Questions on the Proposed Topical Classification System (TCS)

and What To Do About It

PQRI BTC Webinar Conference on Advancing Product Quality:

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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.

Patient Access to Topical Generics

- 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
  - Comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations
  - The relatively smaller 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 affordable for patients
  - Increase the likelihood that patients will actually purchase the medicine prescribed for them and receive therapeutic benefit
  - 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

Enhancing the Availability of Generics

- Power of "efficient" BE standards

  Overall Availability of Generic Drug Products [2]

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

  The *Proposed* Topical Classification System (TCS)? [3,4]

  - 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] AAM 2017 Generic Drug Access & Savings in the United States Report
[3] Shah, VP et al. Int J of Pharmaceut 491 (2015): 21–25
[4] Shah, VP et al. Int J Pharmaceut 509 (2016) 35–40

The TCS Proposed by Shah et al.

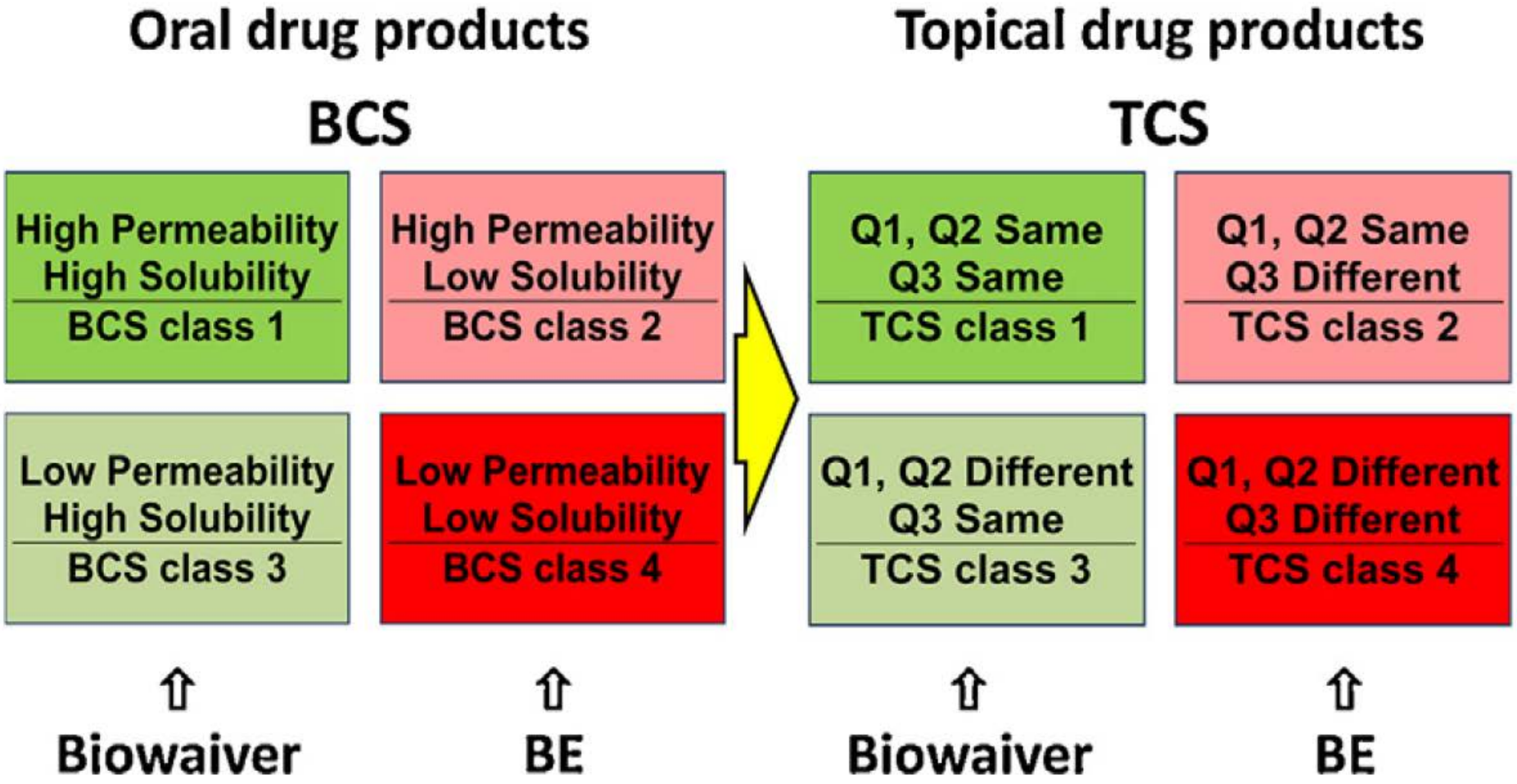
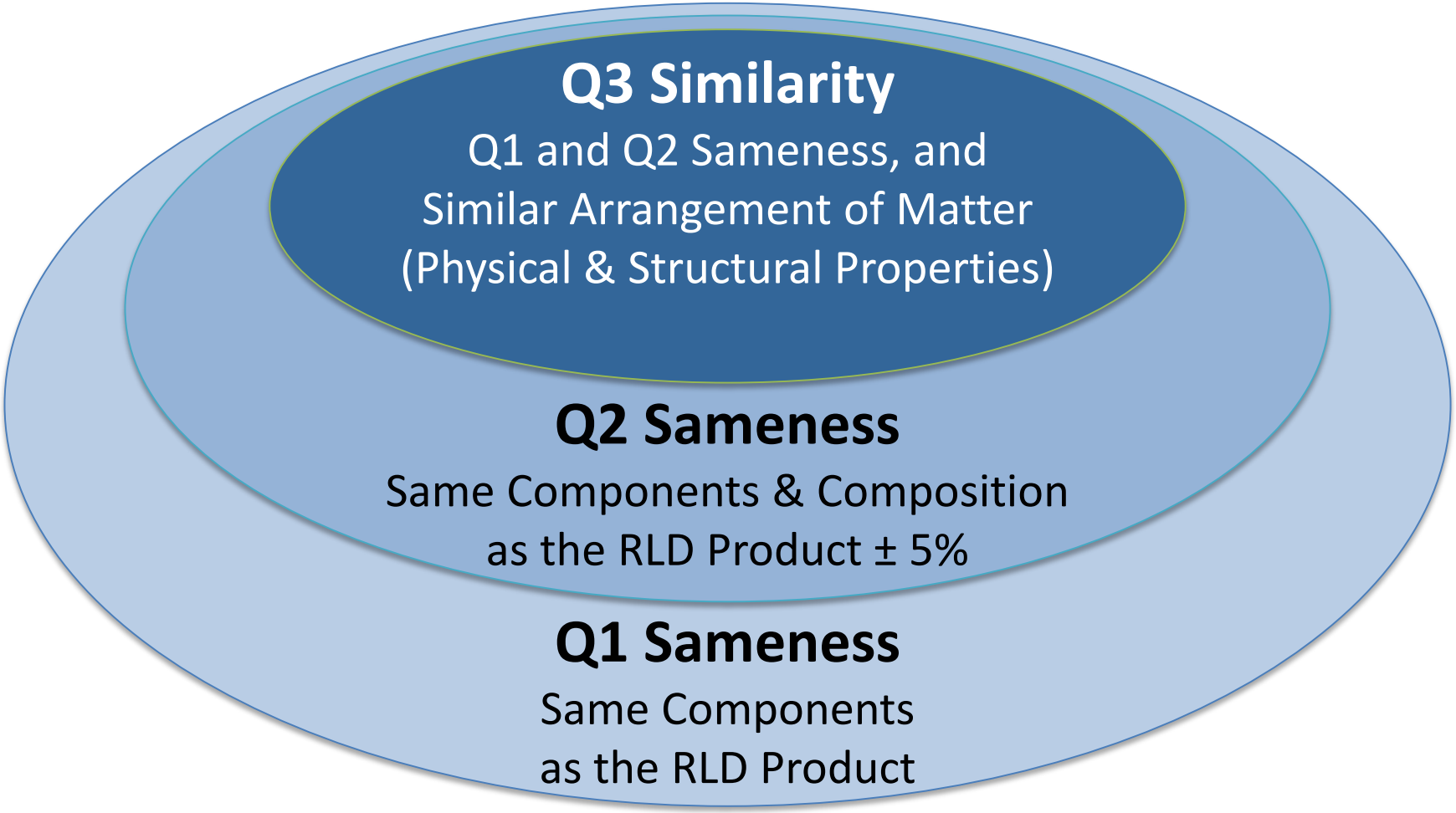


