In Vitro Bioequivalence Data for a Topical Product:

Bioequivalence Review Perspective

FDA Public Workshop

Topical Dermatological Generic Drug Products:
Overcoming Barriers to Development and Improving Patient Access

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Suman Dandamudi, Ph.D.
U.S. Food and Drug Administration, Office of Generic Drugs
Division of Bioequivalence III, Office of Bioequivalence

Disclaimer

- The views expressed in this presentation do not reflect the official policies of the FDA, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

Challenges in Bioequivalence Assessment

- Bioequivalence assessment of locally acting topical dosage forms is challenging.

- Historically, there were limited options for alternate approaches to clinical endpoint BE studies.

- FDA recognized the need to find more sensitive and efficient surrogate approaches to demonstrate BE for topical dermatological products.

- Development of new alternate BE approaches using a collective weight of evidence from in-vitro studies (e.g. IVRT, IVPT).

Product Specific Guidances: Semisolid Topical Products

- Acyclovir Ointment: Q1/Q2/Q3 + IVRT
- Silver Sulfadiazine Cream: Q1/Q2/Q3 + IVRT

- Acyclovir Cream: Q1/Q2/Q3 + IVRT + **IVPT**
- Benzyl Alcohol Lotion: Q1/Q2/Q3 + IVRT + **Lice Assay**

Current BE Recommendations in Product Specific Guidance for Acyclovir Cream- In Vitro Options

- **Formulation Q1/Q2 Sameness:** The test and RLD products are qualitatively and quantitatively same.

- **Q3 Similarity**: The physicochemical properties of test and RLD products are similar.

- **In Vitro Release Test (IVRT) Studies**: The test and RLD products have an equivalent rate of acyclovir release.

- **In Vitro Permeation Test (IVPT) Studies**: The rate and extent of acyclovir permeation through excised human skin from the test and reference products are comparable.

In Vitro Release Test (IVRT)

- IVRT is well established for characterizing and evaluating the performance of semi-solid dosage forms.
- IVRT can be a sensitive and discriminating method that is generally responsive to physicochemical changes in semisolid drug products.
- IVRT serves as a valuable tool for the demonstration of comparative in vitro drug release rates between the test and reference products.
- IVRT is not expected to correlate with or be predictive of in vivo bioavailability or bioequivalence.

Conducting an IVRT

The IVRT pivotal study comparing the [drug] release rates between the test and RLD products should be performed in a manner compatible with the general procedures and statistical analysis method specified in the United States Pharmacopeia (USP) General Chapter <1724>, Semisolid Drug Products – Performance Tests.

Conducting an IVRT

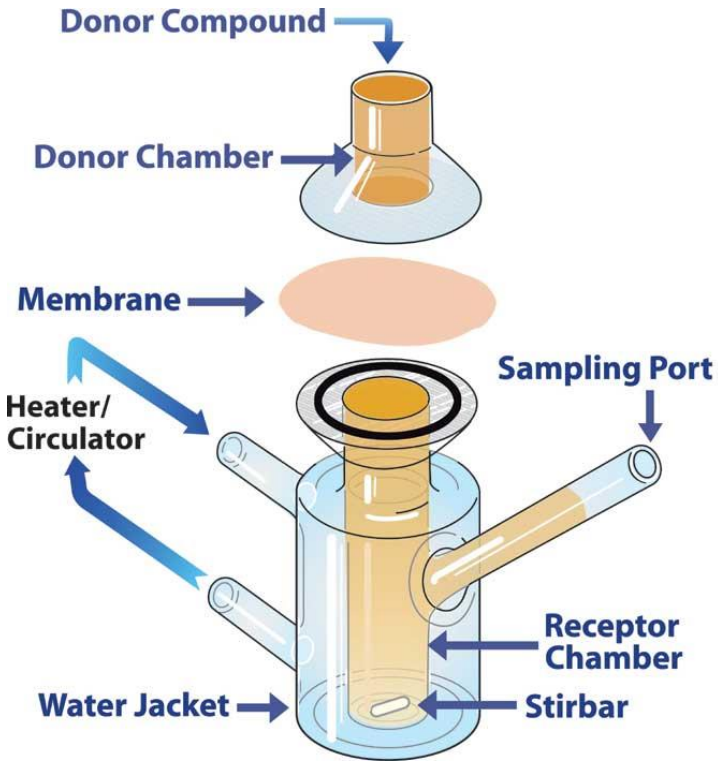
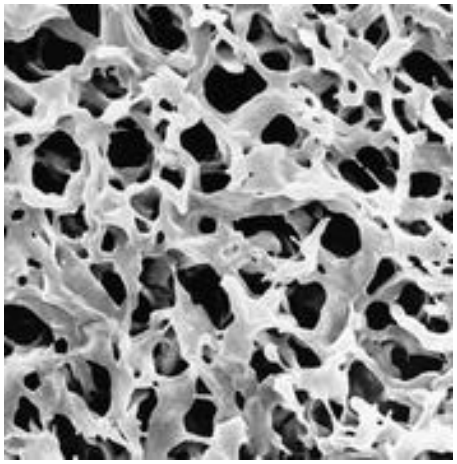


Image courtesy of PermeGear



In Vitro Release Test

What should be submitted for evaluation?

- IVRT Method Development Report
- IVRT Method Validation Report
- IVRT Pivotal Study Report

IVRT Method Development

Method Parameters:

- **Product dose amount:** Pseudo-Infinite dose to obtain steady state kinetics

- **Stirring rate:** High stirring rate may result in a change at the membrane and receptor media interface, which may affect diffusion. If too low, the drug in the receptor solution may not be homogenous

- **Sampling times:** First sample after the diffusion cell has reached a steady state of diffusion (after the lag time), and the last sample should be during the steady state and before excessive drug depletion occurs

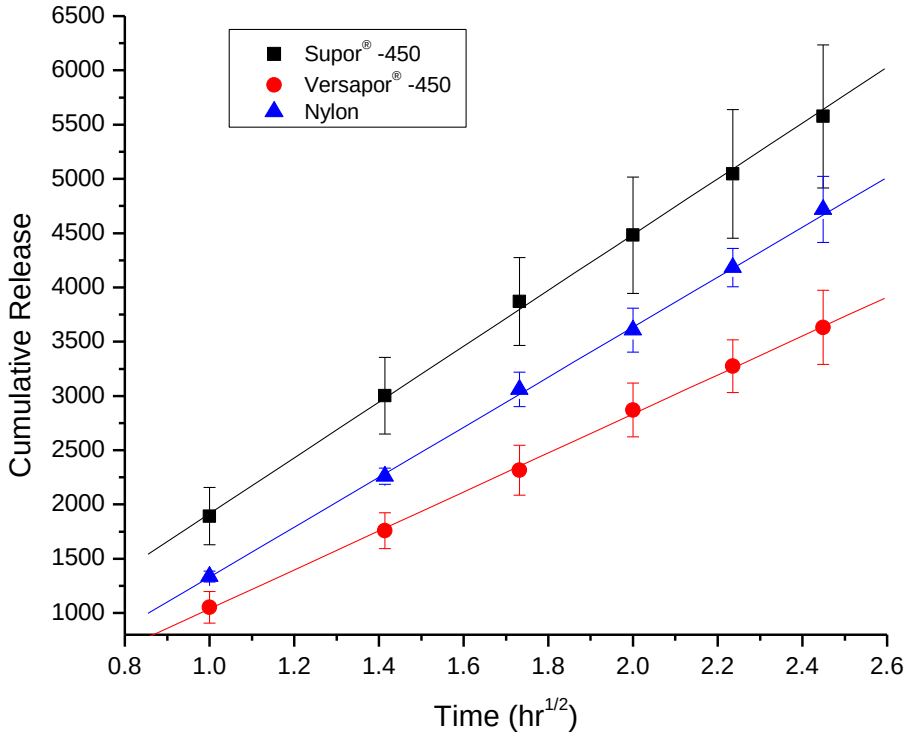
- **IVRT apparatus:** Vertical diffusion cell (Franz Cell)

