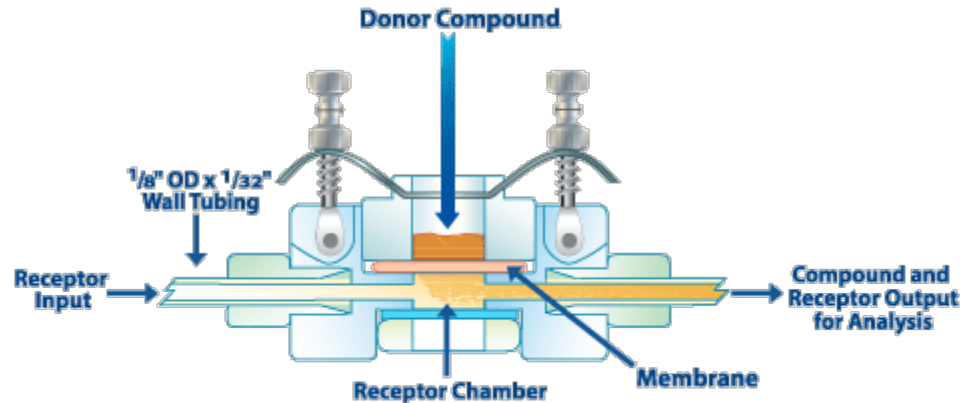
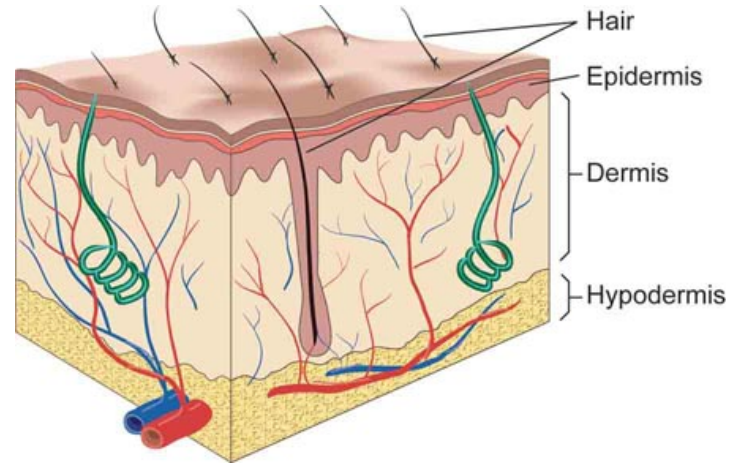
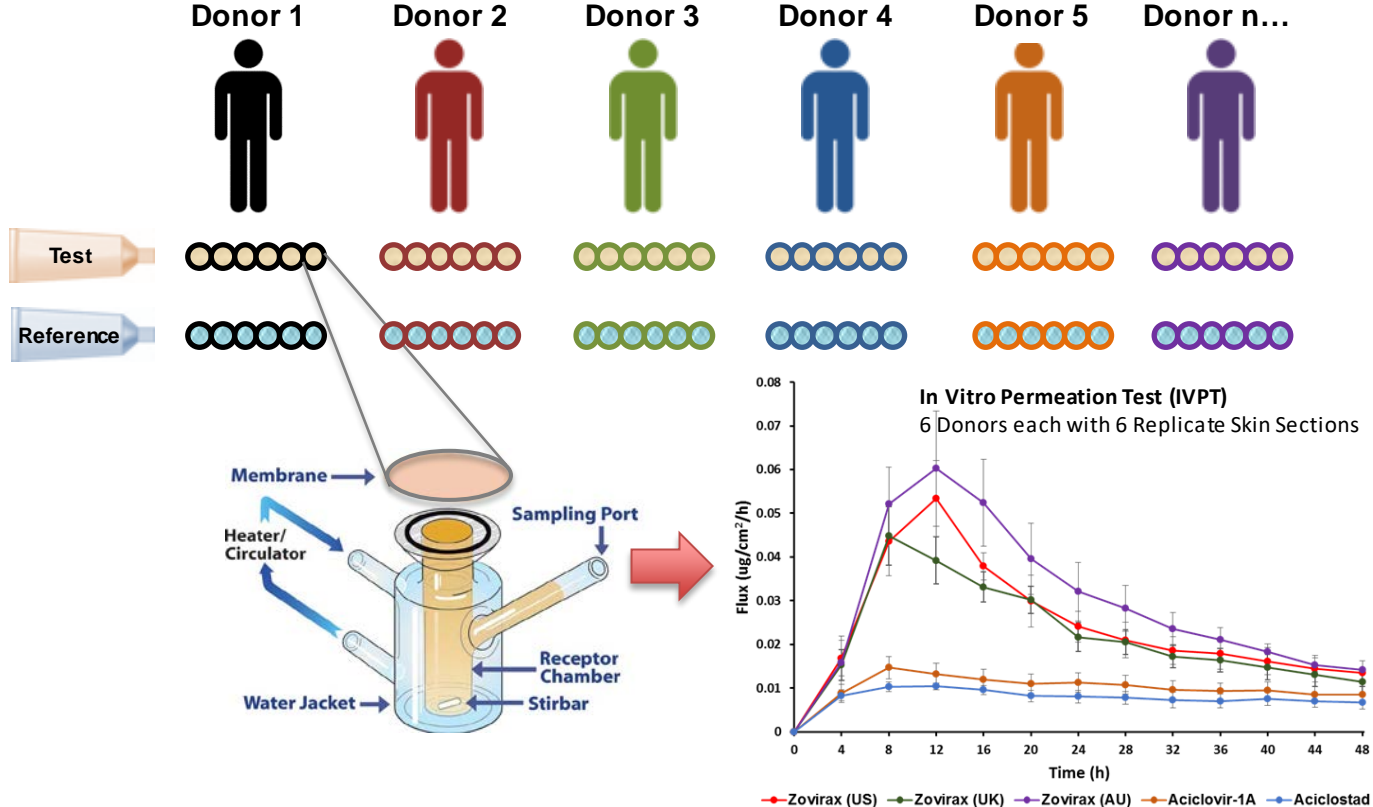