Figure Source: Shah, VP et al. International Journal of Pharmaceutics 509 (2016) 35–40

Topical Formulation Quality Concepts

- What are Q1, Q2, and Q3?



Why Does Q1/Q2 Matter for Generics

- Q1/Q2 Sameness (components and composition)

  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

Why Does Q3 Matter for Generics

- Q3 Similarity (Arrangement of Matter)

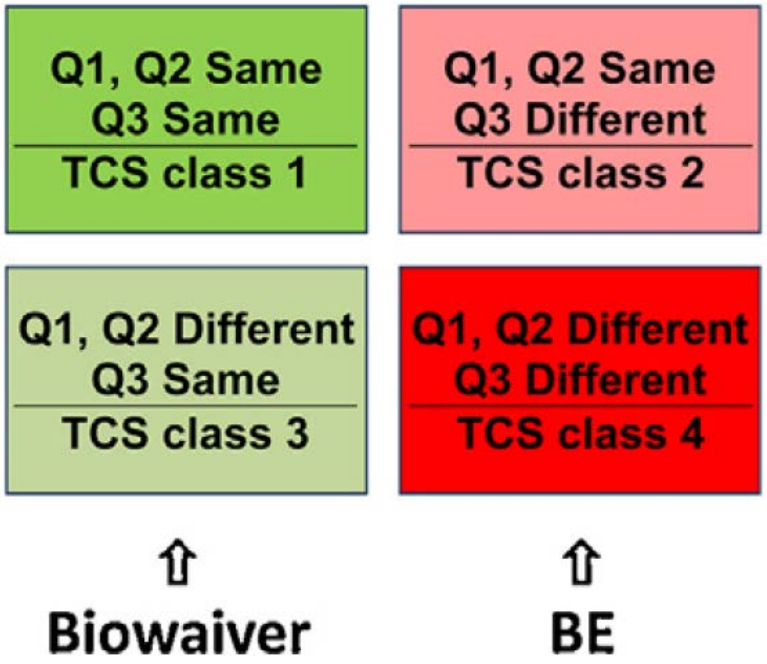
  Mitigates the risk of potential failure modes related to:

  - Differences in Q1/Q2 sameness (± 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

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"* [3]



