

Strategies to Improve Patient Access to High Quality Topical Products

AAPS Workshop
Dermatological Drug Products:
Developmental & Regulatory Considerations
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Patient Access to Topical Products

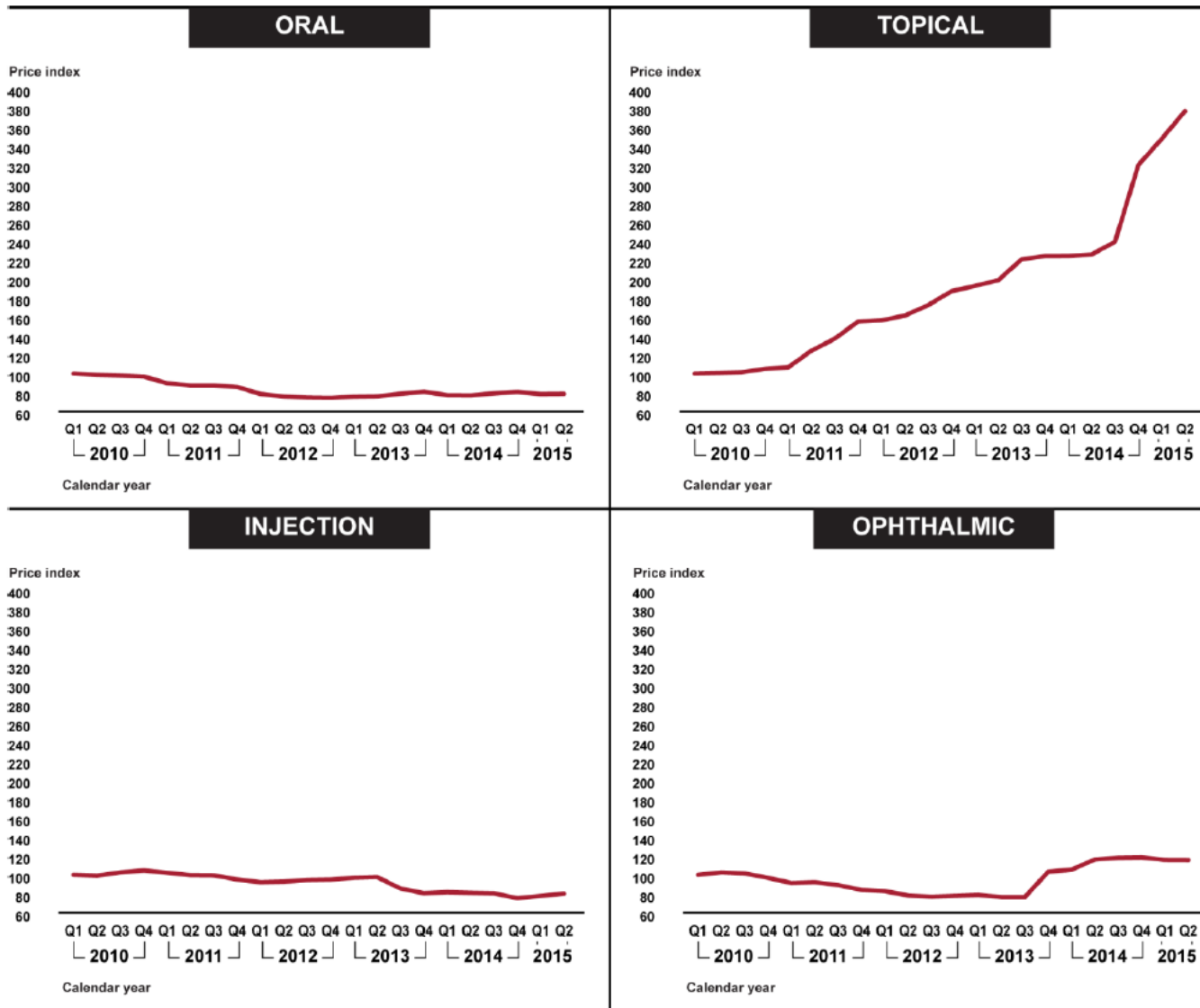


- Product lifecycle factors affecting patient access to topical dermatological drug products
 - Approval of a Reference Listed Drug (RLD) product
 - Market distribution/shortage of the RLD product
 - Cost of the RLD product
 - Reimbursement that requires prior authorizations
 - Approval of generic versions of the RLD product
 - Market distribution/shortage of the generic product
 - Cost of the generic products
 - Other factors

The GAO Report (GAO-16-706)

- The U.S. Government Accountability Office (GAO) Report in Aug 2016 analyzed a period spanning Q1 of 2010 through Q2 of 2015
- 57% of the topical drug products experienced an extraordinary price increase in that period
- The average price of topical generic drugs was 276% higher by the end of the period analyzed
- The factors impacting the rising costs of topical generic drug products were all related to competition among generic manufacturers

The GAO Report (GAO-16-706)



Retail Prices for Dermatologic Drugs



Drug	Type	Price, US \$				Absolute Change, 2009-2015	% Change, 2009-2015
		2009	2011	2014	2015		
Altabax, 15 g	I	92.50	106.18	168.75	196.86	104.36	112.82
Benzaclin, 50 g	A	166.79	205.80	451.29	503.85	337.06	202.08
Carac cream, 30 g	N	159.40	227.16	2939.68	2864.70	2705.30	1697.18
Clobex spray, 4 oz	S	389.57	500.29	827.11	958.01	568.44	145.91
Cloderm cream, 30 g	S	96.47	132.92	220.75	360.02	263.55	273.19
Cutivate lotion 120 mL	S	305.00	493.92	918.63	1067.25	762.25	249.91
Derma-Smoothe FS oil, 4 oz	S	45.70	47.23	247.84	322.67	276.97	606.06
Finacea, 50 g	A	124.42	185.42	288.92	284.30	159.88	128.51
Olux-E foam, 100 g	S	307.58	382.79	750.79	841.76	534.18	173.67
Oracea, 40 mg (30 tablets)	A	439.01	416.09	632.80	702.46	263.45	60.01
Oxistat cream, 30 g	I	76.50	119.25	399.00	544.66	468.16	611.97
Oxsoralen-Ultra, 10 mg (50 capsules)	P	1227.32	2150.49	4568.54	5204.31	3976.99	324.04
Retin-A Micro, 0.1%, 50 g	A	178.05	335.73	791.47	914.52	736.47	413.64
Solaraze gel, 100 g	N	442.89	618.56	1738.91	1883.98	1441.09	325.38
Soriatane, 25 mg (30 capsules)	P	757.75	958.50	1452.50	1595.27	837.52	110.53
Taclonex, 60 g	P	465.99	522.58	848.21	962.90	496.91	106.64
Targretin gel, one 60-g tube	N	1686.78	1787.97	15 708.40	30 320.12	28 633.34	1697.51
Tazorac cream, 0.1%, 60 g	A	266.18	464.96	656.20	722.27	456.09	171.34
Xolegel, 30 g	I	212.50	278.00	389.25	641.96	429.46	202.10

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Source: Miranda E. Rosenberg, BA and Steven P. Rosenberg, MD (2016) *Changes in Retail Prices of Prescription Dermatologic Drugs From 2009 to 2015*. JAMA Dermatology. 152(2):158-163. doi:10.1001/jamadermatol.2015.3897

Patient Access to Topical Products



- The vast majority (approximately 80%) of topical dermatological drug products have fewer than three generic competitors, and in many cases, have no approved generics at all.¹
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
 - The use of clinical endpoint bioequivalence (BE) studies
 - The complex nature of topical formulations
 - The relatively small market capitalization for some products

¹ FDA Office of Generic Drugs Topical & Transdermal Products Database

Patient Access to Topical Generics



- Availability of Topical Generic Drug Products can
 - Help to make medicines more affordable for patients
 - Improve patient compliance and therapeutic outcomes
 - Stabilize the drug supply against shortages
- High Quality Topical Generic Drug Products can
 - Ensure that there are no differences in quality or performance between the generic drug product and the RLD product
 - Help satisfy perceptions of quality by patients and prescribers
 - Help eliminate “dispense as written” substitution concerns
 - Help establish or maintain confidence in generic substitution

Patient Access to Topical Generics



- **Mission** of the Office of Generic Drugs (OGD)
 - To make **high quality**, affordable medicines **available** to the public.
- **Vision** to support OGD's commitments:
 - Product Quality Characterization
 - Supports **high quality** medicines
 - Efficient BE Standards
 - Helps make medicines **available**

High Quality Drug Products



- What does “quality” mean for a drug product?