Membrane: Inertness (low binding of drug, free resistance to diffusion and chemical compatibility with receptor solution)

Receptor Solution: Solubility and stability of drug in receptor solution

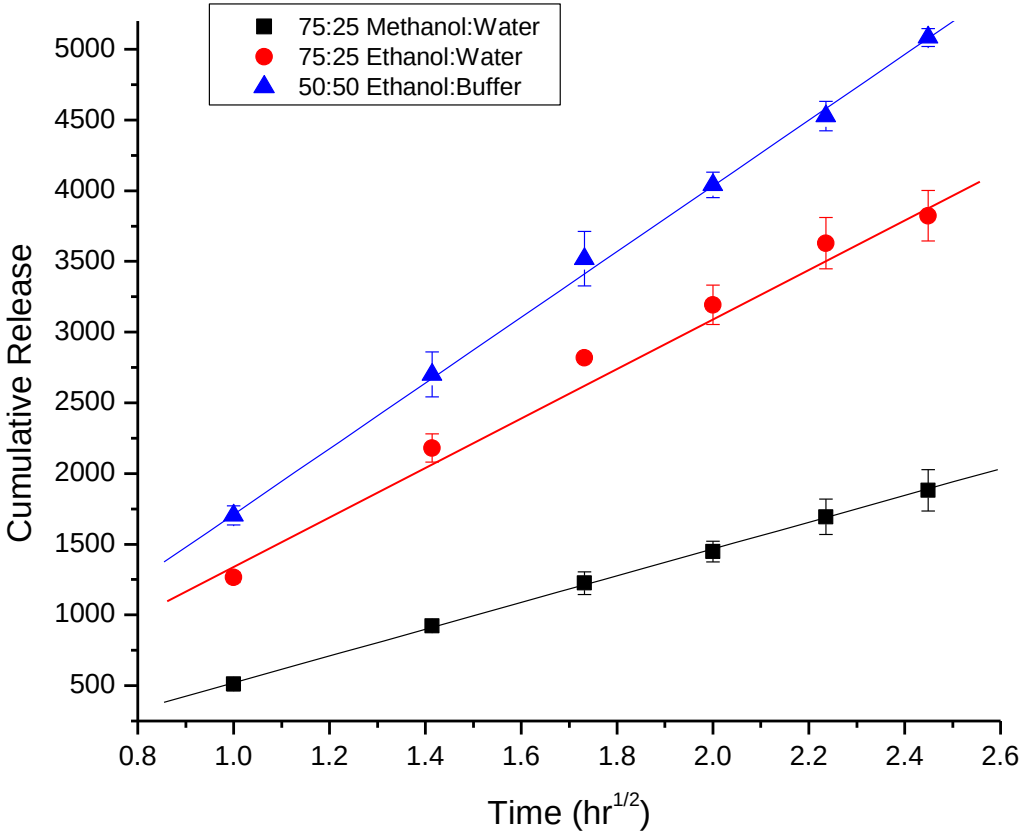
IVRT Method Development

Membrane Evaluation



IVRT Method Development

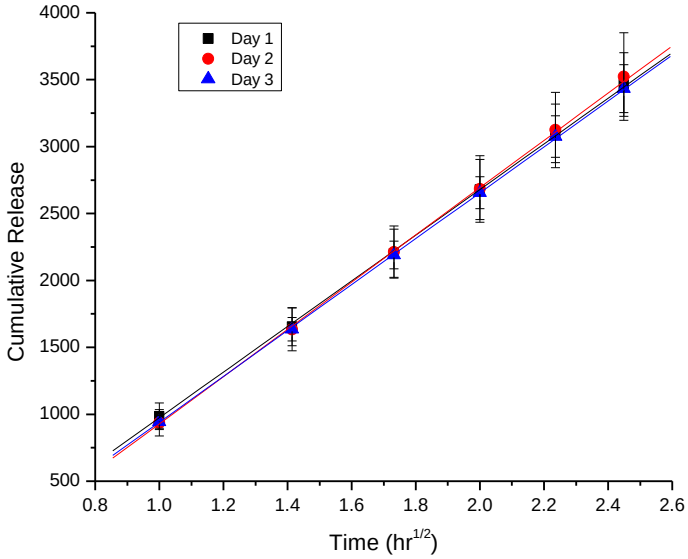
Receptor Solution Evaluation



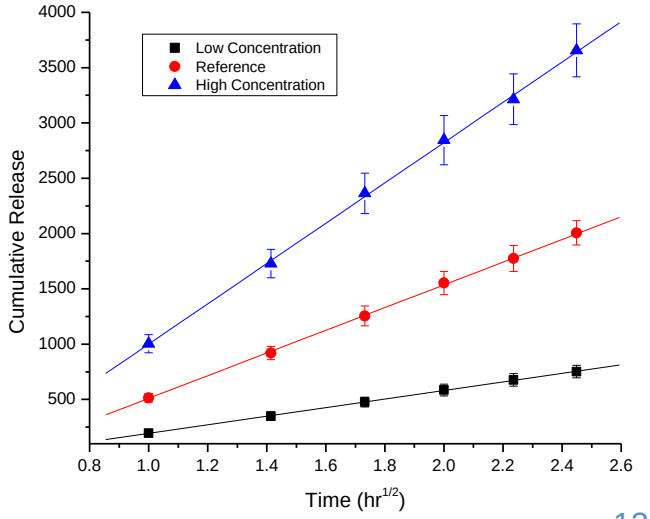
IVRT Method Validation

Validation Components

- Linearity and Range
- Accuracy/Precision and Reproducibility
- Recovery, Mass Balance & Dose Depletion