Image courtesy of PermeGear



# IVPT STUDY DESIGN

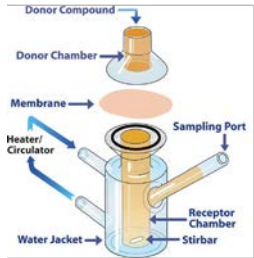


# IVPT Method Development (MD)

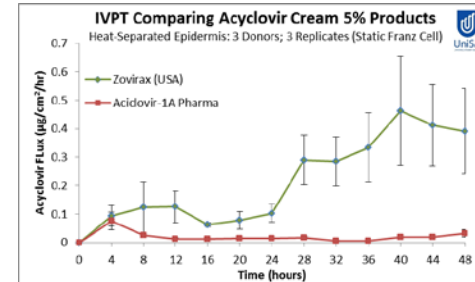
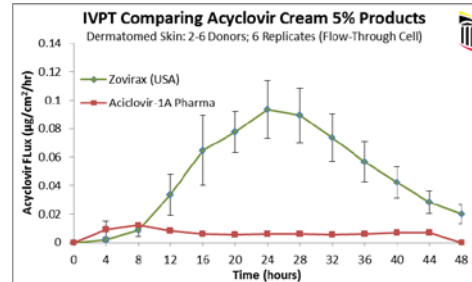
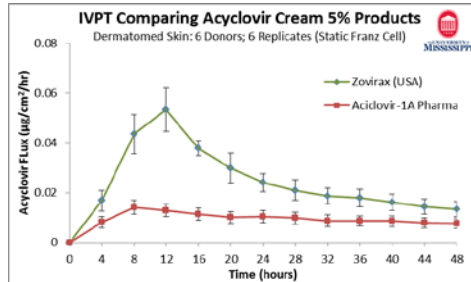
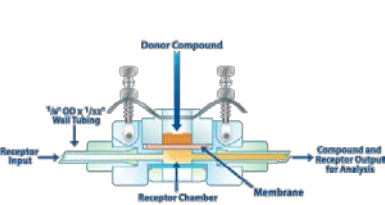
- *Apparatus Selection*
- *Selection of Skin Source*
- *Selection of Receptor Solution*
- *Assessment of the Barrier Integrity*
- *Selection of Dose Amount, Dosing Technique, and Dose Duration*
- *Selection of Study Duration, Sampling Schedule/ Methodology*

# IVPT MD Challenges

## Apparatus Selection



	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm <sup>2</sup>		
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 <sup>2</sup> )	In-Line Flow through cell (0.95 cm <sup>2</sup> )	Franz diffusion cell (1.3 cm <sup>2</sup> )
Skin Integrity	Electrical Resistance	Trans Epidermal Water Loss	Electrical resistance