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

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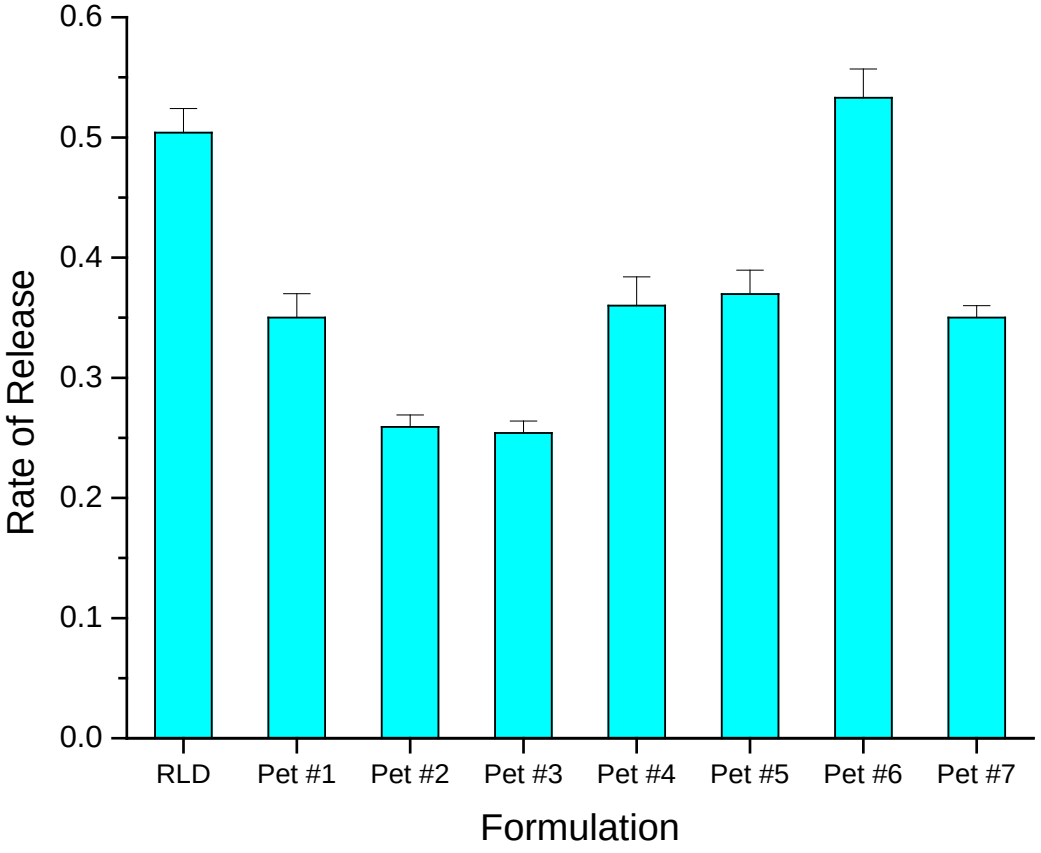
- *"Based on composition and IVR similarity, the compared dosage forms are classified as TCS class 1, 2, 3 and 4. …TCS class 1 and TCS class 3 dosage forms are eligible for biowaiver"* [3]
- *"The proposed topical drug classification system is based on qualitative and quantitative equivalence of composition (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."* [3]
- *"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"* [3]
- *"The IVR (Q3) reflects the microstructure, arrangement of the matter and the state of aggregation of the dosage form."* [3]

[3] 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

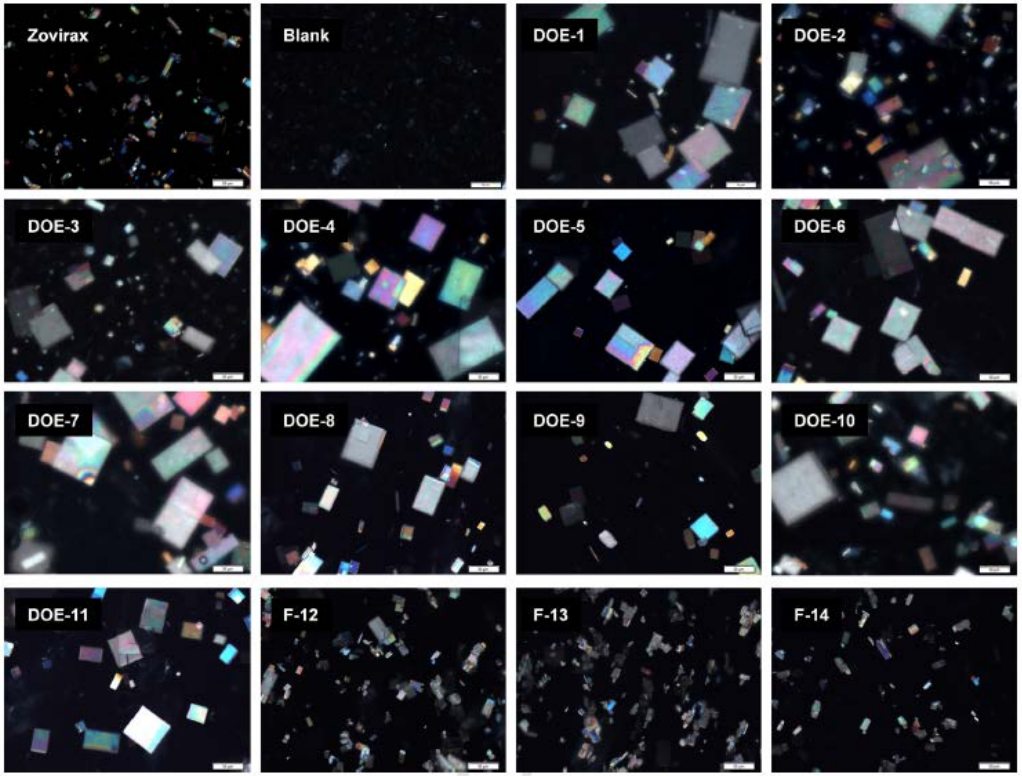


Fig 3. Polarized light microscopy images of various acyclovir cream formulations (200× magnification, the bar represents 50 μm). At least 10 images were taken for each sample with total of 200–500 particles in order to calculate the size distribution.