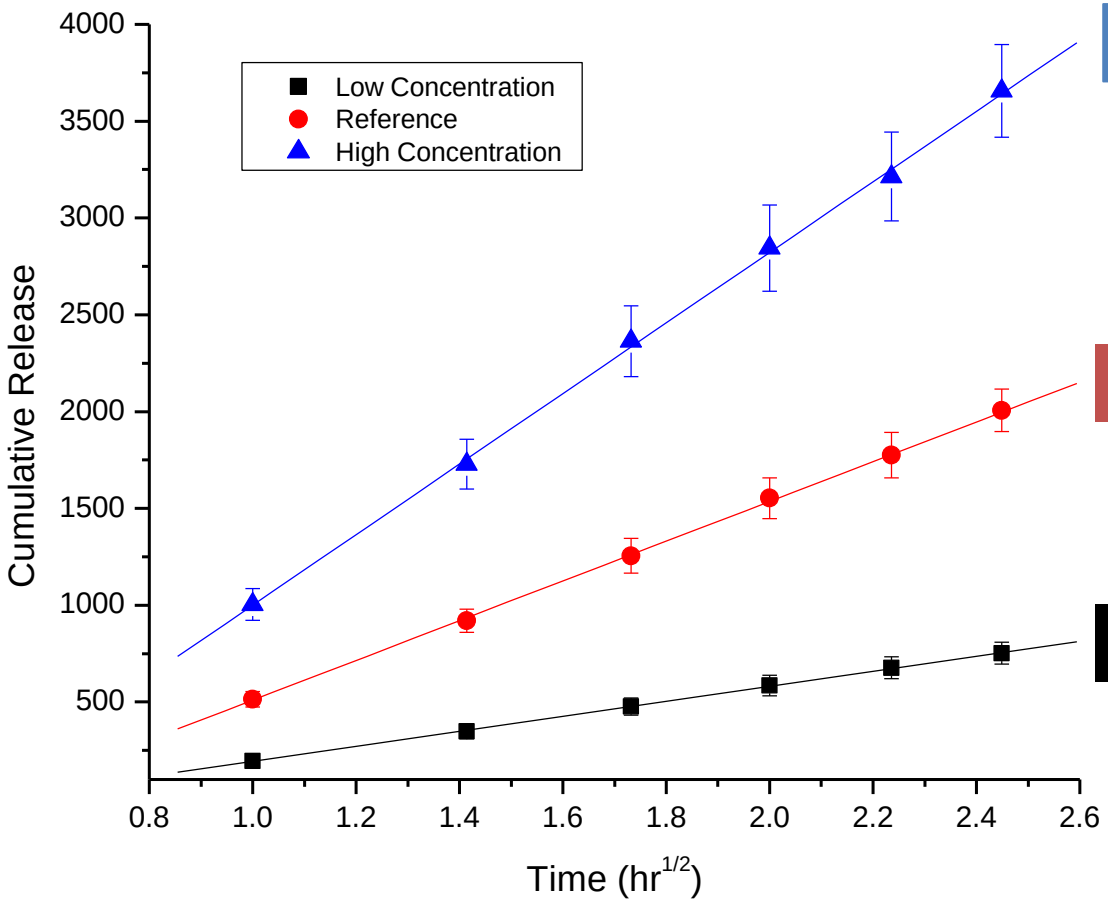
- Sensitivity and Specificity
- Selectivity



- Robustness
- Membrane Inertness
- Receptor Solution Solubility
- Apparatus Qualification

IVRT Method Validation

Sensitivity



7.5% Product **Slope- 1470**

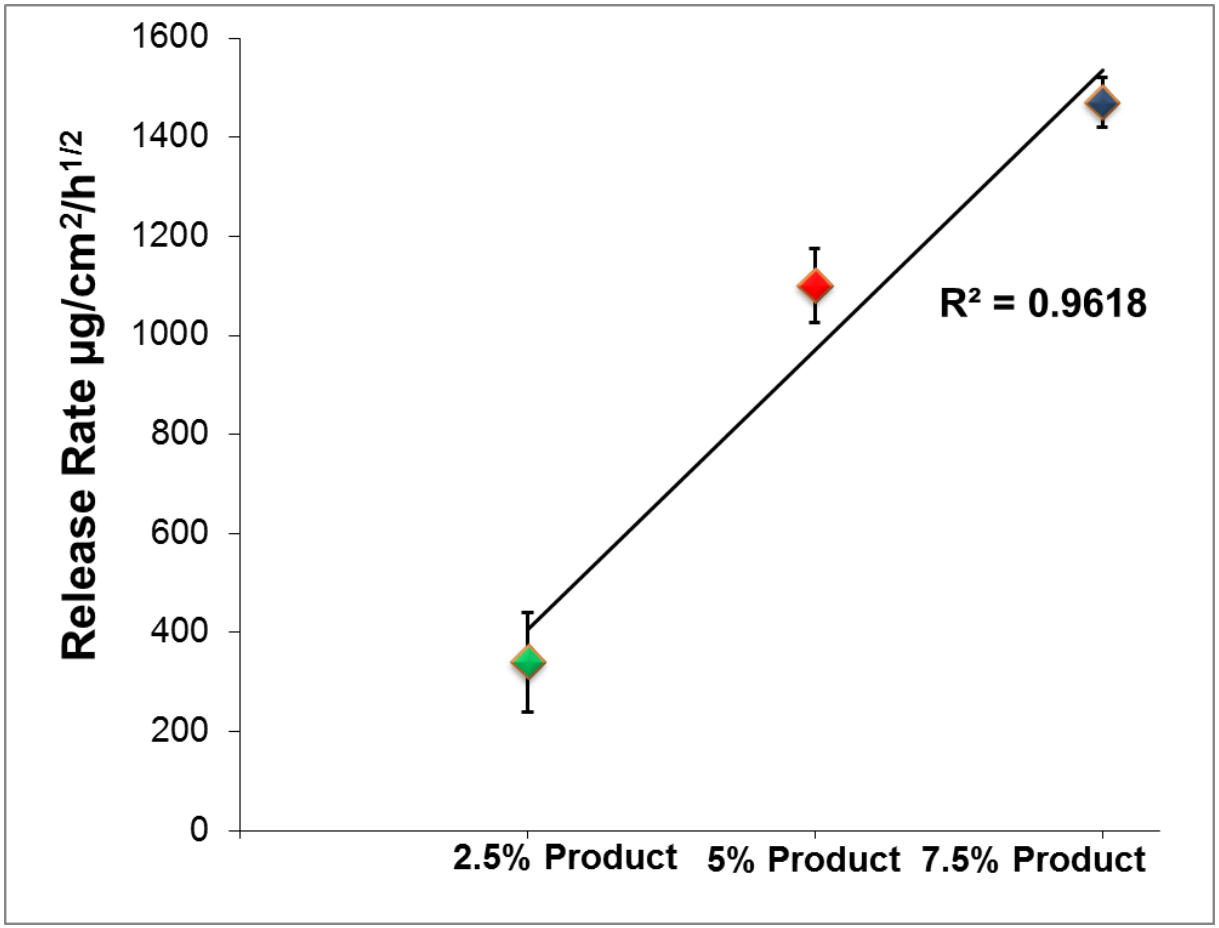
5% Product **Slope- 1100**

2.5% Product **Slope- 340**

Ability to detect change in release rate as a function of drug concentration in formulation