# IVPT MD Challenges

## *Skin Source and Anatomical Site (Storage and Preparation)*

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

- *Control of skin harvesting and dermatoming*
- *Control of skin preparation protocols, prevent damage to the SC*
- *Control of skin setup prior to evaluation of barrier integrity*

# IVPT MD Challenges



## ***Selection of Receptor Solution***

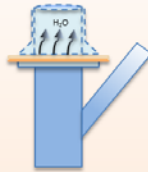
- *Adequate solubility and stability of active ingredient, based on apparatus of choice*
- *Physiologically relevant receptor solutions should be used, not appropriate to utilize “solubilizers” that may impact the barrier properties of the skin, e.g., ethanol*
- *Equilibrate skin in the presence of the receptor solution, on the apparatus of choice, prior to barrier integrity evaluation*



# IVPT MD Challenges

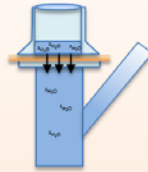
## *Assessment of the Barrier Function*

Trans-Epidermal Water Loss (TEWL) Skin Barrier Integrity Test



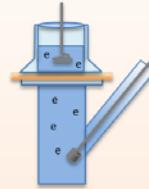
Test results reported as TEWL ( $\text{g}/\text{m}^2/\text{hr}$ )

Tritiated Water Skin Barrier Integrity Test



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

Trans-Epidermal Electrical Resistance (TEER) skin barrier integrity test



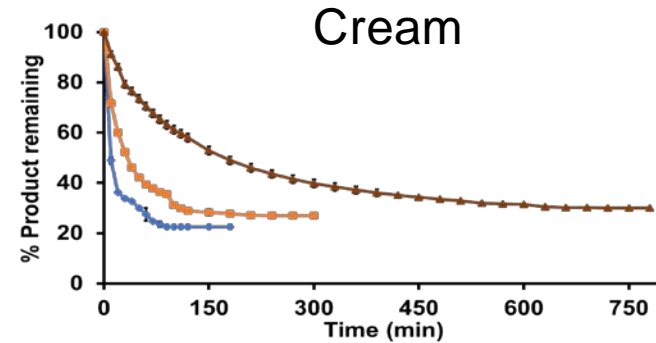
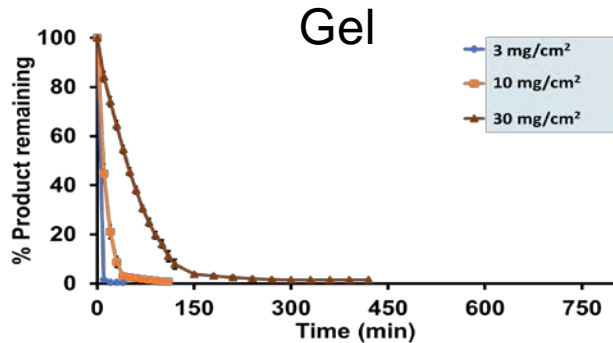
Test results reported as resistance ( $\text{k}\Omega$ ) or conductance ( $1/\text{k}\Omega$  or  $\text{mS}$ ). Units may also involve normalization of skin area.

- Role of external factors (temperature & relative humidity)

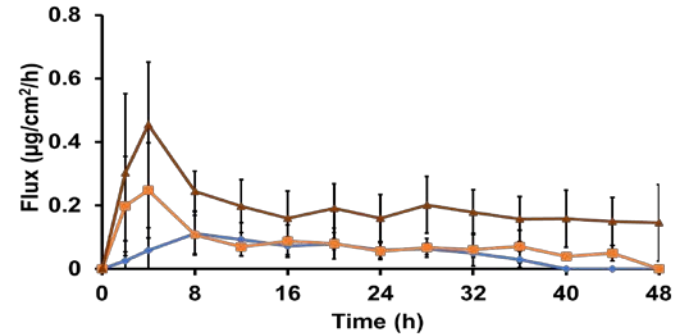
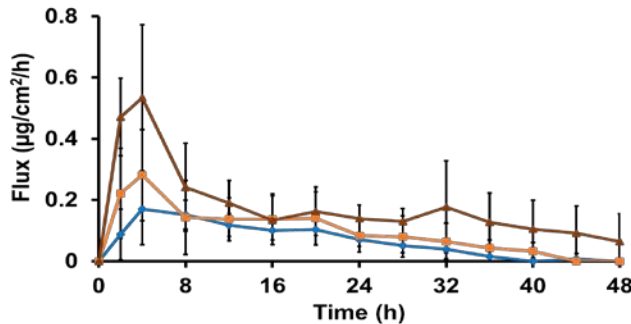
# IVPT MD Challenges