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

The *Proposed* TCS

- Scientifically wrong to assume that IVRT ≈ Q3
- IVRT alone ***cannot*** assure Q3 similarity
- Therefore, all the failure modes for bioequivalence that are mitigated by Q3 similarity are not necessarily mitigated simply by a passing IVRT

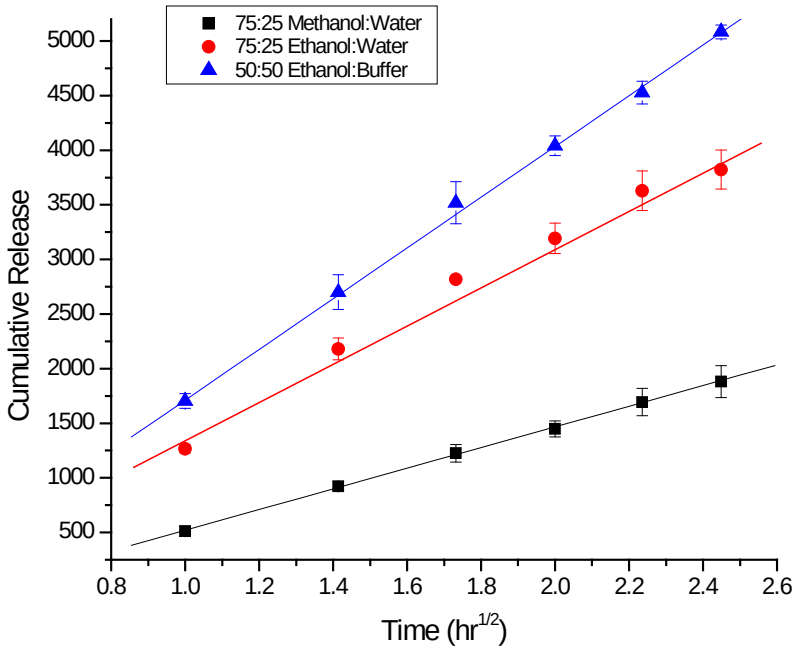
Is the inability to ensure Q3 similarity based upon IVRT alone a **fatal flaw** of the *proposed* TCS?

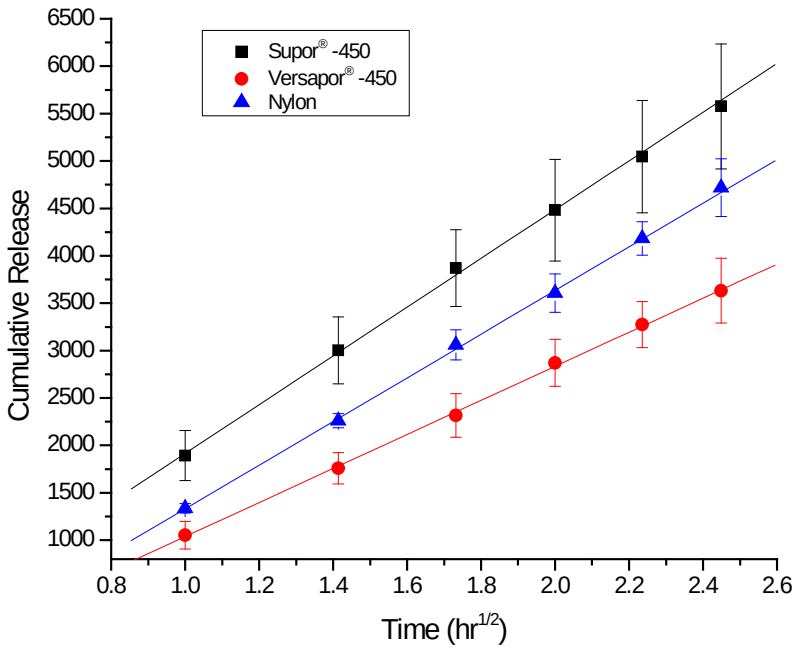
- As long as IVRT indicates that the drug release rate is the same, isn't that all that matters?

IVRT Release Rate is not Biorelevant

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 measured by an IVRT is **arbitrary**

- It can be modulated by IVRT method parameters like the choice of receptor solution or membrane
- The dose applied in an IVRT is a pseudo-infinite, occluded dose that 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 undergoes metamorphosis and dries on the skin.

