Bioequivalence of Topical Products: Scientific Considerations

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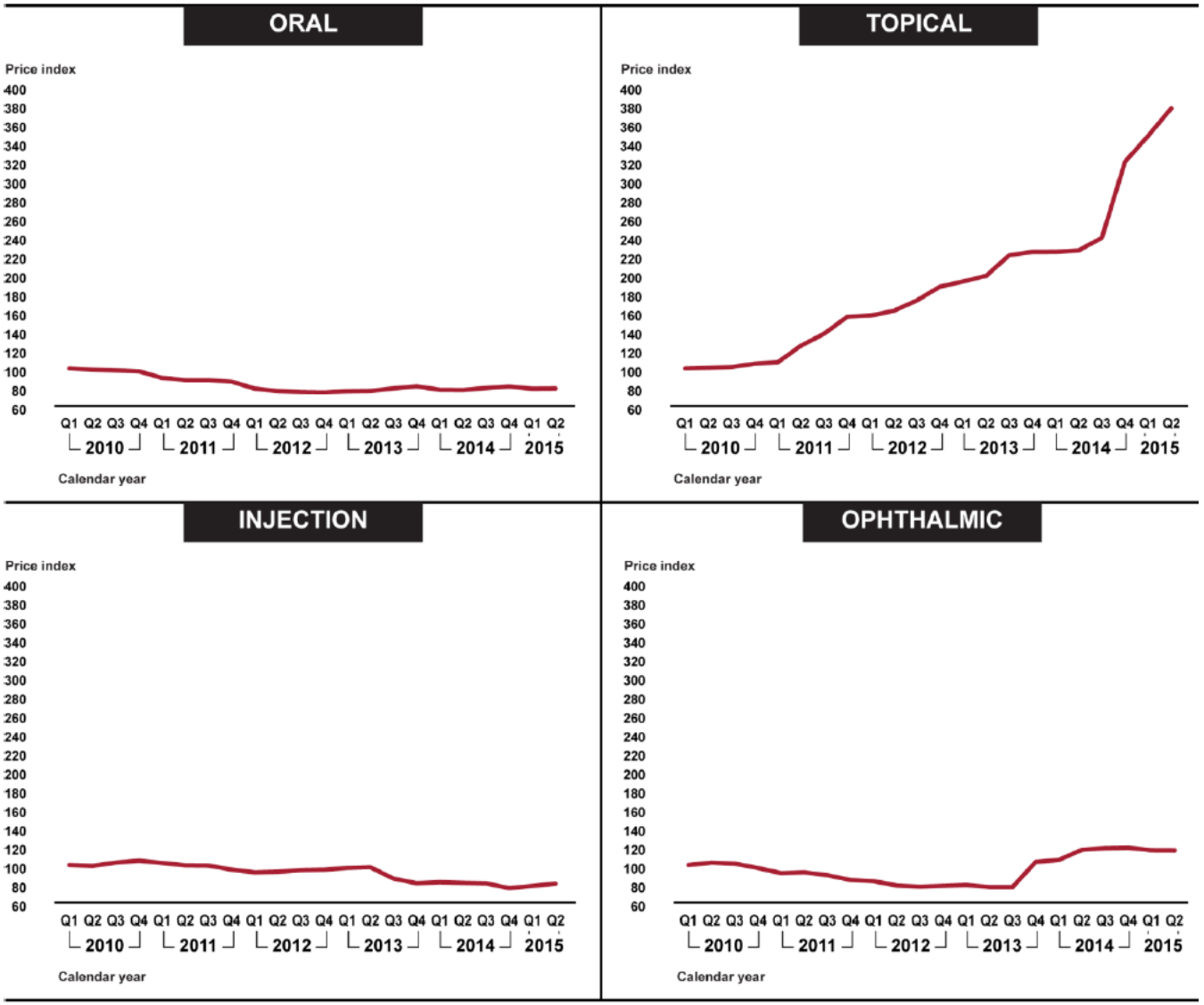
Disclaimer

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

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
- Manufacturers and other stakeholders reported that market **competition**, influenced by various factors, drives generic drug prices

The GAO Report (GAO-16-706)



Source: GAO analysis of Medicare Part D prescription drug event data. | 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. This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  - Comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations
  - The relatively small market capitalization for some products

Available (and Affordable) Products

- Power of "efficient" BE standards

Overall Drug Products [1]

- In 2017, 9 out of every 10 prescriptions in the U.S. were dispensed using generic drugs.
- Efficient **Pharmacokinetics (PK)-based** methods available

Topical Drug Products 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?