Fitness for Purpose

*“The totality of **features and characteristics of a product...** that bear on its ability to satisfy stated or implied needs”*

- International Organization for Standardization (ISO)

Control of Failure Modes

*“Good pharmaceutical quality represents **an acceptably low risk of failing** to achieve the desired clinical attributes.”*

- Dr. Janet Woodcock, Director, FDA CDER

Woodcock, J. (2004) The concept of pharmaceutical quality. Am Pharm Review 7(6):10-15

Available (and Affordable) Products



- Power of “efficient” BE standards

Overall Drug Products ²

- **89%** of prescriptions dispensed in 2016 were for generics
- Efficient Pharmacokinetics (PK)-based methods available

Topical Drug Products ³

- Most topical products have few or no generics available
- Efficient Local and Systemic PK-based methods may be useful
- Efficient In Vitro BE standards may be useful
- Efficient BE approaches supported by a collective weight of evidence from in silico, in vitro and/or in vivo studies?

² AAM 2017 Generic Drug Access & Savings in the United States Report

³ FDA Office of Generic Drugs Topical & Transdermal Products Database

Developing Rational BE Standards



- **A Modular Framework for In Vitro BE Evaluation**
 - **Q1/Q2** sameness of inactive ingredient components and quantitative composition
 - **Q3 (Physical & Structural Characterization)** as relevant to the nature of the product
 - **IVRT** (In Vitro Release Test) for moderately complex products
 - **IVPT** (In Vitro Permeation Test) or another bio-relevant assay for more complex drug products
- **A Scalable Framework for BE Evaluation**
 - **In Vivo** systemic PK studies may be appropriate
 - **In Silico** computational modeling may be useful

Developing In Vitro BE Standards



- **Q1/Q2 Sameness** (components and composition of excipients)
Mitigates the risk of known failure modes related to:
 - Irritation and sensitization
 - Formulation interaction with diseased skin
 - Stability, solubility, etc. of the drug
 - Vehicle contribution to efficacy

Developing In Vitro BE Standards



- **Q3 (Physical and Structural) Similarity**

Mitigates the risk of potential failure modes related to:

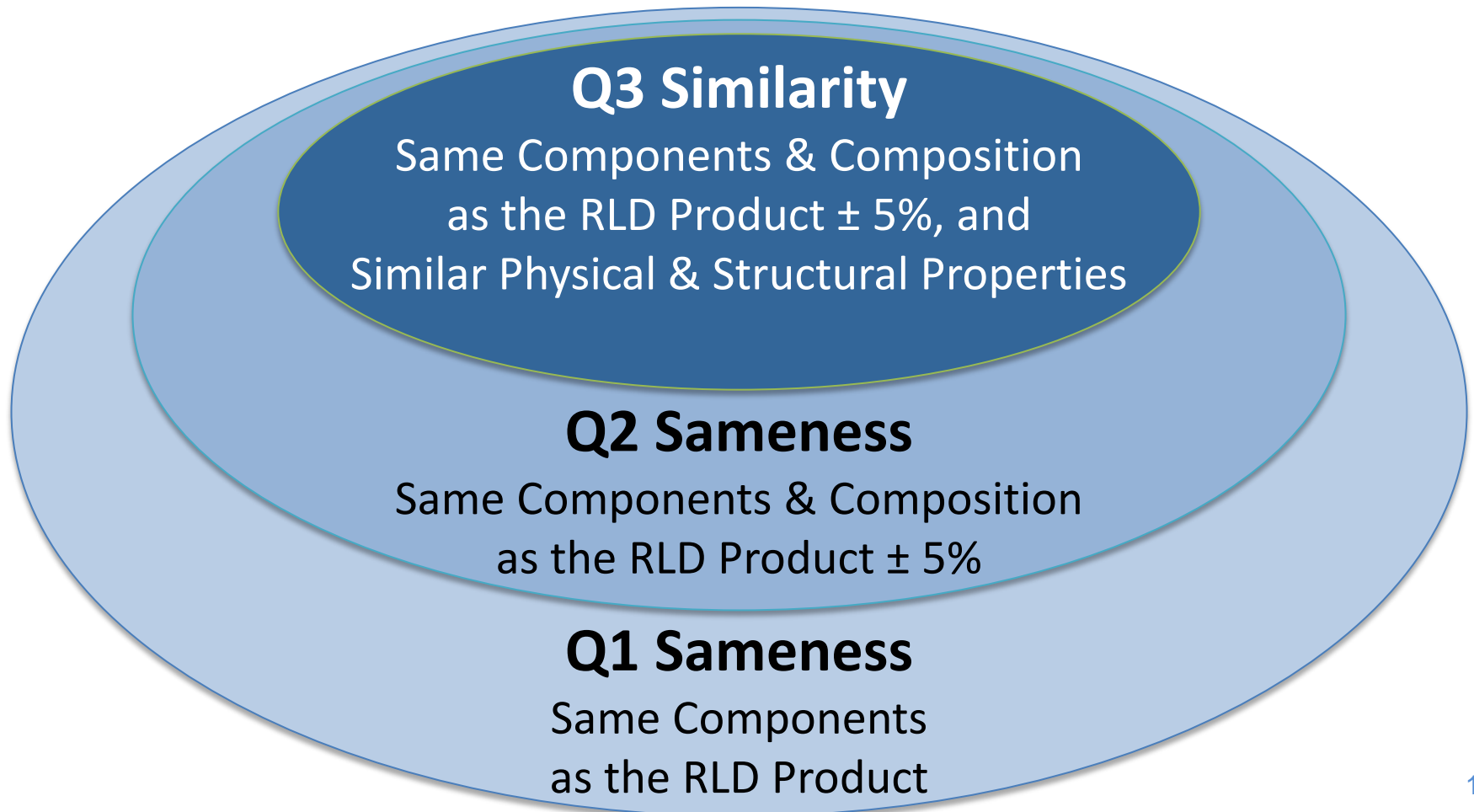
- Differences in Q1/Q2 sameness ($\pm 5\%$ tolerances)
- Differences in pH that may sting or irritate diseased skin
- Differences in the polymorphic form of the drug
- Differences in rheology that alter the spreadability, retention, surface area of contact with the diseased skin
- Differences in entrapped air and drug amount per dose
- Differences in phase states and diffusion, partitioning, etc.
- Differences in metamorphosis and drying rates
- *Many of these Q3 concepts and the associated test methods had not been developed or standardized*

Developing In Vitro BE Standards



- **Q3 (Physical and Structural) Similarity**

An evolving regulatory concept:



Effects of Excipients on Bioavailability

- It is widely understood that the formulation of a topical semisolid dosage form matters greatly
- It is now increasingly clear how excipients exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form
- The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability

Effects of Excipients on Bioavailability



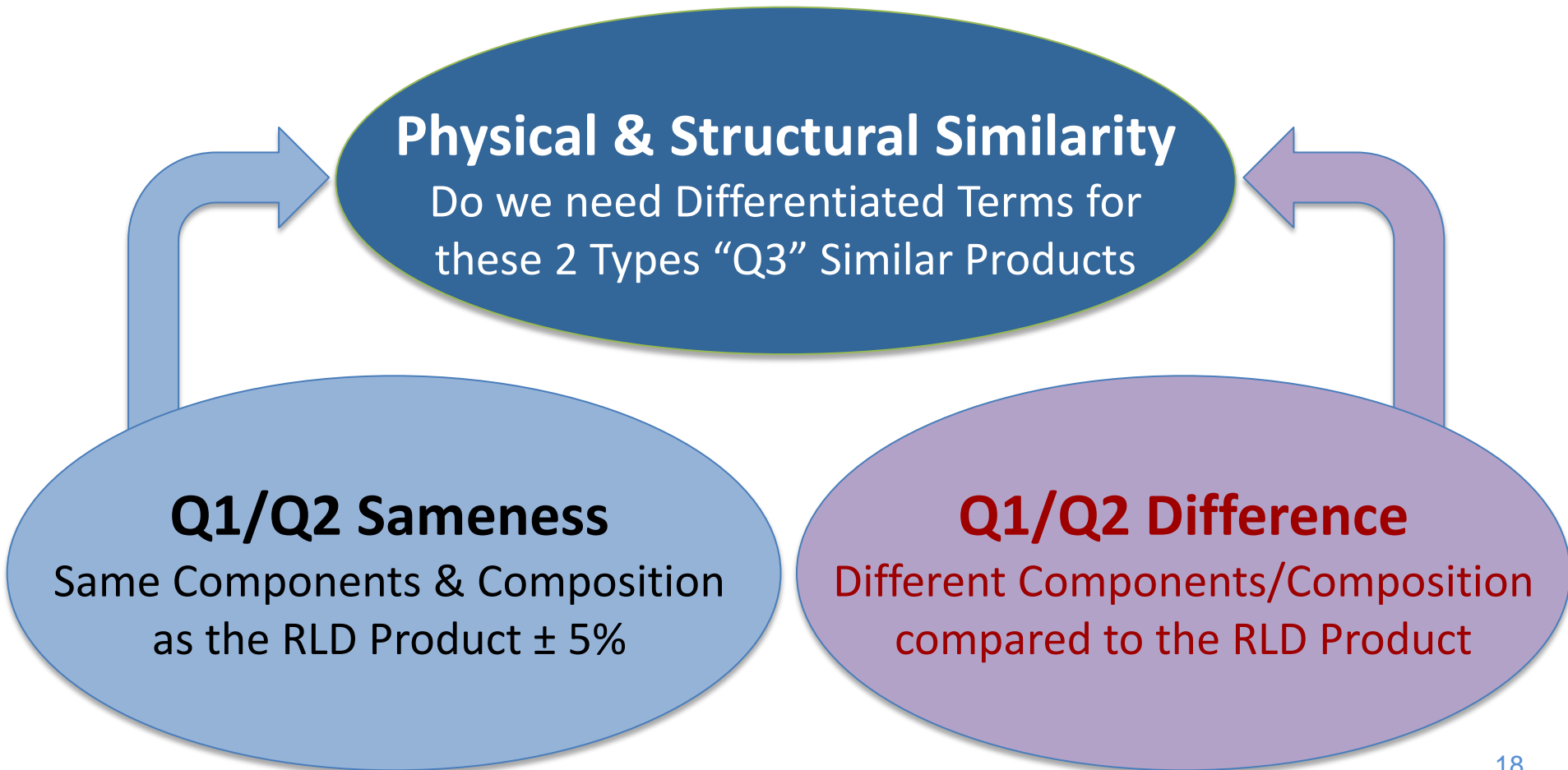
- Excipient quality and composition can affect:
 - The phase states and the arrangement of matter
 - Drug diffusion within the dosage form
 - Drug partitioning from the dosage form into the SC
 - Alteration of skin structure and chemistry
 - Drug diffusion within the skin itself
 - Drug delivery & bioavailability at the target site
 - Skin (de)hydration, irritation or damage
 - Metamorphosis of the dosage form on the skin

Developing In Vitro BE Standards



- **Q3 (Physical and Structural) Similarity**

An evolving regulatory concept:



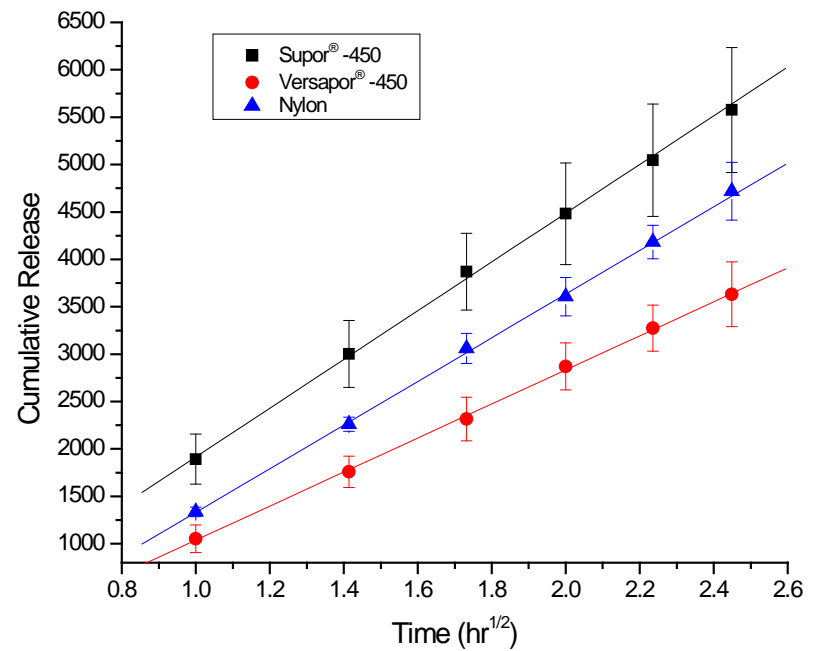
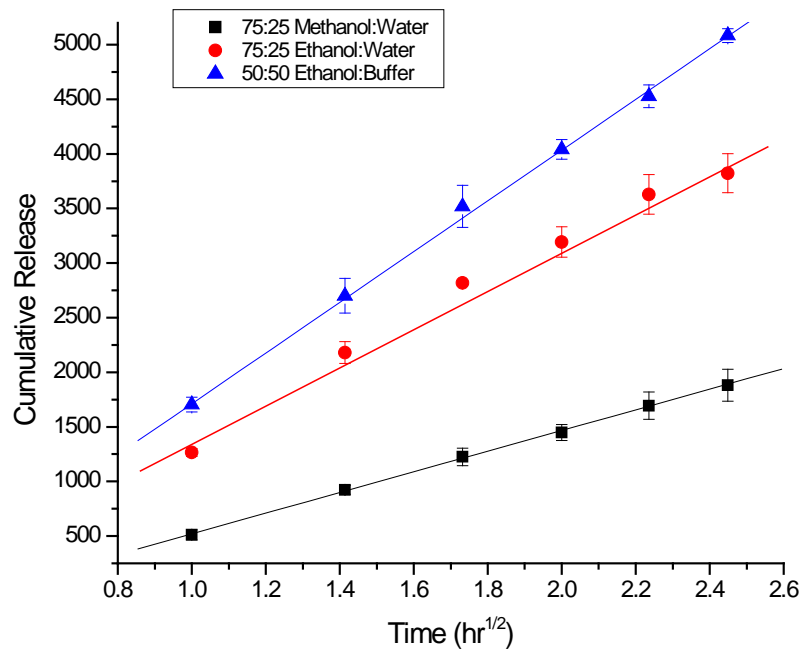
Developing In Vitro BE Standards

- **IVRT (In Vitro Release Test)**

Mitigates the risk of unknown failure modes related to:

- Differences in Q1/Q2 sameness ($\pm 5\%$ tolerances)
- Differences in physical and structural similarity
- Differences that may not be identified by quality tests
- IVRT is a sensitive, discriminating compendial method with established statistical analyses
- However, no In Vitro – In Vivo Correlation (IVIVC) is expected
- *Standard procedures for IVRT method development and validation had not been established*

IVRT Method Development



IVRT Qualifications & Validations



1. IVRT APPARATUS QUALIFICATION

- Cell Capacity
- Cell Orifice Diameter
- Receptor Medium & Membrane Temp.
- Stirring Speed
- Dispensed Sampling Volume
- Environmental Conditions