IVRT Method Validation

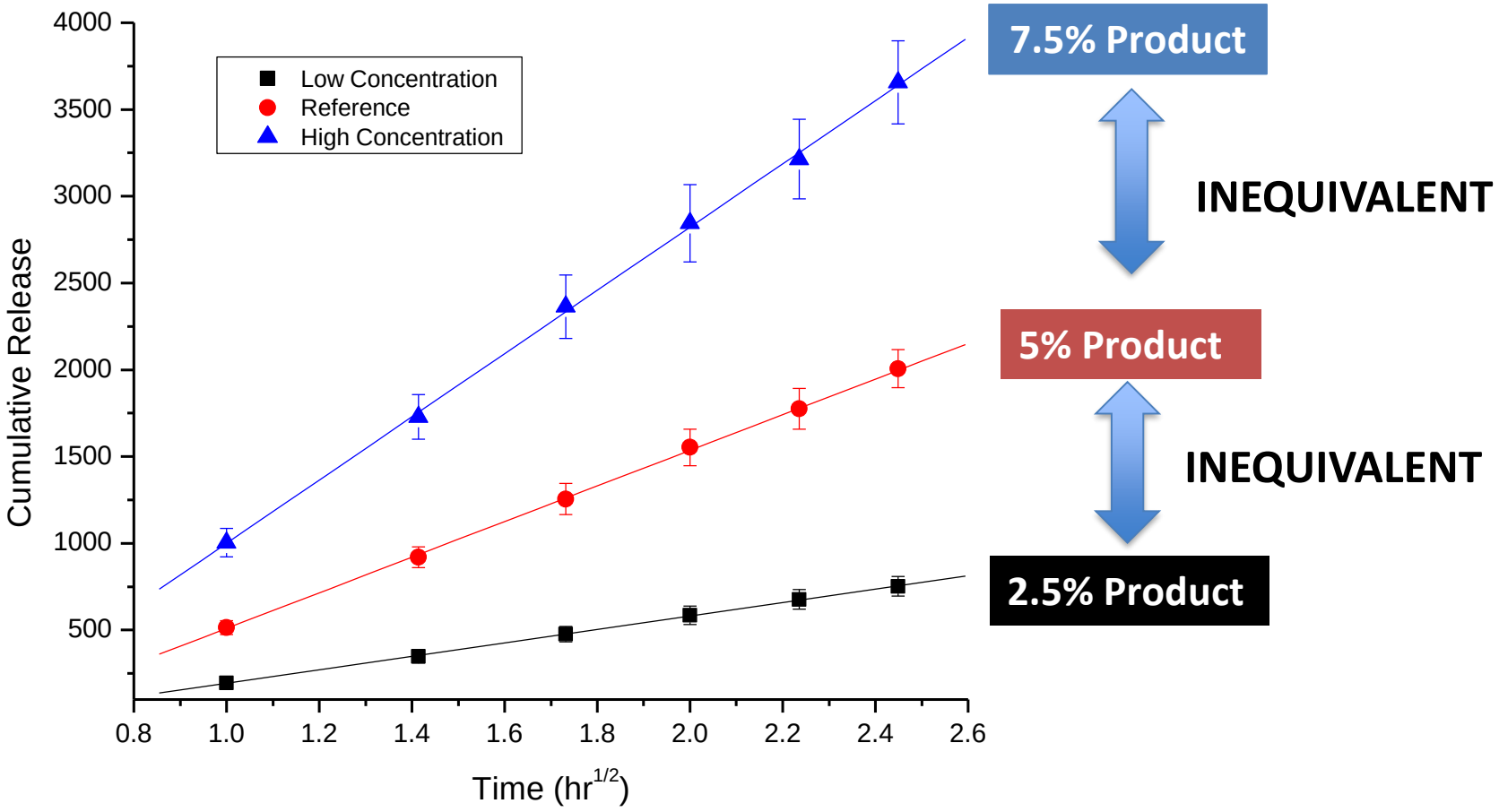
Specificity (Proportionality)



Monitor the proportionality of changes in release rate as a function of drug concentration in formulation

IVRT Method Validation

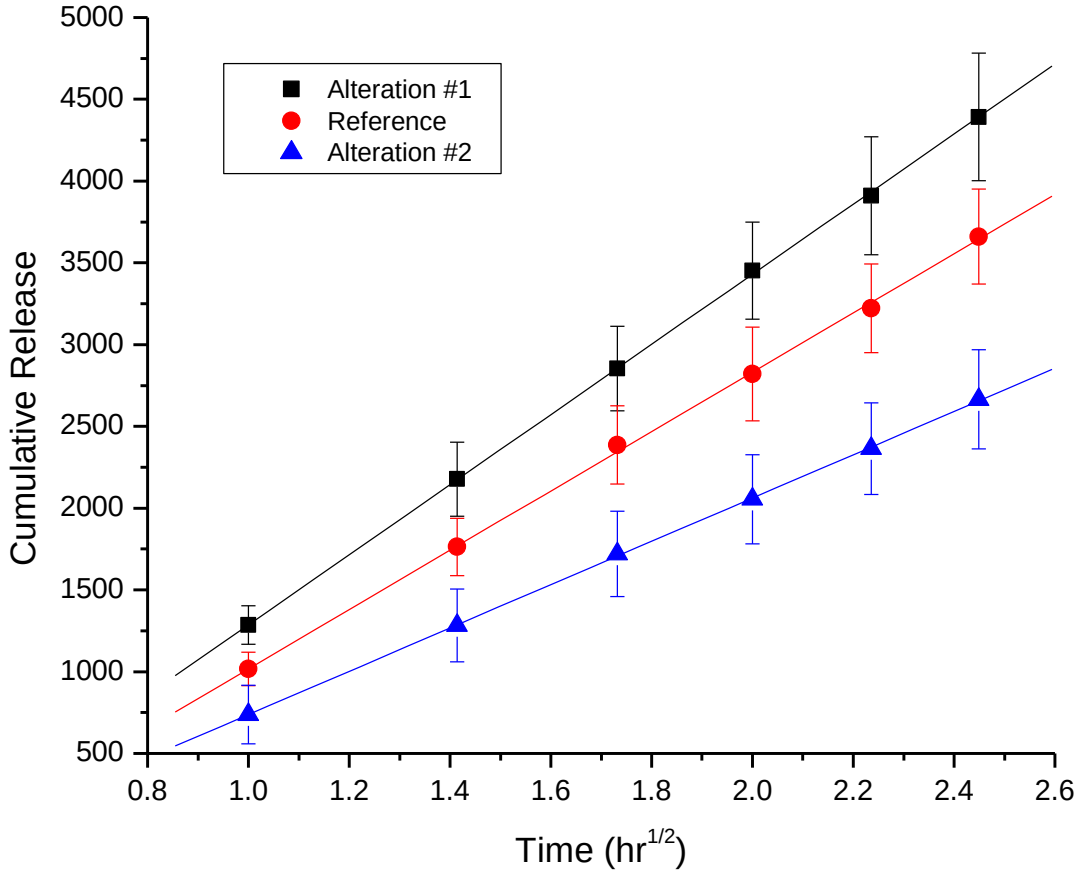
Selectivity



Identify that the altered concentration formulations are inequivalent to reference formulation