[1] AAM 2018 Generic Drug Access & Savings in the United States Report

Developing Rational BE Standards

- 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
- With a sufficient product and process understanding, relevant complexities can be identified and addressed systematically for the generic drug product

Developing Rational BE Standards

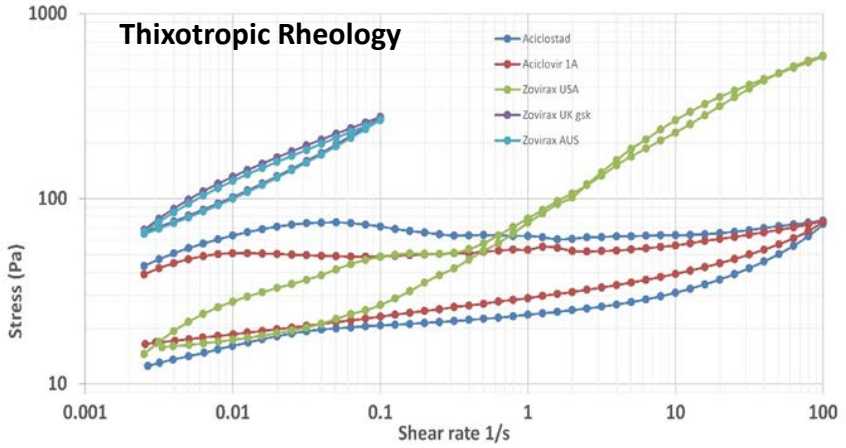
- **A <u>Modular</u> and <u>Scalable</u> Approach to BE Evaluation**
  - **Q1/Q2** sameness of inactive ingredient components and quantitative composition
  - **Q3 (Physical & Structural Characterization)** as relevant to the nature of the product
  - **IVRT** (In Vitro Release Test) for moderately complex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