## *Selection of Dose Amount*

Drying Rate

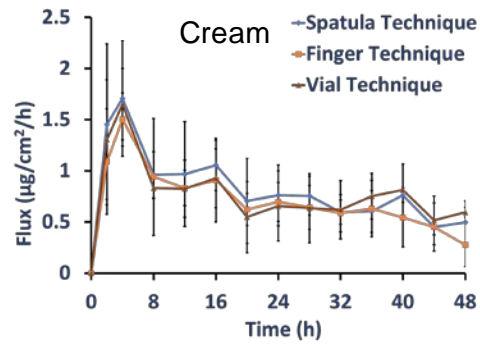
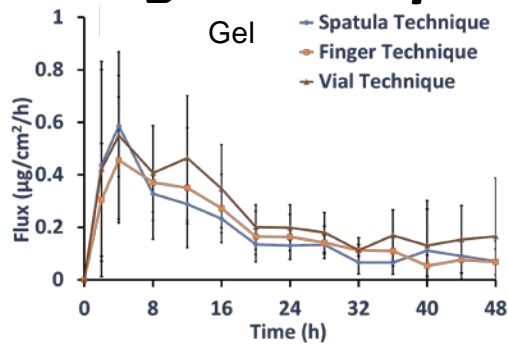


IVPT

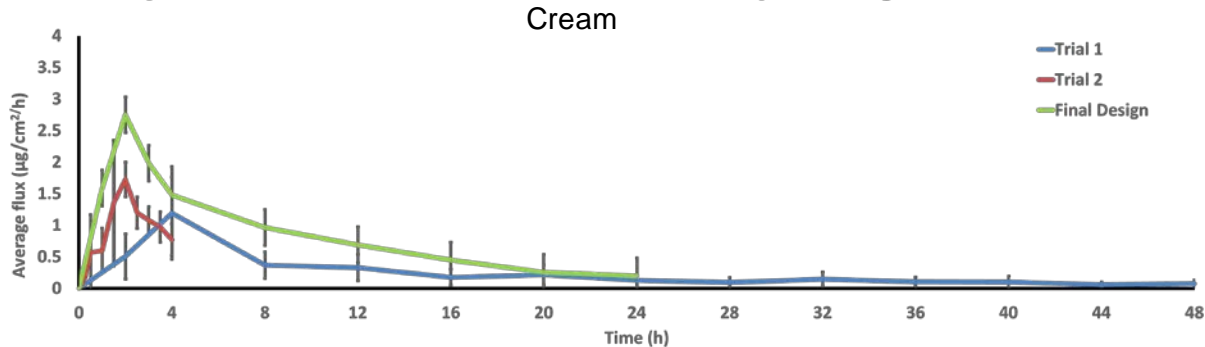


# IVPT MD Challenges

## *Selection of Dosing Technique and Dose Duration*



## *Selection of Study Duration and Sampling Schedule/Method*



# IVPT MD Report



- Include tabular information related to all studies conducted, chronologically, to demonstrate how the final study conditions/parameters were identified
- Specifically, if apparatus, methodologies or study conditions, that are different than those recommended in guidances are utilized consider documenting why such changes were necessary and scientifically justifiable

# IVPT Method Validation (MV)

- *Apparatus Qualification*
- *Membrane (Skin) Qualification*
- *Receptor Solution Qualification*
- *Receptor Solution Sampling Qualification*
- *Discrimination Sensitivity and Selectivity*
  - *Sensitivity*
  - *Selectivity*