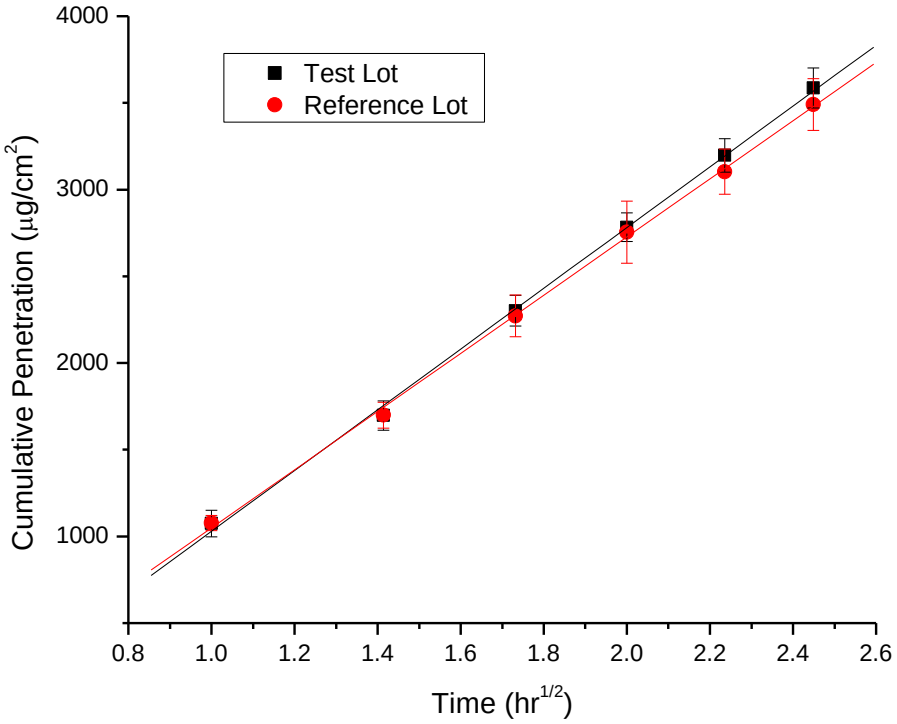
IVRT Method Validation

Supplemental Selectivity



Identify that the altered formulations are inequivalent to reference formulation

IVRT Results



Reference Product	Test Product	Lower Limit	Upper Limit	Pass/Fail
(Details Redacted)	(Details Redacted)	100.881%	109.068%	Pass

In Vitro Permeation Test (IVPT)

- Equivalent drug release from the formulations *in vitro* (by IVRT) does not guarantee of bioequivalence in vivo because IVRT is not a bio-relevant test, and is not expected to exhibit IVIVC

- Therefore an IVPT study is recommended comparing the cutaneous pharmacokinetics of a drug from the test and reference products using excised human skin with a competent skin barrier mounted on a qualified diffusion cell system.

IVRT vs IVPT

- IVRT (Release)
  - **Synthetic Membrane**
  - Occluded Dose
  - Infinite Dose
  - Release Rate (slope)
  - Alcoholic Media
  - µg to mg Range
  - Specific to the Formulation
  - Relative Consistency
- IVPT (Permeation)
  - **Human Skin**
  - Unoccluded Dose
  - Finite Dose
  - Flux Profile (J_{max}, etc.)
  - Physiological Media
  - pg to ng Range
  - *IVIV* Correlation
  - Donor Variability

IVPT: *In Vitro In Vivo* Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

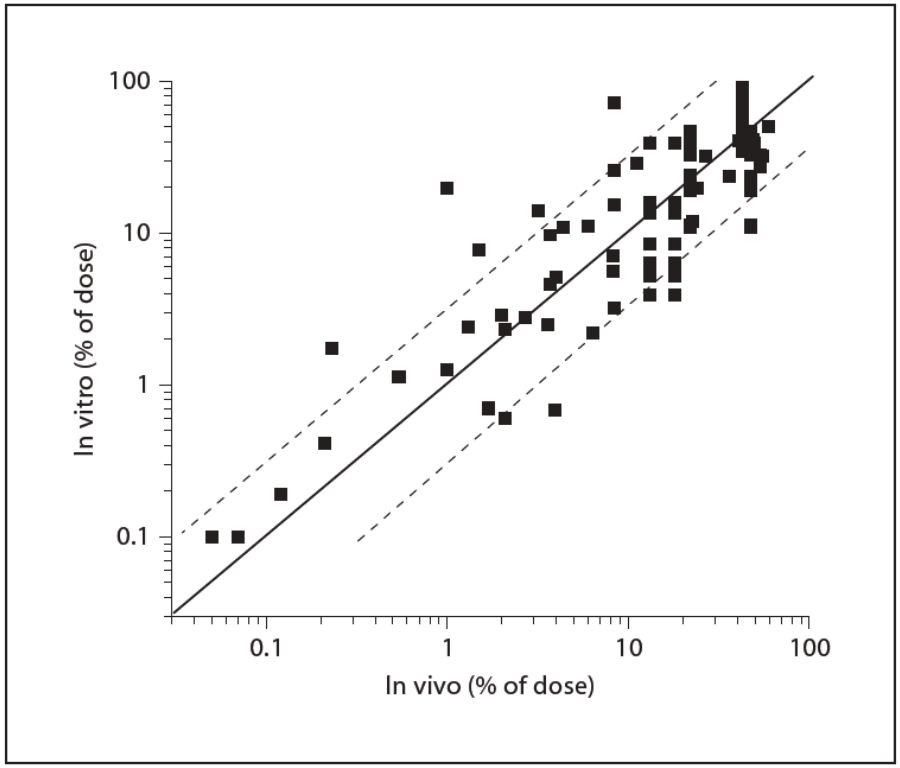


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

IVPT: *In Vitro In Vivo* Correlation

- Lehman et al., 2011 (11 IVIVC Data Sets)