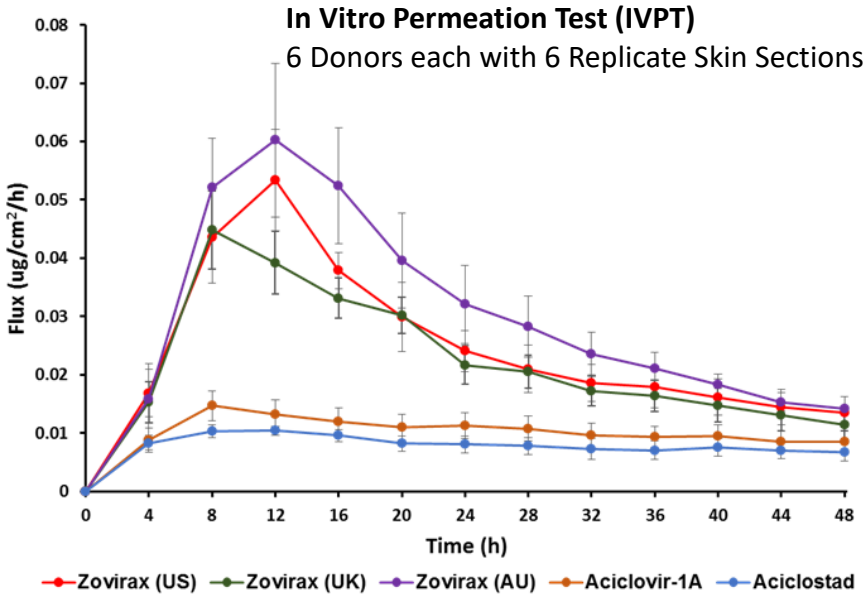
Developing Rational BE Standards

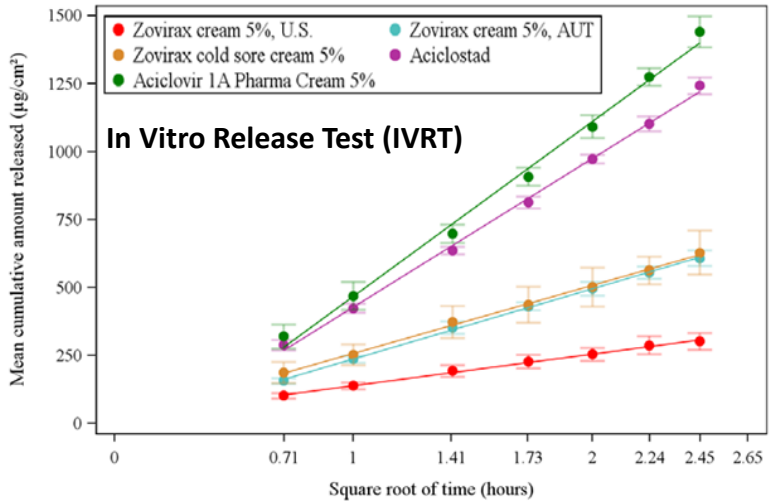
- **Other Methodologies of Interest**
  - **In Vivo** Cutaneous PK Studies
    - ✓ Dermal Open Flow Microperfusion (dOFM)
    - ✓ Dermal Microdialysis (dMD)
    - ✓ Epidermal and/or Dermal Pharmacokinetic Tomography
- **Other Methodologies *Not of Interest***
  - **In Vivo** Cutaneous PK Studies
    - ✓ Tapestripping "Dermatopharmacokinetics" (DPK)

Product Quality and Performance

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS	[redacted]	[redacted]
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
	[redacted]	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95







Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner

Enhancing the Availability of Generics

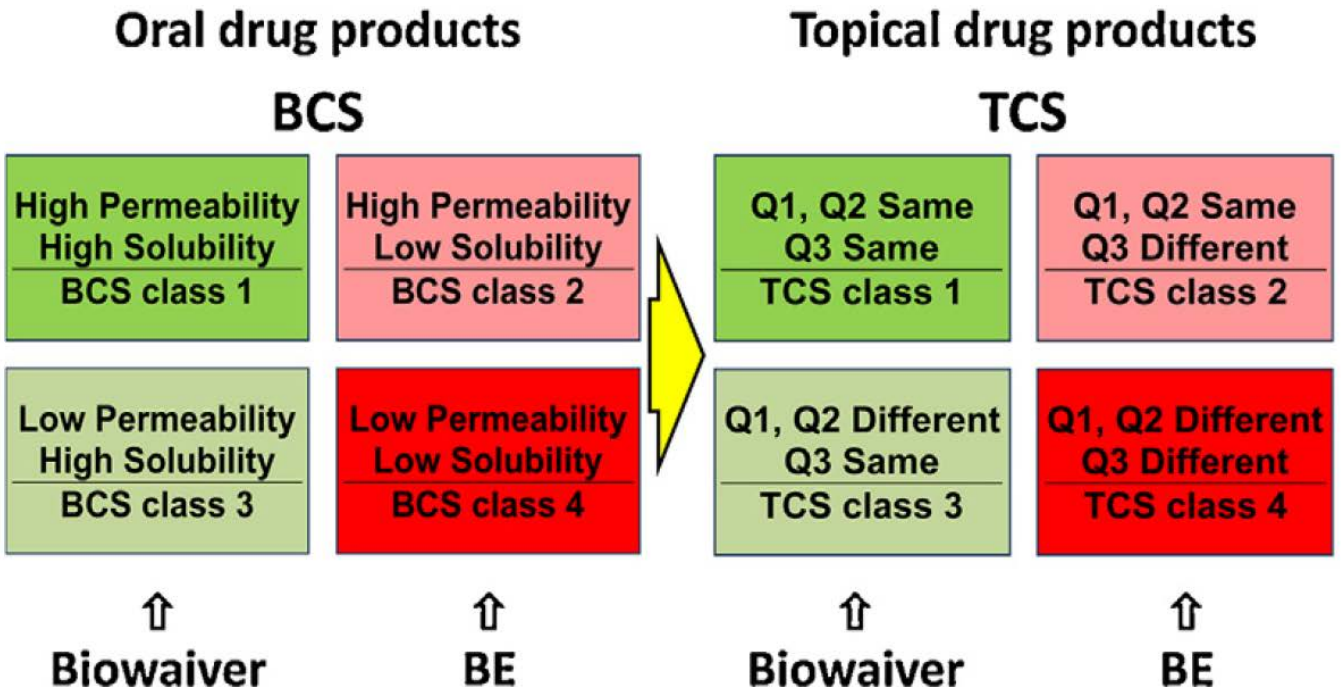
- The *Proposed* Topical Classification System (TCS)[2,3]
  - Modeled on the Biopharmaceutics Classification System (BCS)
  - By the TCS scheme, topical formulations that pass an in vitro release test (IVRT) would be eligible for a biowaiver
  - It may be an **efficient** way to develop topical generics, and it has generated some interest in the field, so let's explore it…