2. IVRT LABORATORY QUALIFICATION

- Inter-run Variability
- Intra-run Variability
- Product Sameness Test

3. IVRT SAMPLE HPLC METHOD VALIDATION

- Selectivity and Specificity
- Linearity
- Accuracy, Precision and Robustness
- Stability

4. IVRT METHOD VALIDATION

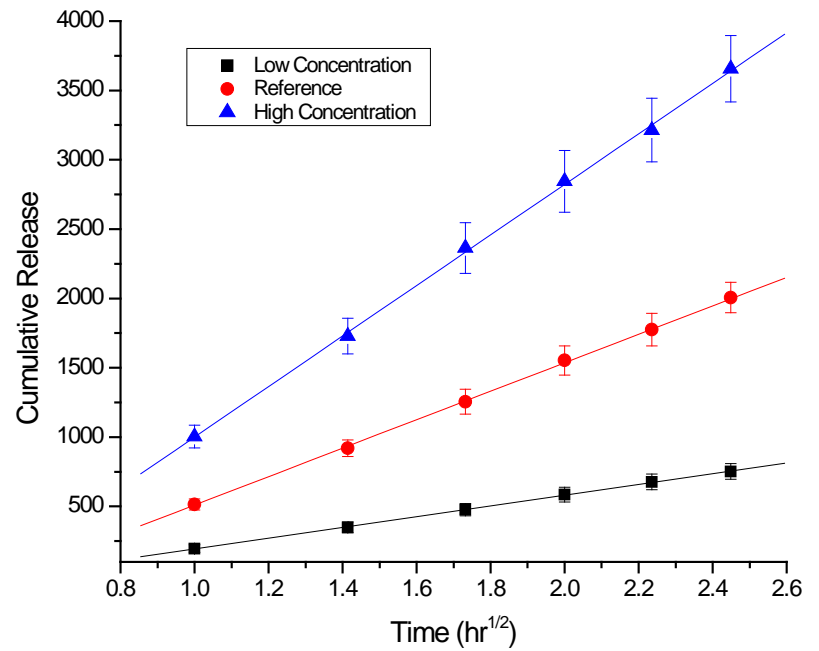
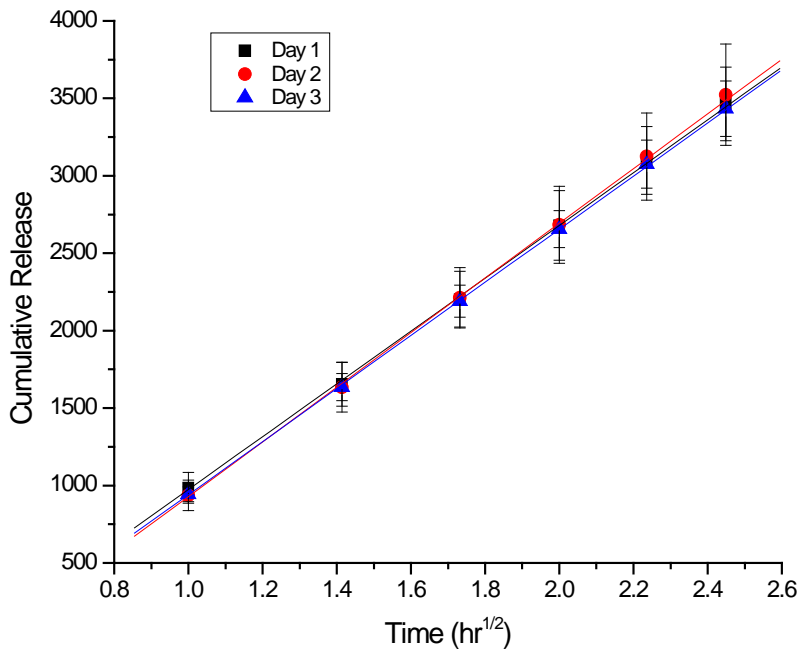
- Linearity and Range
- Precision and Reproducibility
- Recovery Mass Balance, and Dose Depletion
- Sensitivity, Specificity, and Selectivity
- Apparatus Qualification
- Membrane Inertness
- Receptor Solution Solubility
- Robustness

Refer to Tiffner et al. (2017) *A Comprehensive Approach to Qualify and Validate the Essential Parameters of an In Vitro Release Test (IVRT) Method for Acyclovir Cream, 5%*. International Journal of Pharmaceutics. <http://dx.doi.org/10.1016/j.ijpharm.2017.09.049> (Funded, in part, by FDA through award U01FD004946) ²¹

IVRT/IVPT Apparatus Qualification

- The IVRT or IVPT method, and implicitly, the apparatus utilized should be appropriately validated
- Qualification of the IVRT apparatus is described in USP <1724>
 - *Unless the method specifies otherwise, the qualification of the apparatus has been verified when*
 - *analysts determine that the **test temperature** and **stirring rate** are within their specified requirements and*
 - *a satisfactory performance verification test (i.e., drug release rate) results.*
- Equipment Manufacturers may provide
 - Supporting documentation (e.g. certificates of conformance)
 - Guidelines for IQ, OQ and PQ of VDC apparatus and accessories
 - Recommended schedules for maintenance and re-qualification

IVRT Method Validation

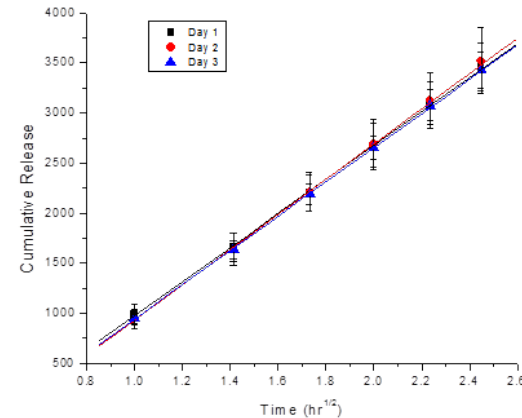
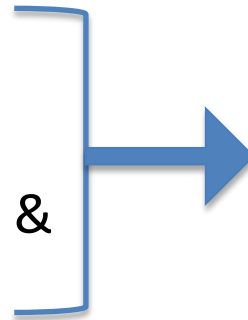