**A validated analytical method should be used for the MV studies**

# IVPT MV Challenges

## ***Discrimination Sensitivity and Selectivity***

### – Sensitivity

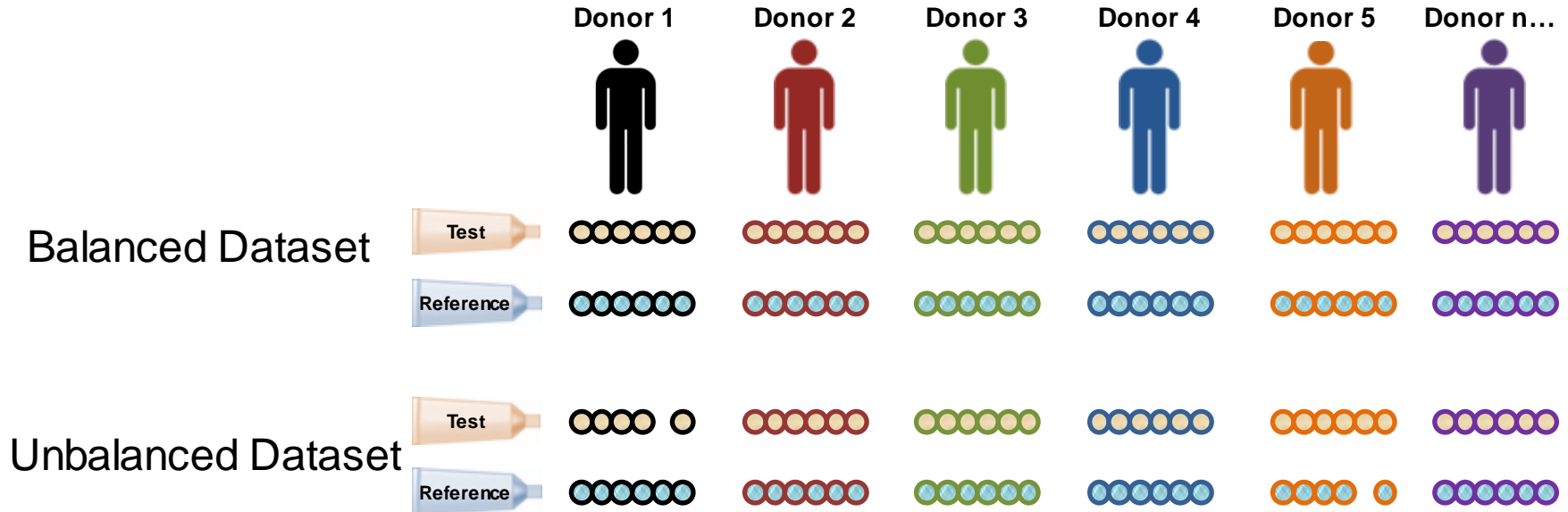
- Modulation of Dose Amount
- Modulation of Dose Duration

### – Selectivity

- Test product, Reference Product, and Altered Product

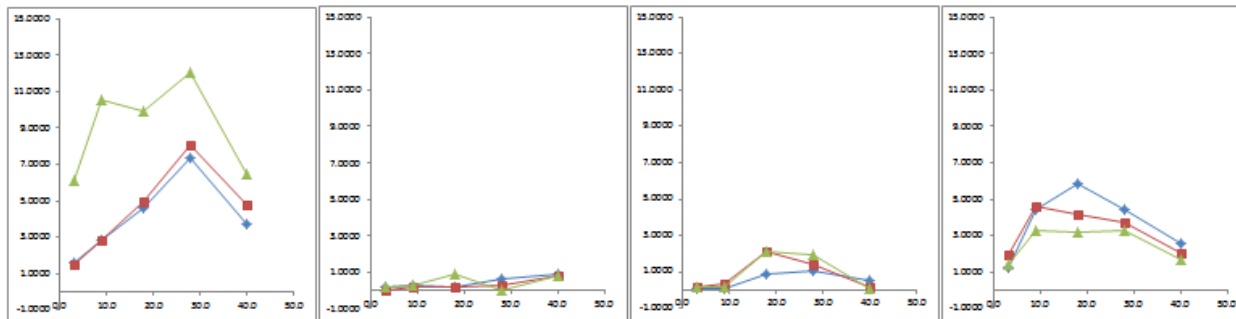
# Challenges with Data Analysis

## *Balanced and Unbalanced Data*



# Outstanding Challenges with IVPT

## *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



# Challenge Question #1

***What is the role of an IVPT study as a component of a characterization-based approach***

- A. An IVPT is used to deformulate the drug product
- B. An IVPT is used to characterize the physical properties of a drug product
- C. An IVPT is used to quantify the release of the active ingredient from the drug product
- D. An IVPT characterizes the rate and extent to which the drug becomes available at or near the site of action**

# Summary

- An IVPT study is typically recommended to assess drug availability from multiphasic formulations by understanding the interaction of the drug product with the skin during metamorphosis
- For IVPT MD studies, it is important to systematically identify study conditions that are relevant for a given drug product, and to clearly outline the considerations/ data within the method development report
- For IVPT MV studies, it is important to validate the study conditions identified during MD, and establish the selectivity of the IVPT method
- For the IVPT pivotal study, it is important to implement controls to minimize variability and loss of data during the conduct of the study

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# Questions?

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CDER | U.S. FDA

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