[2] Shah, VP et al. Int J of Pharmaceut 491 (2015): 21–25
[3] Shah, VP et al. Int J Pharmaceut 509 (2016) 35–40

The TCS Proposed by Shah et al.

Scientific Issue: TCS suggests that IVRT ≈ Q3

- *"Based on composition and IVR similarity, the compared dosage forms are classified as TCS class 1, 2, 3 and 4. …TCS class 1 and TCS class 3 dosage forms are eligible for biowaiver"* [2]



[2] Shah, VP et al. Int J of Pharmaceut 491 (2015): 21–25
Figure Source: Shah, VP et al. Int J Pharmaceut 509 (2016) 35–40

The Arrangement of Matter (Q3)

- Physicochemical & Structural Properties Affect:
  - The drug state(s) and phase(s) of the dosage form
  - The distribution of the drug in the dosage form
  - 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

Tests of the Arrangement of Matter

- **Quality** Tests to Study the Arrangement of Matter
  - Microscopic Analyses of Microstructure (e.g., Globules)
  - Dissolved vs. Undissolved Amounts of the Drug
  - Concentration of Drug in the Continuous Phase
  - Size Distribution of Globules/Particles
  - Drug Polymorphic State (Raman, XRD, etc.)
  - Solvent/Water Activity (Drying Rate)
  - Density
  - pH
  - Etc.

- The tests themselves are not the arrangement of matter
- No single test characterizes all the arrangement matter
- The collective results from all the tests help us to infer various details about the underlying arrangement of matter

The *Proposed* TCS

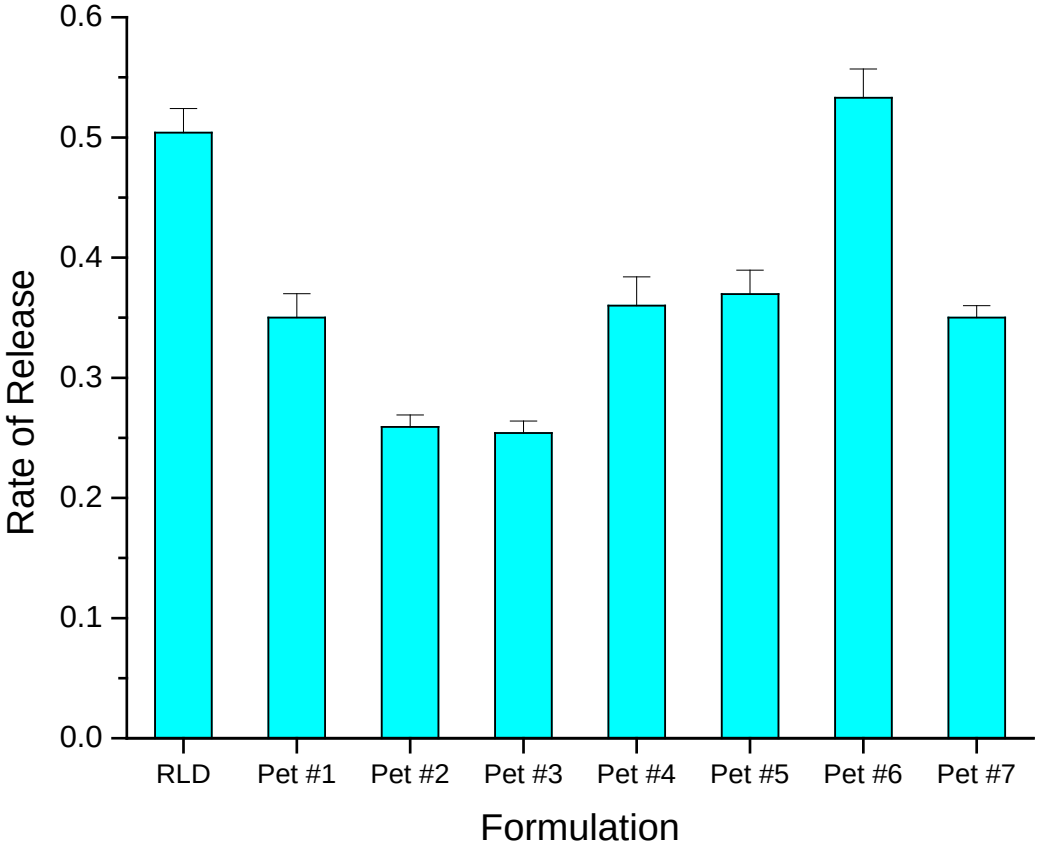
Scientific Issue: TCS suggests that IVRT ≈ Q3