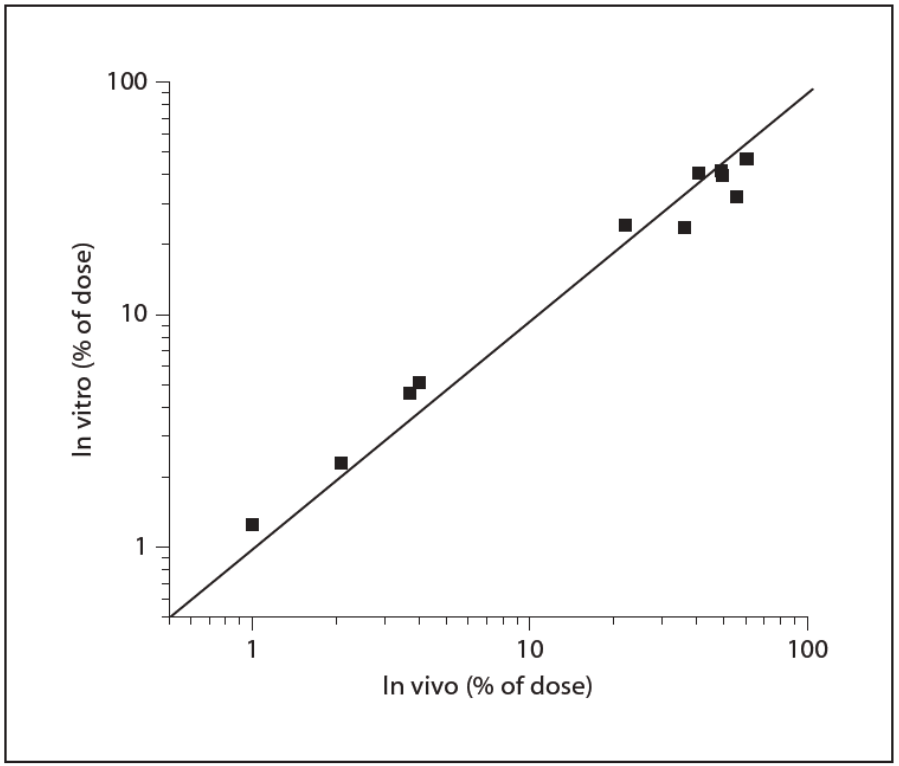
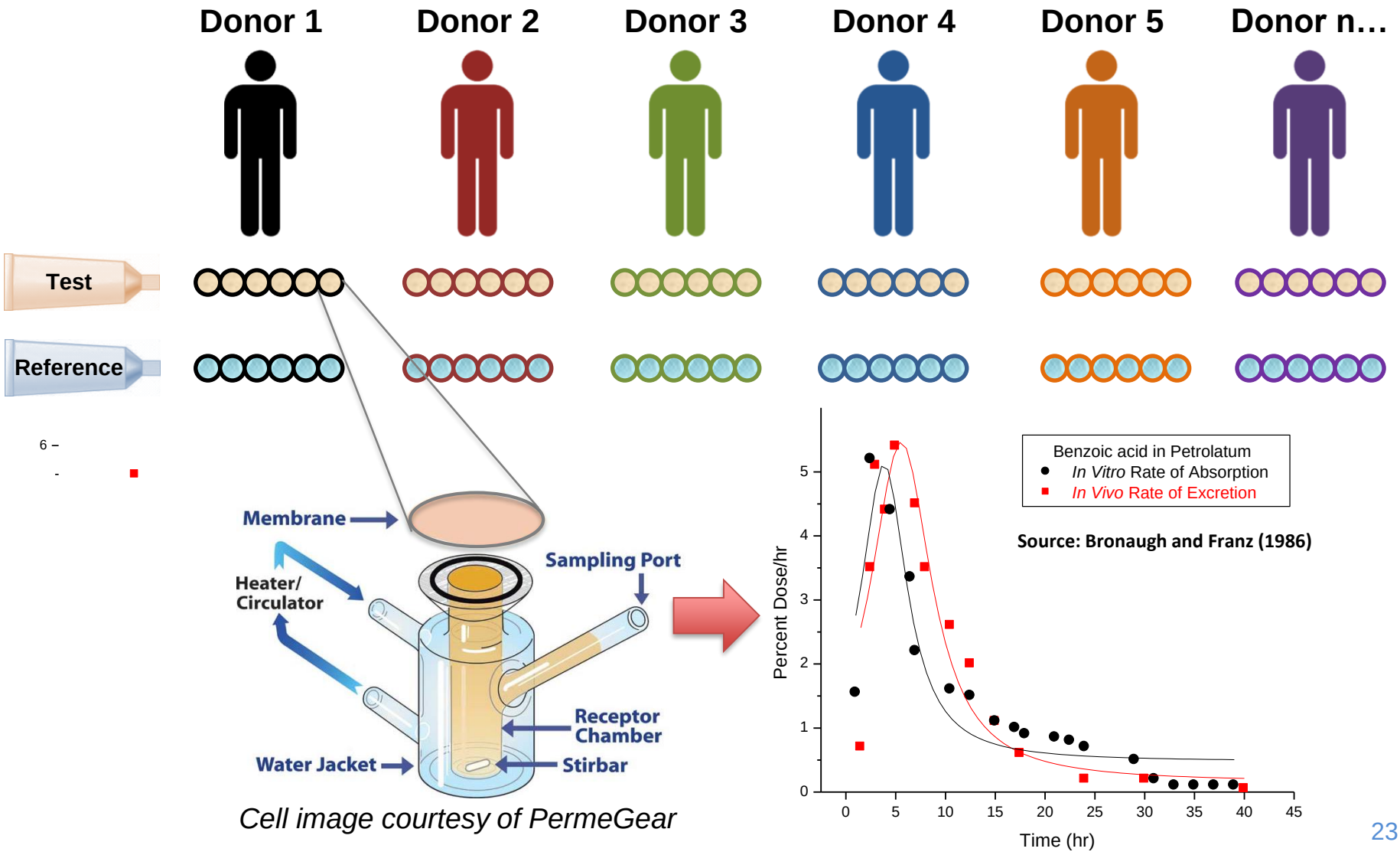