Steady State Diffusion Kinetics

- Katz & Poulsen, 1971 (Fick's Law of Diffusion)

$$J = \frac{P \times D \times \Delta C}{l}$$

- J = Flux (e.g. µg/cm^2/hour)
- C = Concentration
- P = Partition Coefficient
- D = Diffusion Coefficient
- *l* = Length of Travel

Non-Steady State Diffusion Kinetics

- Franz & Lehman, 1995 (Finite Dose Equation)

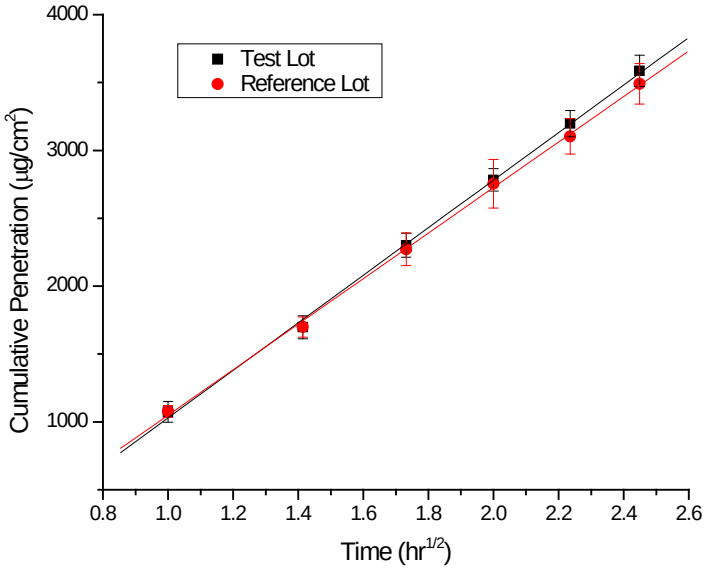
$$J = 2hpDC_0 \sum_{n=1}^{\infty} \frac{\alpha_n e^{-D\alpha_n^2 t}}{\sin \alpha_n l \left[l\left(\alpha_n^2 + h^2\right) + h \right]}$$

- Relevant to clinically applied thin film doses
- Accounts for the thickness of the applied dose as well as dose depletion over time