- *"Based on composition and IVR similarity, the compared dosage forms are classified as TCS class 1, 2, 3 and 4. …TCS class 1 and TCS class 3 dosage forms are eligible for biowaiver"* [2]
- *"The proposed topical drug classification system is based on qualitative and quantitative equivalence of composition (Q1 and Q2) and on the similarity of IVR rates (as estimator of microstructural sameness, Q3) between two compared formulations, a generic product and RLD."* [2]
- *"If the product is Q1 and Q2, and if it meets IVR (Q3) comparison criteria and confidence intervals identified in SUPAC-SS, a biowaiver can be provided"* [2]
- *"The IVR (Q3) reflects the microstructure, arrangement of the matter and the state of aggregation of the dosage form."* [2]

[2] Shah, VP et al. International Journal of Pharmaceutics 491 (2015) 21–25

IVRT ***Can*** Discriminate Some Things

- IVRT **did discriminate** 8 formulations made with Petrolatum, USP from different sources



Data provided courtesy of Paul A. Lehman and Dr. Thomas J. Franz

IVRT ***Cannot*** Discriminate Some Things

- IVRT **did not discriminate** 14 formulations with substantial variations in particle size

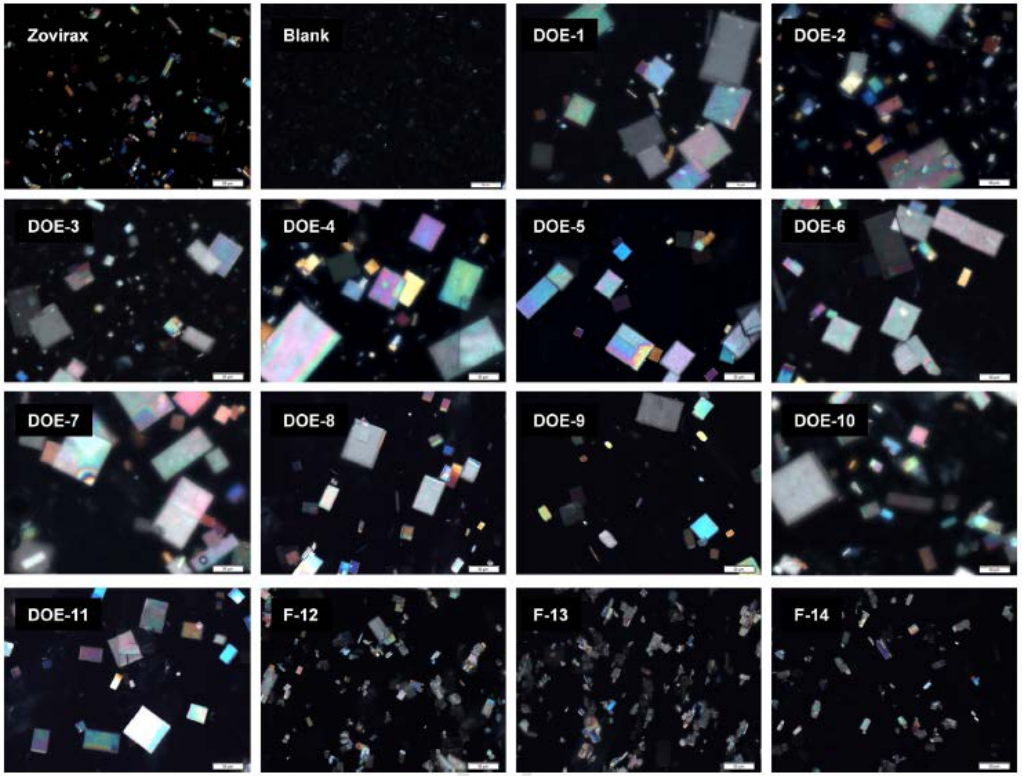


Fig 3. Polarized light microscopy images of various acyclovir cream formulations (200× magnification, the bar represents 50 μm). At least 10 images were taken for each sample with total of 200–500 particles in order to calculate the size distribution.