IVRT Method Validation

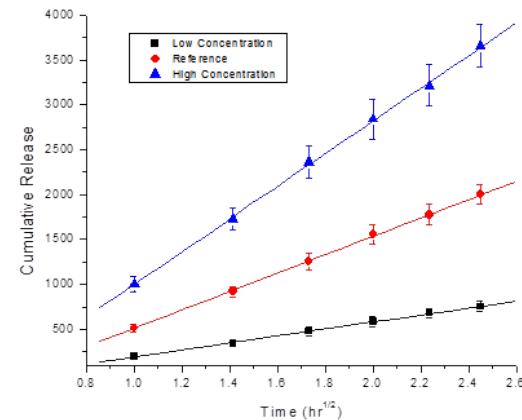


- **Validation Components**

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



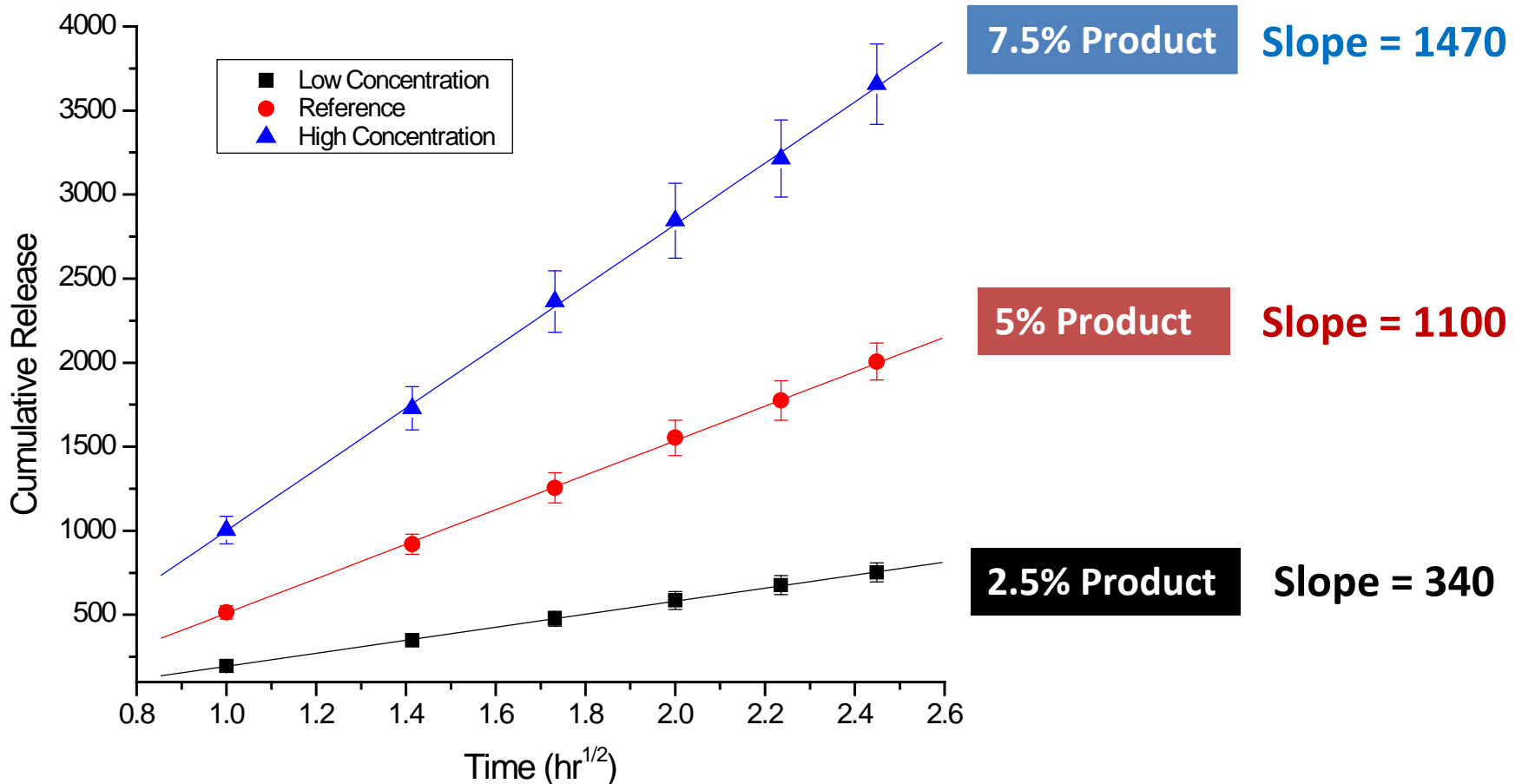
- Sensitivity
- Specificity
- Selectivity



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

IVRT Method Validation

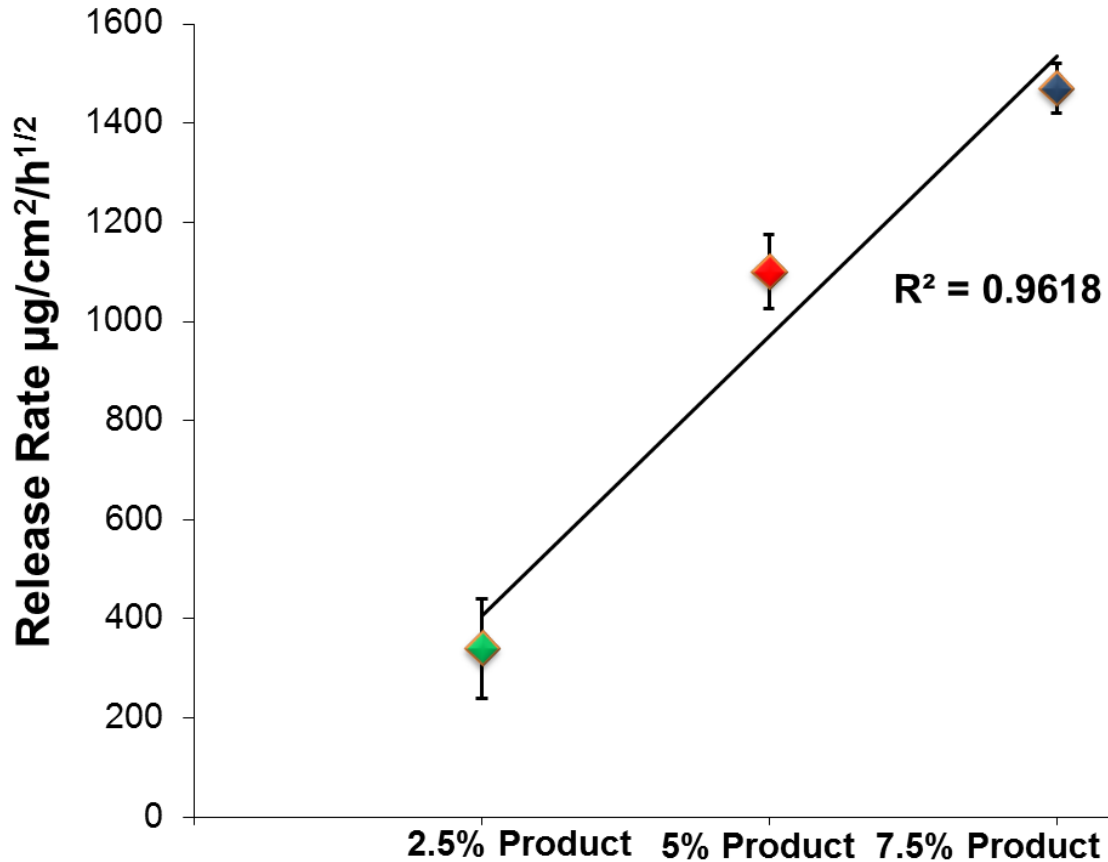
Sensitivity (to an increase or decrease in release)