IVRT Release Rate is not Biorelevant

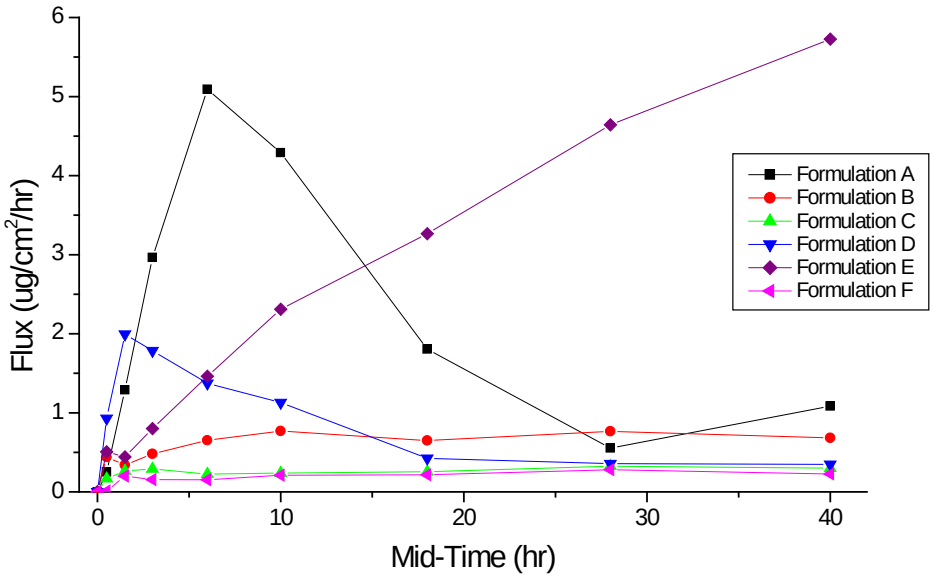
IVRT Infinite Dose

Steady State Kinetics

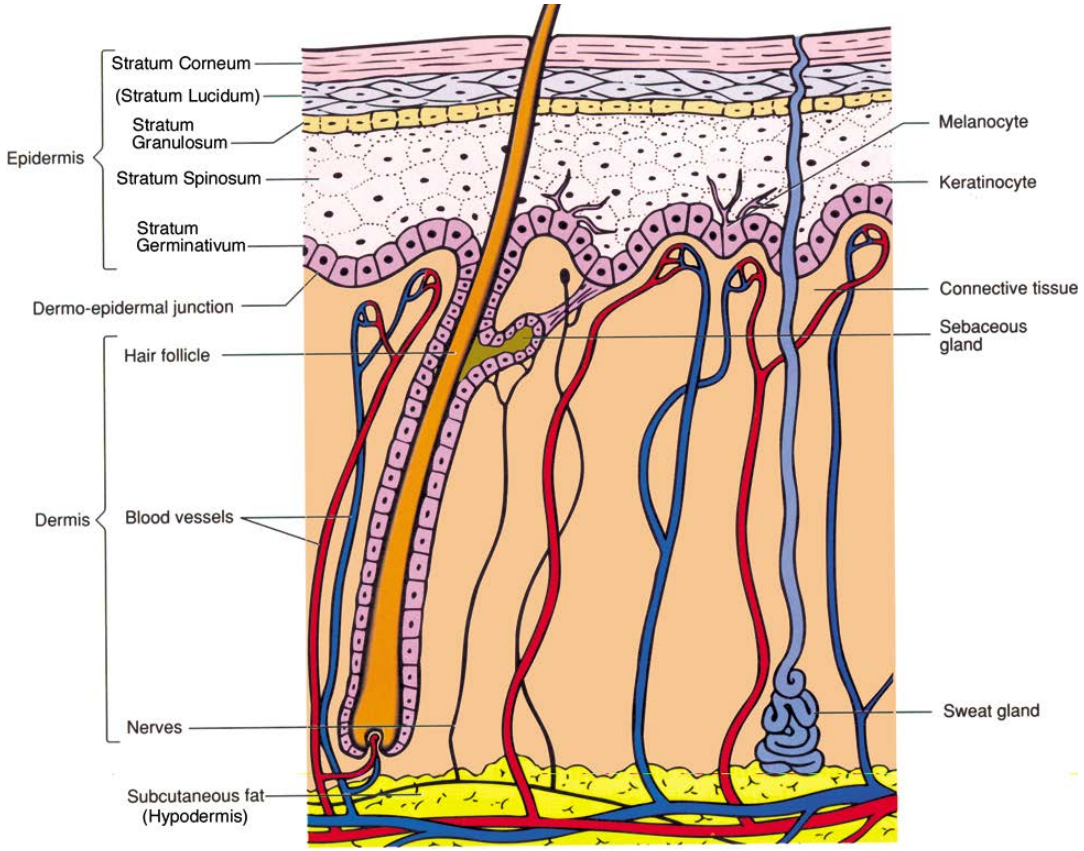


Clinical Finite Dose

Non-Steady State Kinetics



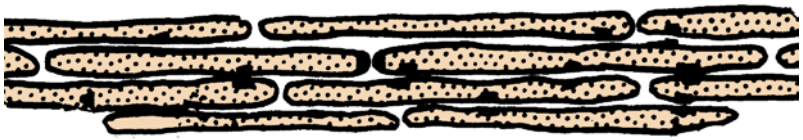
Human Skin Structure

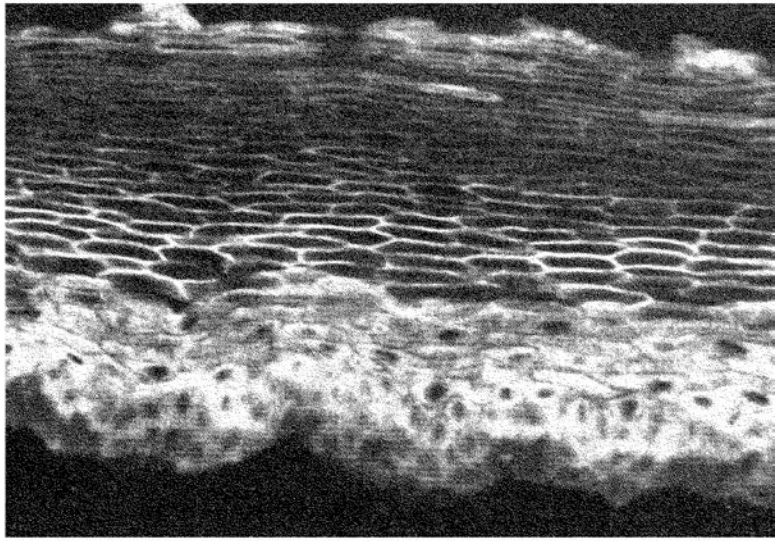


Adapted from Cerio and Archer, 1998

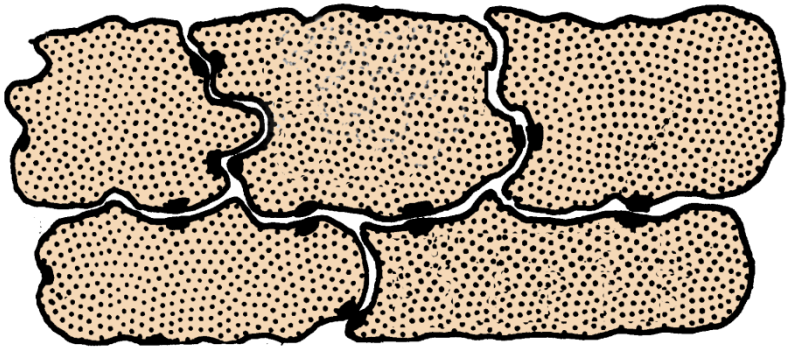
Skin Permeation Pathway

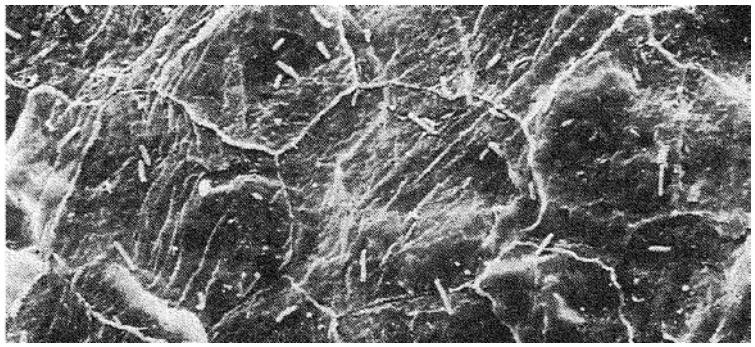
SIDE VIEW





TOP VIEW



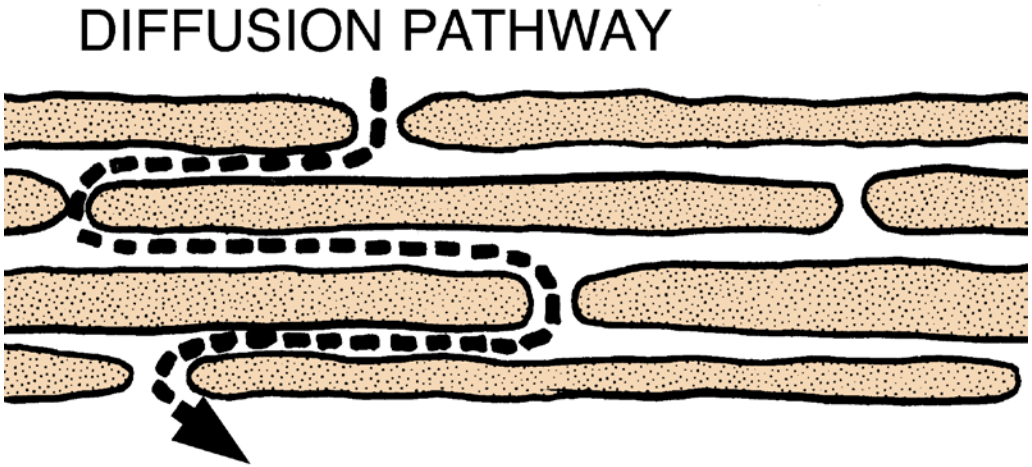


Drawings adapted from Odland, 1971.

Micrograph accompanying “side view” from Christophers and Laurence, 1976.