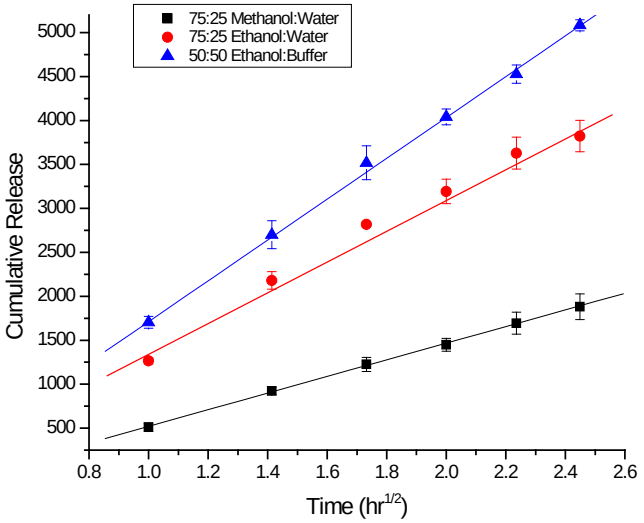
Figure Source: Krishnaiah, Y.S.R., et al., Development of performance matrix for generic product equivalence of acyclovir topical creams. Int J Pharmaceut 475 (2014):110-22

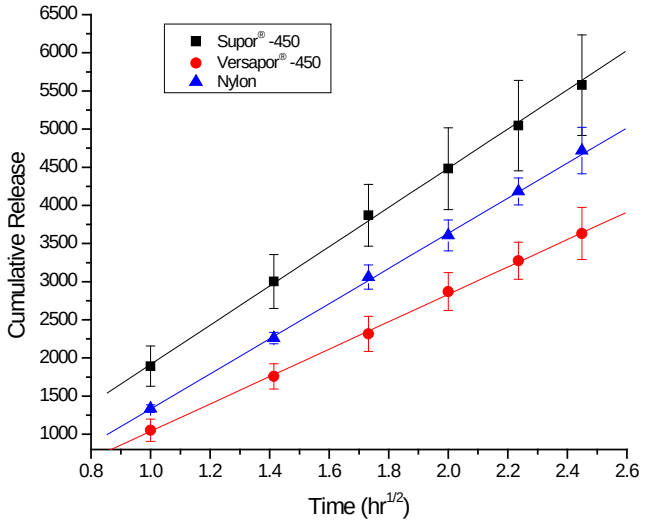
IVRT Release Rate is not Biorelevant

- As long as IVRT indicates that the drug release rate is the same, isn't that all that matters?

The release rate measured by an IVRT is **arbitrary**

- It can be modulated by IVRT method parameters like the choice of receptor solution or membrane