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

IVPT Study Design



Cell image courtesy of PermeGear

IVPT Study Conduct

IVPT Study Conduct

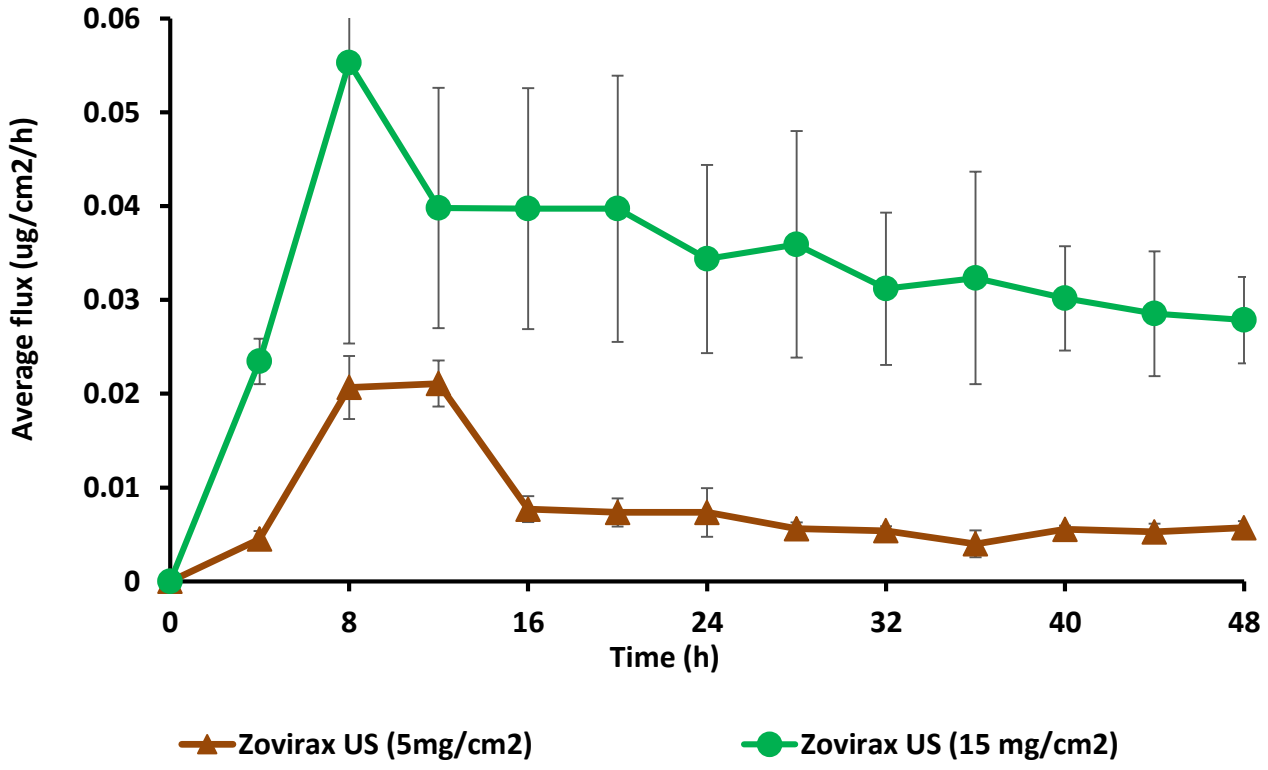
In Vitro Permeation Test

What should be submitted for evaluation?

- IVPT Method Development Report
- IVPT Method Validation Report
- IVPT Pilot Study Report
- IVPT Pivotal Study Report

IVPT Method Development

Method Parameters: Product dose amount, Sampling times, Stirring rate



Results from Dr. Narasimha Murthy, University of Mississippi; GDUFA Award U01FD005223

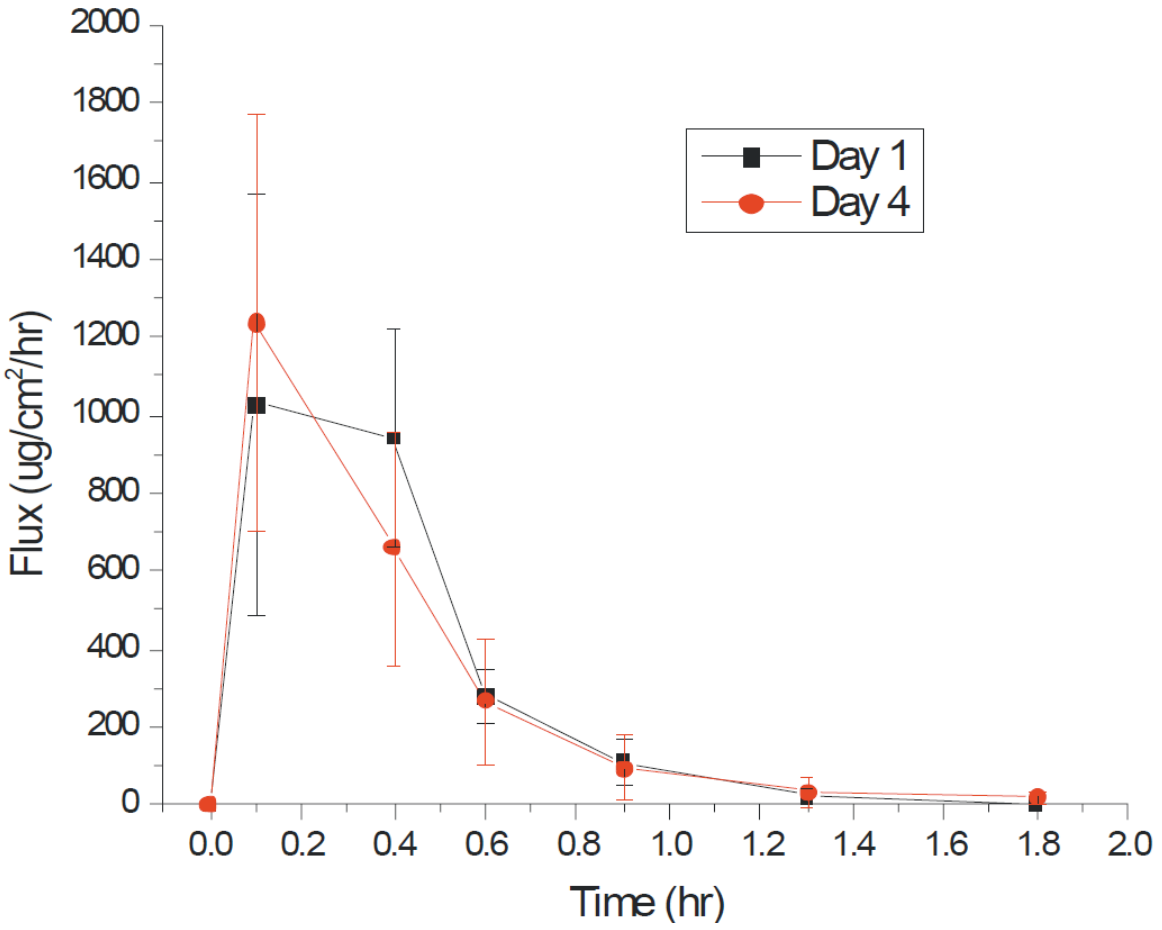
IVPT Method Validation

Validation Components:

- Membrane (skin) qualification
- Receptor Solution Qualification
- Receptor Solution Sampling Qualification
- Receptor Solution Sample Analytical Method Validation
- Environmental Control
- Permeation Profile and Range
- Precision and Reproducibility
- Recovery, Mass Balance & Dose Depletion
- Discrimination Sensitivity and Selectivity
- Robustness

IVPT Method Validation

Membrane (Skin) Qualification:



Results from Paul Lehman and Dr. Tom Franz

IVPT Method Validation

Receptor Solution Qualification:

Figure 1: Percutaneous Absorption Profile for Metronidazole from MetroGel®

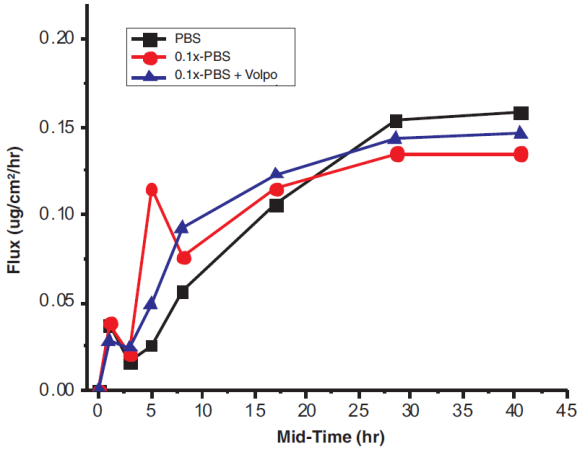


Figure 2: Percutaneous Absorption Profile for Testosterone from Testim®

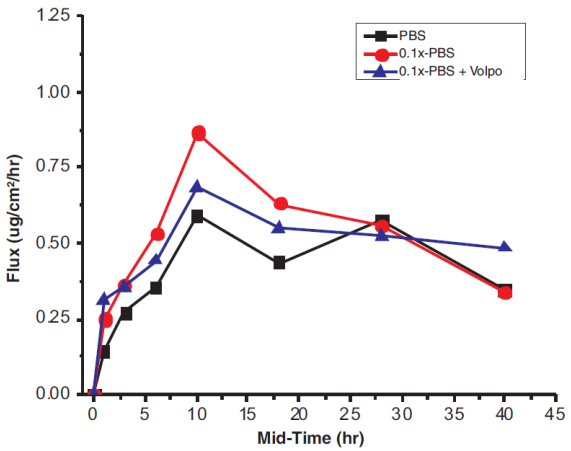
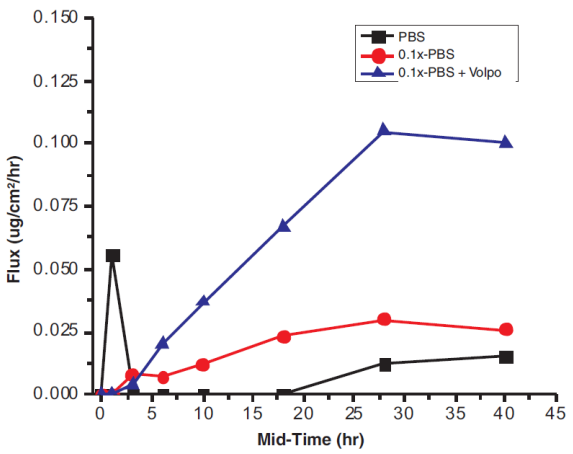


Figure 4: Percutaneous Absorption Profile for Imiquimod from Aldara®



Chemical Characteristics of Study Drugs

Drug	MW	Melting Point	Water Solubility	Log P
Testosterone	288.4	155	~ 23 µg/mL	3.6
Imiquimod	240.3	293	~ 250 µg/mL	2.7
Metronidazole	171.2	160	~ 6 mg/mL	-0.1

Results from Dr. Sam Raney, Paul Lehman and Dr. Tom Franz

IVPT Pilot Study

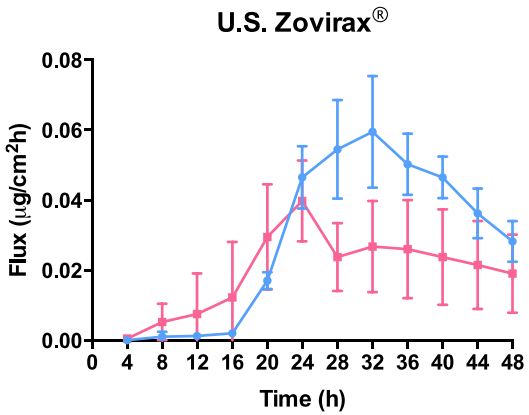
- To estimate number of donors required for the pivotal study.
- Multiple skin donors and a minimum of 4 replicate skin sections per donor per treatment group.
- Parallel assessment should be performed with a third product or formulation that is known or designed to be different from the RLD.
- The results from the pilot study should not be combined with the IVPT pivotal study.

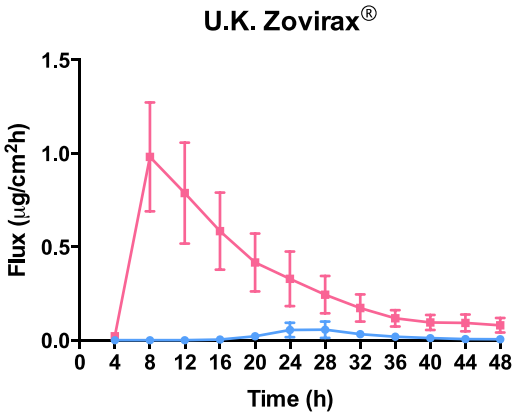
IVPT Study Design

- Study Design: Parallel, single-dose, multiple-replicate per treatment group study
- The number of donors required is to be determined by applicant
- A consistent source of skin
- A single, unoccluded dose in the range of 5-15 mg cream/cm2
- Non-dosed control skin section from each donor
- Pre-dose zero sample from each diffusion cells
- The duration of an IVPT study: sufficient to identify the maximum flux and a decline in the flux thereafter across subsequent time points
- Dose staggering and sampling synchronization

IVPT Results

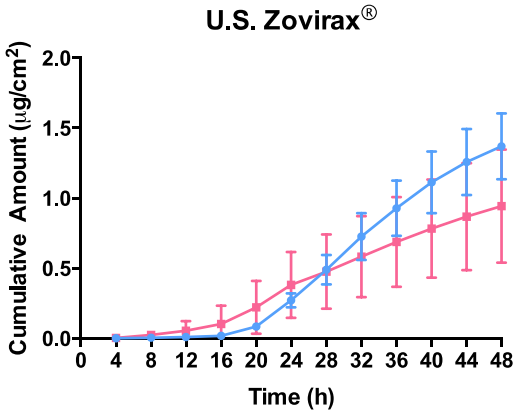
Percutaneous Bioavailability (Flux vs. Cum Data)

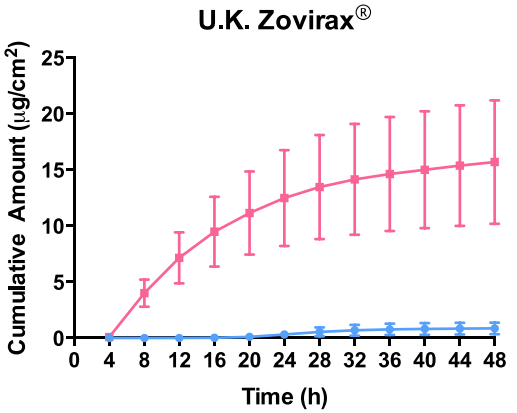




Positive Displacement Pipette
Inverted HPLC Vial

Mean ± S.D.
1 Donor, 4 Replicates





Results from Dr. Soo Shin and Dr. Audra Stinchcomb, University of Maryland;
GDUFA Award U01FD004947

Summary

- IVRT/IVPT data reviewed by Division of Bioequivalence.

- Method development studies are usually not performed using validated test method or sample analytical procedures, or within a quality management system that is compatible with applicable GLP principles.

- The method validation should be performed using validated sample analytical procedures under principles of GLP.

- Inadequate submission of the data (e.g. missing/incomplete method development reports, raw numerical data, IVRT/IVPT data in SAS Transport format) may often lead to the delay in the review process and the final approval of the application.

Summary

- Reserve samples are required for both, IVPT and IVRT studies, and should be randomly selected prior to dispensing.

- Applicants can submit a controlled correspondence to OGD with a proposal for a reduction in the amount of reserve samples required, if needed, based on the cost or difficulty associated with obtaining the reference standard product.

- Refer to 58 FR 25918, 21 CFR 320.38, 21 CFR 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding considerations for retention of study drug samples and to 21 CFR 320.36 for requirements for maintenance of records of BE testing.

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