IVRT Method Validation



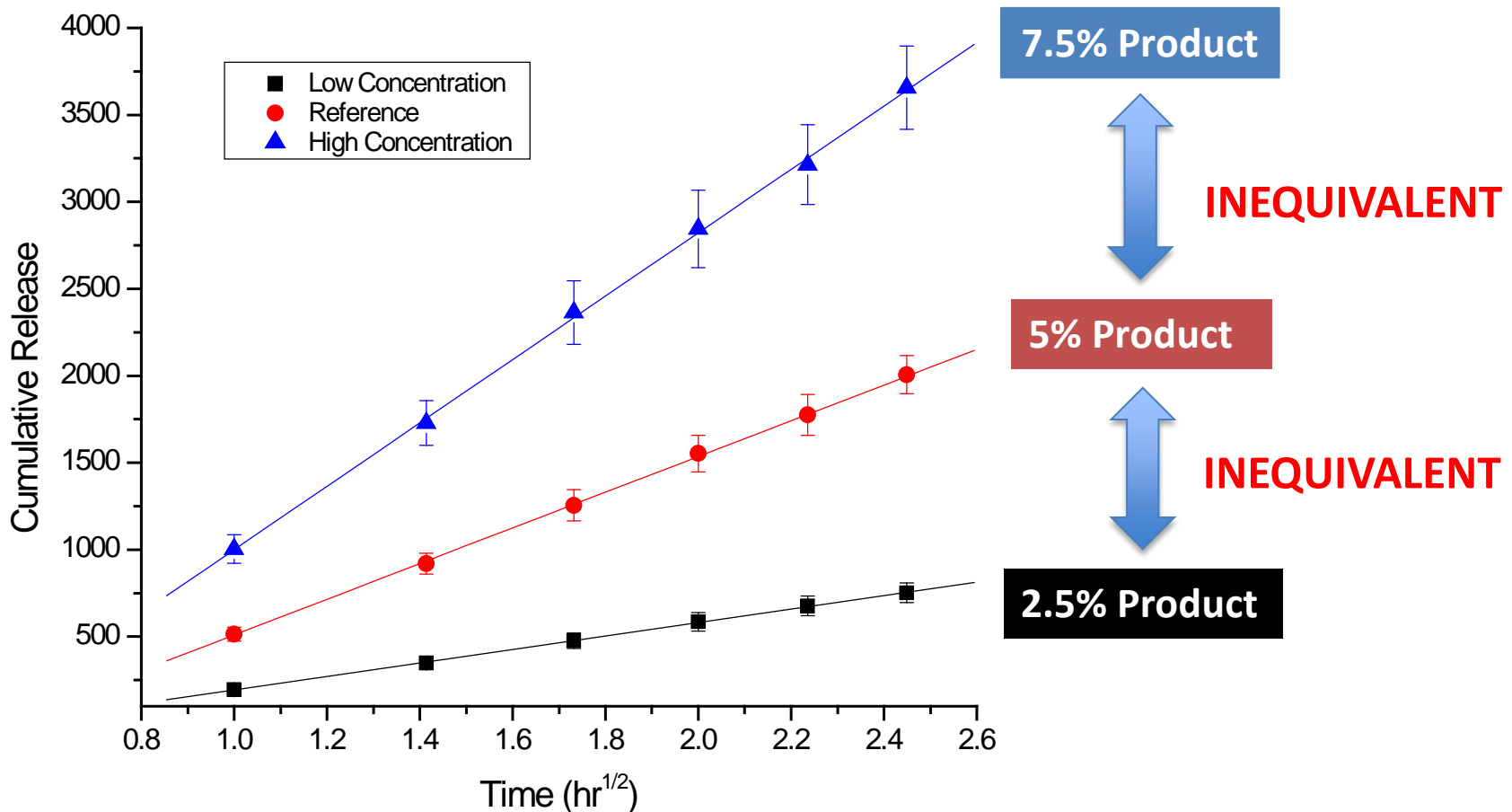
Specificity (proportional response to a change in release)



IVRT Method Validation



Selectivity (to discriminate inequivalent release rates)



Developing In Vitro BE Standards

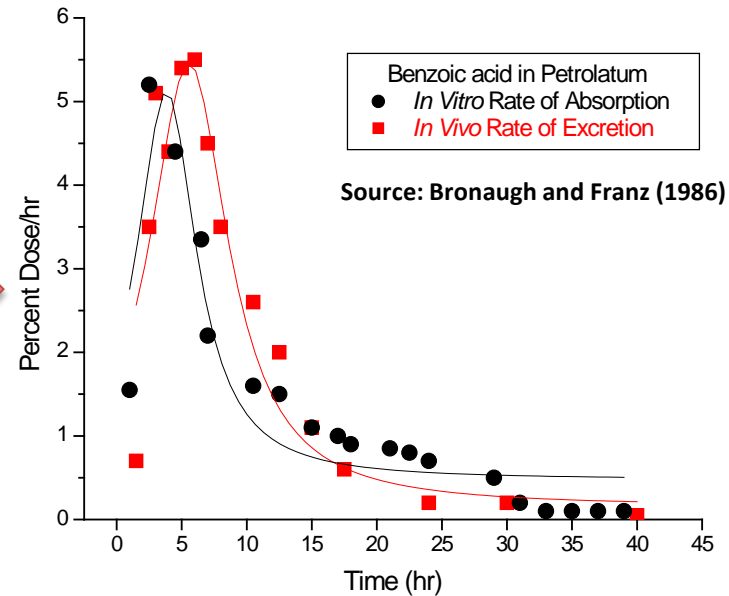
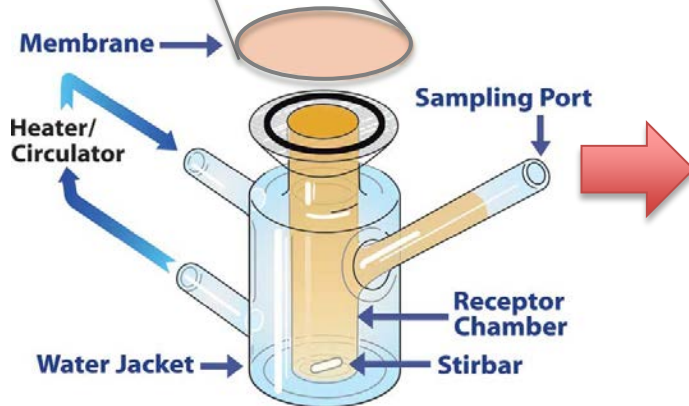
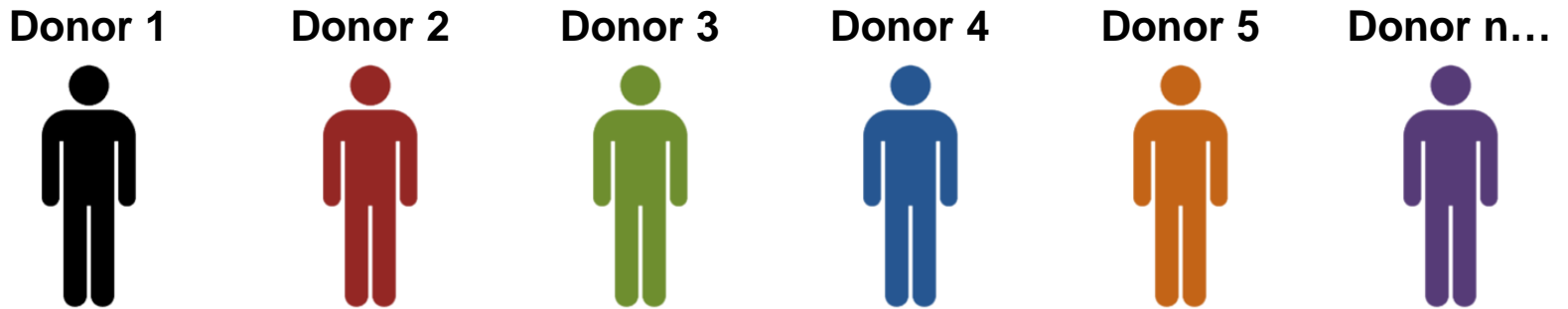


- **IVPT (In Vitro Permeation Test): Cutaneous PK Study**

Mitigates the risk of unknown failure modes related to:

- Differences in Q1/Q2 sameness ($\pm 5\%$ tolerances)
- Differences in physical and structural similarity
- Differences that may not be identified by other tests
- IVPT is a sensitive, discriminating indicator of relative BA
- IVPT results can exhibit IVIVC
- *Standard procedures for IVPT method development and validation had not been established*

IVPT Study Design



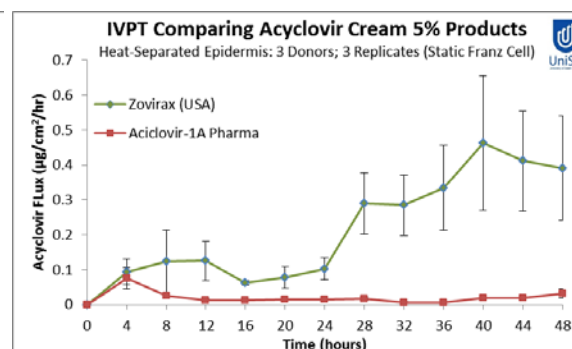
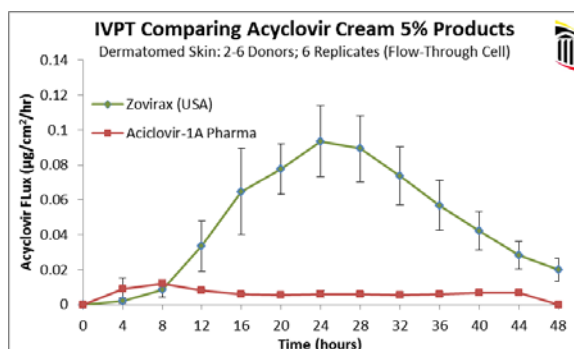
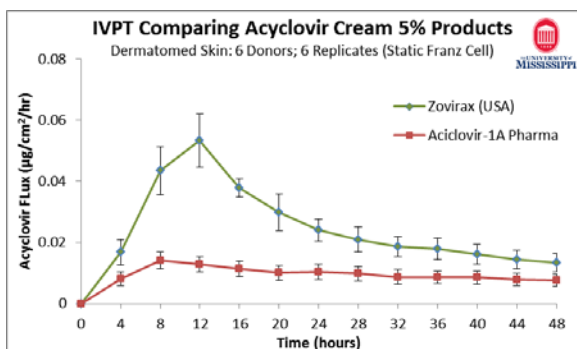
IVPT Results: Acyclovir Cream, 5%