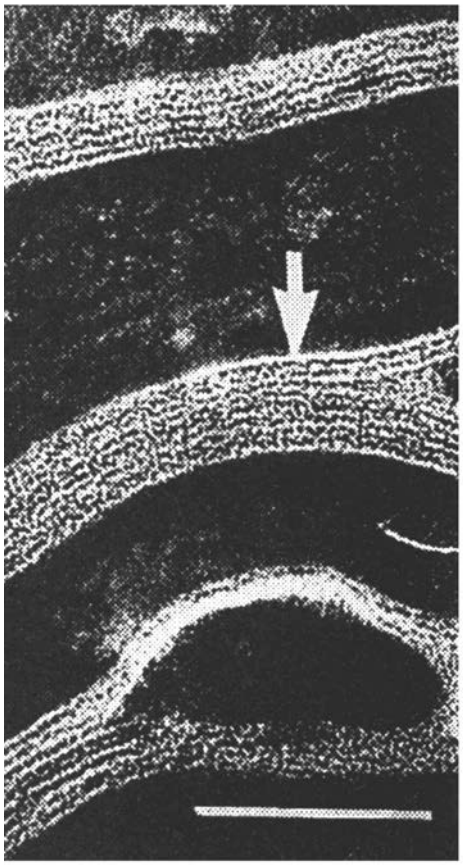
Micrograph accompanying “top view” from Singh and Singh, 1995.

Diffusion of Topical Compounds



Drawing adapted from Odland, 1971.

Micrograph Fartasch et al., 1998.



Topical Dermatological Formulations

- 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

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

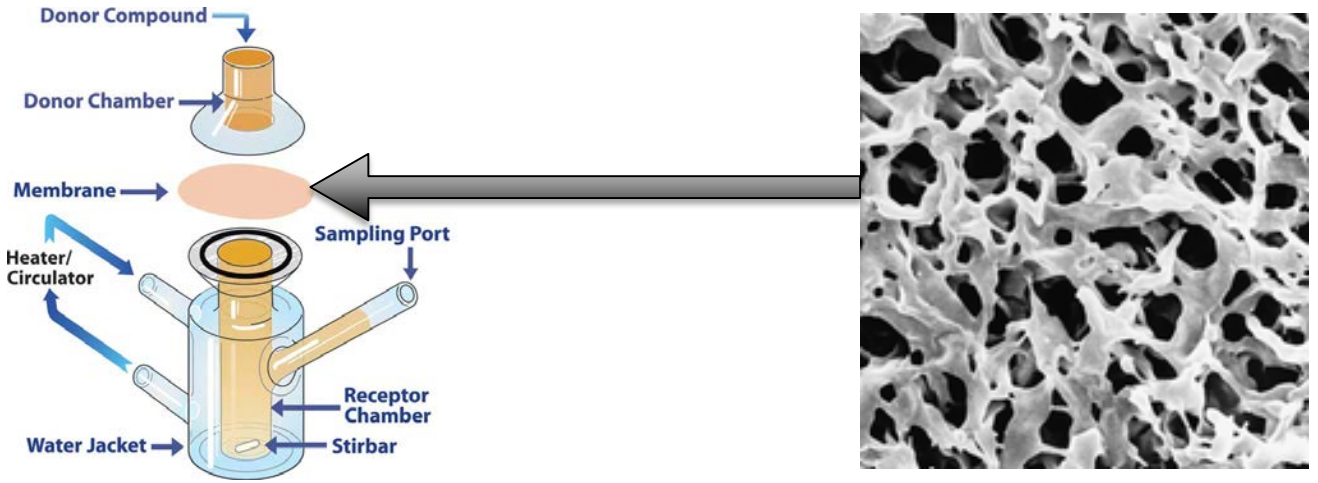
Tests of the Arrangement of Matter

- **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

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
- IVRT Equivalence ≠ Similar Bioavailability