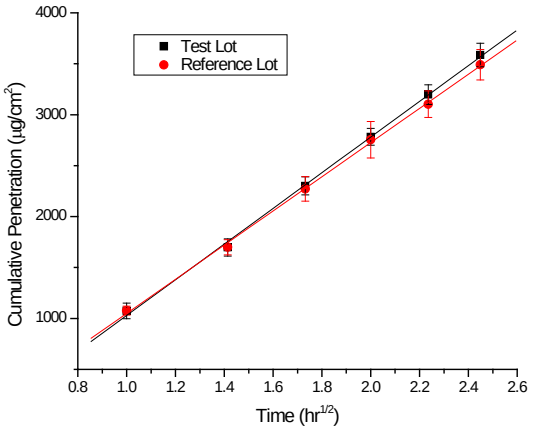


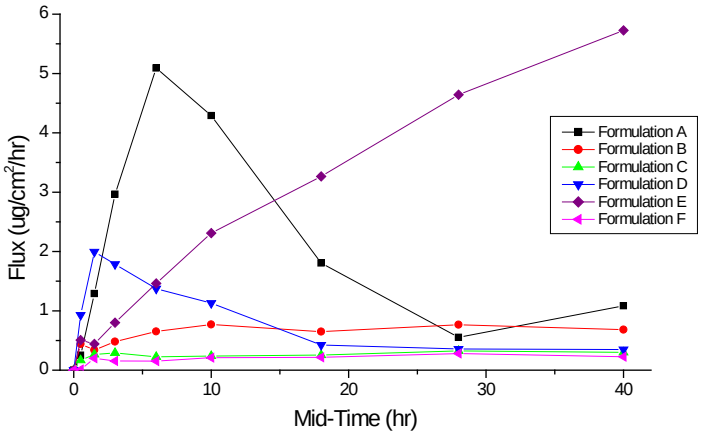


IVRT Release Rate is not Biorelevant

The ‘release rate’ in an IVRT is **not biorelevant**

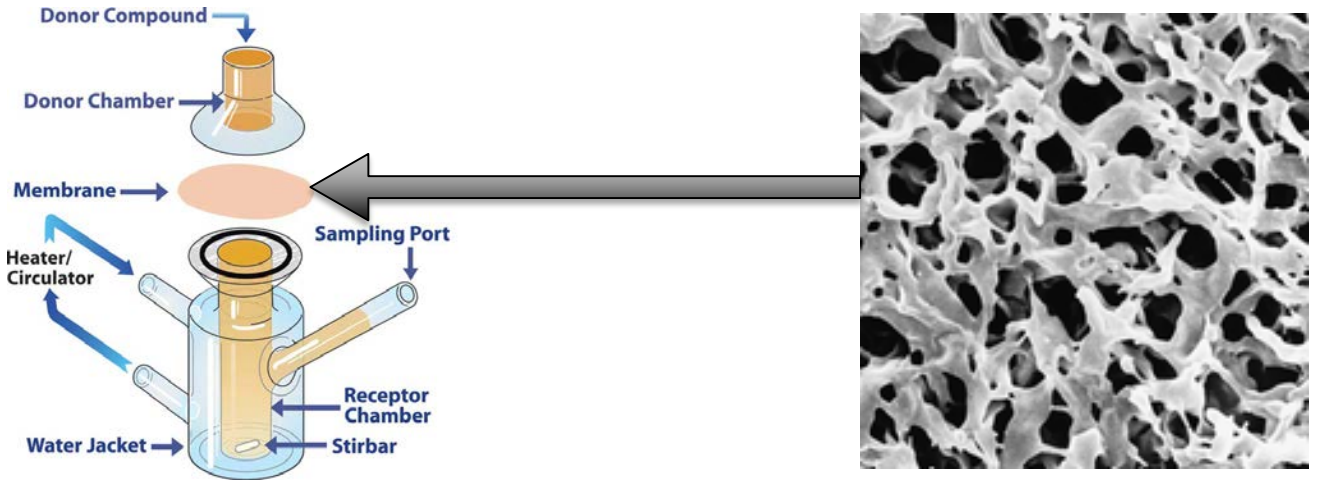
- IVRT pseudo-infinite, occluded dose *artificially* provides a steady-state release rate.
- This is not representative of the drug release kinetics from a finite dose (thin film) of an un-occluded topical product that dries on the skin.





Tests of the Arrangement of Matter

- **Performance** Tests to Study the Arrangement of Matter
  - The IVRT (United States Pharmacopeia <1724>) and other tests



- The arrangement of matter, taken all together, defines the rheology, drying rate, release rate (IVRT), etc.
- But, the converse cannot be assumed
- No single test describes all the arrangement of matter
- IVRT does not describe all the arrangement of matter

The *Proposed* TCS

Scientific Issues:

- IVRT Equivalence ≠ Q3 Similarity
  - Scientifically wrong to assume that IVRT ≈ Q3
  - IVRT alone ***cannot*** assure Q3 similarity
- IVRT Equivalence ≠ Similar Bioavailability

- Putting IVRT aside for a moment, are the failure modes for bioequivalence adequately mitigated by Q1 and Q2 sameness?