- Cutaneous Pharmacokinetics by IVPT (15 Donors)

Negative Controls for Bioequivalence

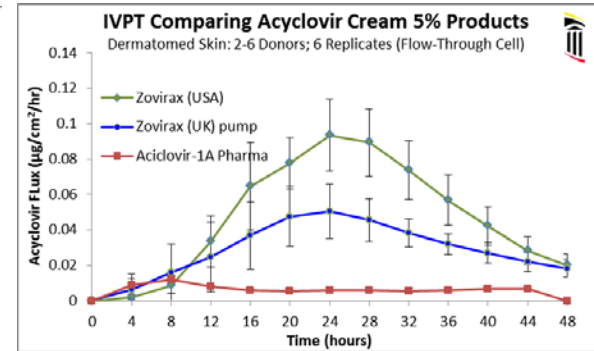
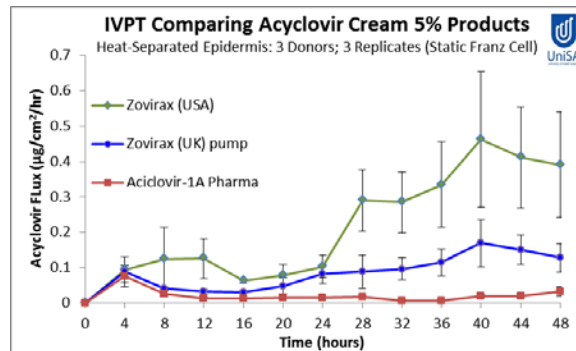
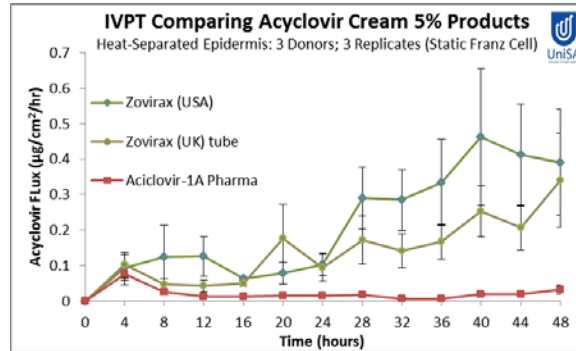
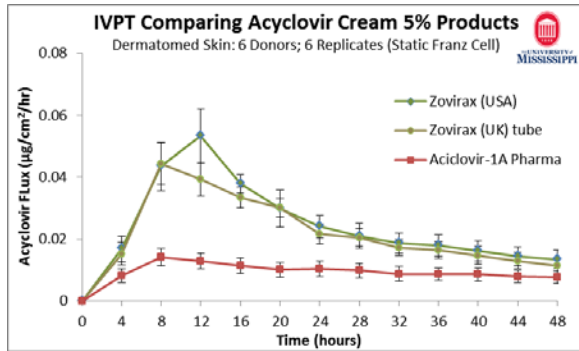
	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm ²		
Dosing technique	Dispensed-Spatula Dispersed-glass rod	Dispensed and dispersed- Positive displacement pipette	Dispensed- Pipette Dispersed- Syringe plunger
Skin type	Torso	Abdomen	Abdomen
Thickness	Dermatomed	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



Influence of Quality on Performance



- Influence of Dose Dispensing on Bioavailability



Developing In Vitro BE Standards

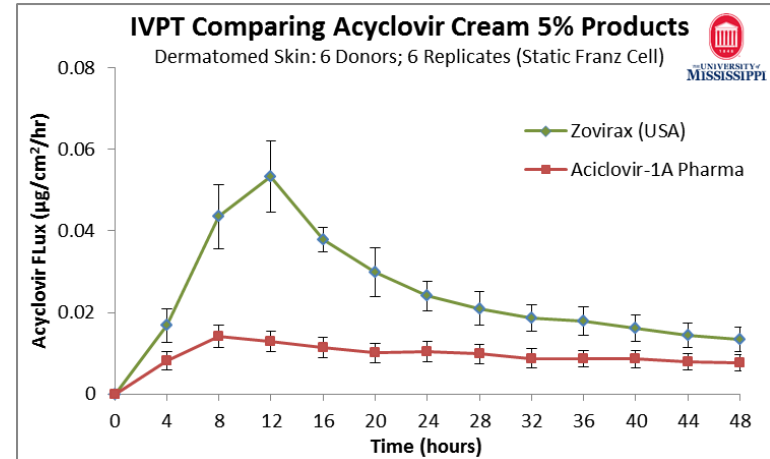
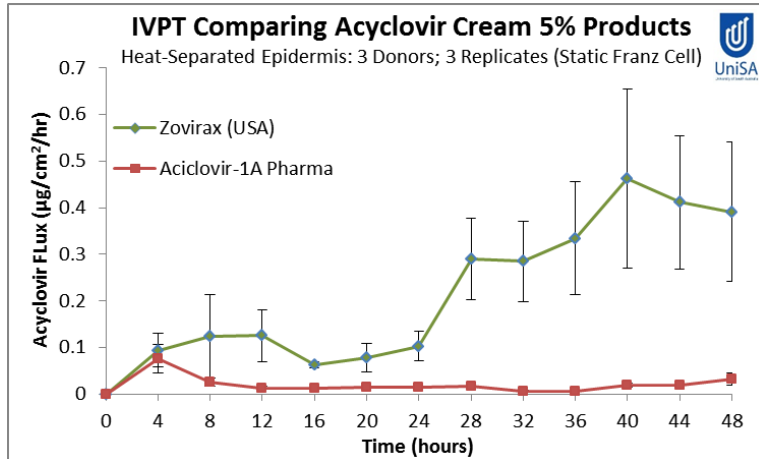


- **IVPT Statistical Analysis of Bioequivalence**
 - The approach for Scaled Average Bio-Equivalence (SABE) analysis of highly variable drugs was modified for the IVPT study design
 - The mixed criterion uses the within-reference variability (σ_{WR}) as a cutoff point for bioequivalence analysis
 - When $\sigma_{WR} \leq 0.294$, Average Bio-Equivalence (ABE) is used
 - When $\sigma_{WR} > 0.294$, Scaled ABE (SABE) is used
- *Standard procedures for IVPT study statistical analysis of BE had not been established*

IVPT Statistical Analysis



- Negative Controls** for BE: Aciclovir-1A[®] vs. Zovirax[®] US



Aciclovir-1A[®] (T) vs. Zovirax[®] US (R)

IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.172	0.104
S _{Within Reference}	0.521	0.551
SABE [0.80, 1.25]	4.433 (Non-BE)	7.236 (Non-BE)
N for [0.80, 1.25] with 3 Replicates	6	8



Aciclovir-1A[®] (T) vs. Zovirax[®] US (R)

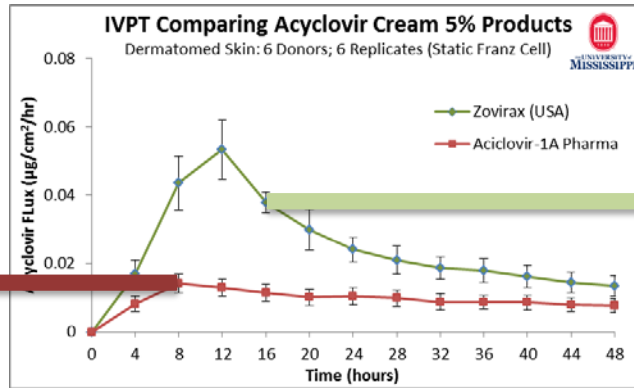
IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.290	0.366
S _{Within Reference}	0.575	0.419
SABE [0.80, 1.25]	2.383 (Non-BE)	1.884 (Non-BE)
N for [0.80, 1.25] with 6 Replicates	8	20



IVPT Statistical Analysis



- **Positive Controls** for BE: Aciclovir-1A[®] and Zovirax[®] US



Comparison to Self by dividing up 6 replicates

Comparison to Self by dividing up 6 replicates

Aciclovir-1A[®] (T) vs. Aciclovir-1A[®] (R)

IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.983	0.958
S Within Reference	0.303	0.318
SABE [0.80, 1.25]	-0.026 (BE)	-0.041 (BE)
N for [0.80, 1.25] with 4 Replicates	26+	15
N for [0.80, 1.25] with 3 Replicates	26+	15

Zovirax[®] US (T) vs. Zovirax[®] US (R)

IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.962	1.101
S Within Reference	0.697	0.469
SABE [0.80, 1.25]	-0.214 (BE)	-0.020 (BE)
N for [0.80, 1.25] with 4 Replicates	12+	14
N for [0.80, 1.25] with 3 Replicates	14	15+



BE Standards for Topical Products



Topical drug products can be complex in multiple ways:

- **Complex Formulations:**
 - e.g., a foam, gel, cream, etc.
- **Complex Route of Delivery:**
 - e.g., locally acting; topical dermatological
- **Complex Dosage Forms:**
 - e.g., a topical patch
- **Complex Drug-Device Combination Products:**
 - e.g., a topical solution in a metered dose pump

BE Standards for Topical Products

- As the complexity of a formulation, dosage form, drug product, route of administration, site of action and/or the mechanism of action increases, so do the potential failure modes for bioequivalence and therapeutic equivalence
- Product specific guidances (PSGs) are developed to be appropriate to the nature and complexity of the relevant drug product

Solution-Based Topical Drug Products



- Less “complex” solution-based topical products
 - Waivers for simple Q1/Q2 topical solutions: *21 CFR 320.22(b)(3)*
 - In vitro comparative physicochemical characterization mitigates the risk of potential failure modes for BE
 - Examples of Product Specific Guidances (PSGs)
 - **Draft Guidance on Ciclopirox** (*Topical Solution*)
“Since the resin imparts important characteristics to the formulation and hence the nail coat, it is important that data be provided showing the polymeric resin has similar physicochemical properties as the RLD.”
 - **Draft Guidance on Erythromycin** (*Topical Swab*)
“...adequate information must be provided to ensure that the composition of the pledgets will not affect the performance of the product.”

Solution-Based Topical Drug Products



- Less “complex” solution-based foam aerosols
 - In Vitro evidence to support a waiver of in vivo evidence of BA or BE per 21 CFR 320.22(b)(3), or a clinical endpoint BE study
 - Comparative physicochemical characterizations:
 - Microscopic Birefringence Analysis (do crystals form upon dispensing?)
 - Time to Break Analysis (conducted at 30°C, 33°C, 35°C & 40°C)
 - Weight per Volume of un-collapsed foam aerosol
 - Examples of PSGs
 - **Draft Guidance on Minoxidil** (*Foam Aerosol*)
 - **Draft Guidance on Clobetasol Propionate** (*Foam Aerosol*)
 - **Draft Guidance on Clindamycin Phosphate** (*Foam Aerosol*)
 - **Draft Guidance on Ketoconazole** (*Foam Aerosol*)
 - **Draft Guidance on Betamethasone Valerate** (*Foam Aerosol*)

Semisolid Topical Drug Products



- Moderately “complex” semisolid topical products
 - Examples of PSGs
 - **Draft Guidance on Acyclovir** (*Topical Ointment*)
 - *Q1/Q2 sameness of the test and RLD formulations*
 - *Comparative physicochemical characterization of test and RLD products*
 - *Equivalent acyclovir release from test and RLD products evaluated by IVRT*
 - NOTE: A clinical endpoint BE study is recommended as an alternative
 - **Draft Guidance on Silver Sulfadiazine** (*Topical Cream*)
 - *Q1/Q2 sameness of the test and RLD formulations*
 - *Physically and structural similarity based upon an acceptable comparative physicochemical characterization of appearance, polymorphic form of the drug, globule and/or particle size distribution and crystal habit, rheological behavior, specific gravity, and pH...*
 - *Equivalent silver sulfadiazine release from test and RLD products evaluated by IVRT*

Semisolid Topical Drug Products

- “Complex” semisolid topical products

- Example of a PSG

- **Draft Guidance on Acyclovir** (*Topical Cream*)

- “To qualify for the in vitro option for this drug product the following criteria should be met:*

- A.** *The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same...*

- B.** *The test and RLD products are physically and structurally similar...*

- C.** *The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT)... using an appropriately validated IVRT method*

- D.** *The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT)... using an appropriately validated IVPT method”*

Semisolid Topical Drug Products

- “Complex” semisolid topical products

- Example of a PSG

- **Draft Guidance on Benzyl Alcohol** (*Topical Lotion*)

“i. Equivalent comparative qualitative and quantitative (Q1/Q2) characterization.

ii. Equivalent comparative physicochemical and microstructural characterization of comparable pH, specific gravity, emulsion globule size distribution ...and viscosity profiles...

iii. Equivalent comparative dosage form performance characterization in vitro, using the USP compendial In Vitro Release Test (IVRT) method. We recommend that the IVRT method be validated...

*iv. Equivalent comparative dosage form performance characterization ex vivo in *Pediculus humanus capitis* (head lice), using an appropriate pediculicide hair tuft assay with relevant controls...”*

Semisolid Topical Drug Products

- “Complex” semisolid topical products with multiple potential mechanisms/sites of action
 - Examples of a PSGs
 - **Draft Guidances on Dapsone** (*Topical Gels*)
 - **Draft Guidance on Ivermectin** (*Topical Cream*)
 - 1) *Q1/Q2 sameness*
 - 2) *Q3 (physical and structural) similarity*
 - 3) *IVRT equivalence*
 - 4) *in vitro BE study with local (cutaneous) PK endpoints (IVPT)*
 - 5) *In vivo BE study with systemic (plasma) PK endpoints*

Moving Forward...

- BE for topical products with complex mechanisms/sites of action may benefit from
 - Modeling and simulation
 - **In silico computational modeling and simulation may supplement in vitro and in vivo evidence that may include:**
 - 1) *Q1/Q2 sameness?*
 - 2) *Q3 (physical and structural) similarity?*
 - 3) *IVRT equivalence?*
 - 4) *in vitro BE study with local (cutaneous) PK endpoints (IVPT) ?*
 - 5) *In vivo BE study with systemic (plasma) PK endpoints?*
 - 6) *Physiologically-based PK (PBPK) modeling and simulation?*

Conclusions

- For products across a range of complexity, consider how failure modes for product performance arise from and convolute among multiple potential critical quality attributes (CQAs)
- Consider how the risk of failure modes can be mitigated once the associated (individual and collective) quality attributes are designed into the product and controlled within a well-characterized design space
- Consider which product quality and performance attributes to characterize and how the collective weight of evidence from complementary orthogonal approaches may support a demonstration of BE

Conclusions

- Developers of complex topical dermatological drug products can ensure that the products are of high quality and can bring greater predictability and timeliness to the review of generic drug applications by
 - Demonstrating a comprehensive understanding of the product complexities and manufacturing issues
 - Providing information that mitigates risks of potential failure modes for therapeutic equivalence
 - Initiating pre-ANDA communication with the FDA during product and program development, if necessary



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