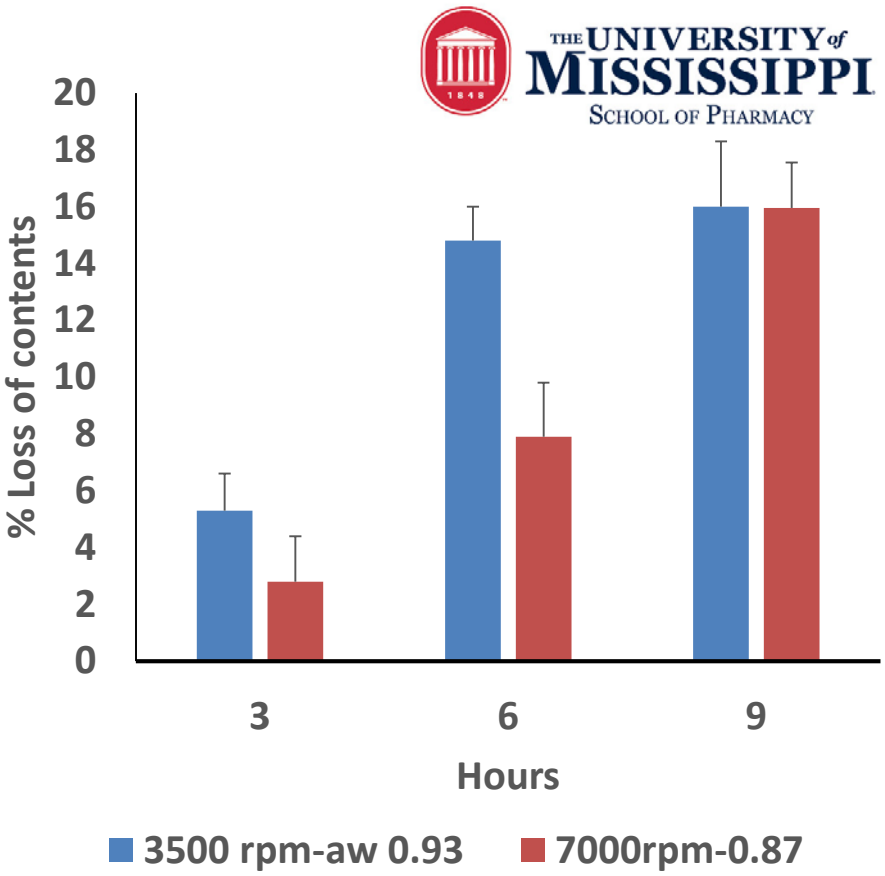
Differences with Q1/Q2 Creams

- Solvent Activity of Q1/Q2 Identical Creams

  Prof. Narasimha Murthy FDA Award U01-FD005223

Ingredients	Quantity (%w/w)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100

Manufacturing Conditions	Solvent Activity (a_w)
3500 RPM (15 min)	**0.931 ± 0.002**
7000 RPM (45 min)	**0.875 ± 0.006**



Data provided courtesy of Prof. Narasimha Murthy

The *Proposed* TCS

- **TCS Class 1**: for a "*biowaiver*"
  - Q1 and Q2 Sameness
  - IVRT Equivalence

Scientific Issue:

- Failure modes for bioequivalence are not necessarily mitigated by Q1 and Q2 sameness alone, and the addition of IVRT still may not ensure bioequivalence because the IVRT cannot ensure similar Q3, obscures metamorphosis, and cannot ensure similar bioavailability.

The *Proposed* TCS

- **TCS Class 3**: for a "*biowaiver*"
  - Q1 and/or Q2 Difference*
  - IVRT Equivalence

  * *"…essential to evaluate the properties of the excipients with respect to safety and efficacy, as well as how excipients affect both the thermodynamic activity of the active pharmaceutical ingredient and the skin permeability. …If the excipients are inert and IVR turns out to be the same …then the dosage form can be provided with a biowaiver"* [3]

Scientific Issue:

- The (placebo) vehicle often contributes to efficacy
- It is unclear what evidence would establish that the "*excipients are inert*"

[3] Shah, VP et al. International Journal of Pharmaceutics 491 (2015) 21–25

The *Proposed* TCS

- **TCS Class 2**: for a bioequivalence study
  - Q1 and Q2 Sameness
  - IVRT Difference

- **TCS Class 4**: for a bioequivalence study
  - Q1 and Q2 Difference
  - IVRT Difference

Scientific Issues:

- It is unclear what bioequivalence studies would be involved, and whether they would be **efficient**

Conclusions (What To Do)

- 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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