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

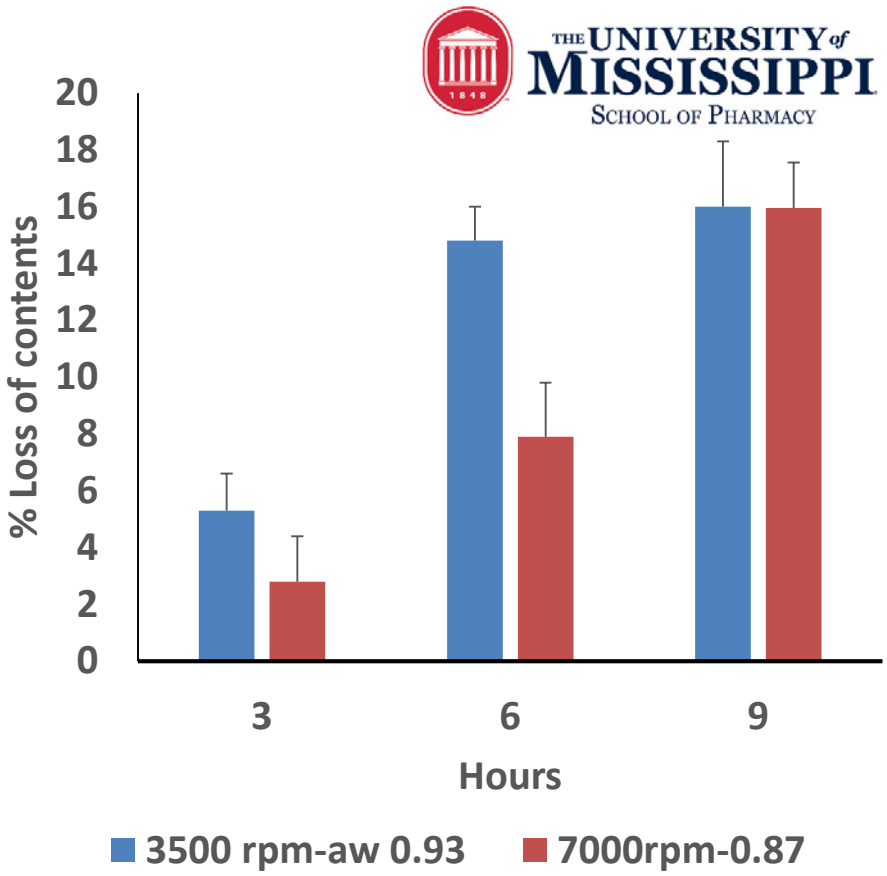
Differences with Q1/Q2 Creams

- 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

Differences with Q1/Q2 Creams

- Solvent Activity (a_s) = ρ/ρ_0

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  - ρ = partial vapor pressure of Solvents in the product
  - ρ_0 = vapor pressure of pure Solvent system

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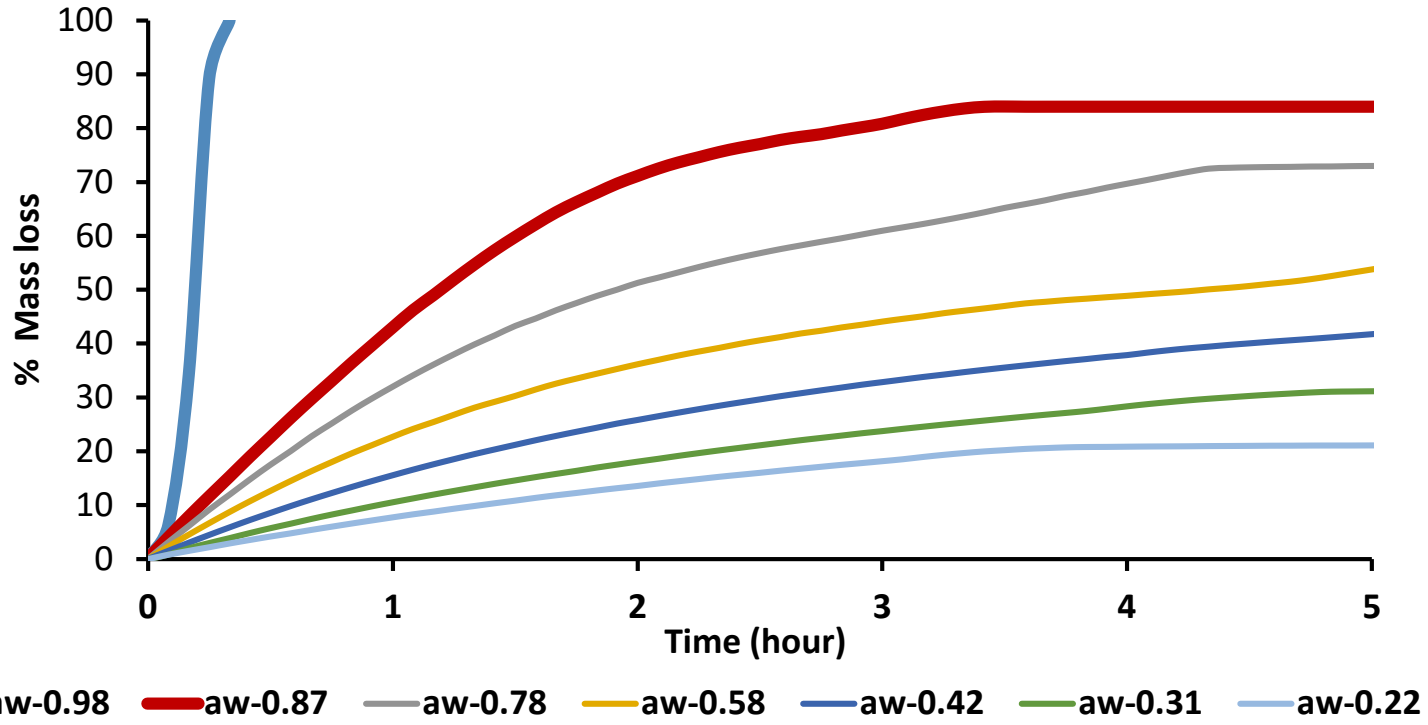

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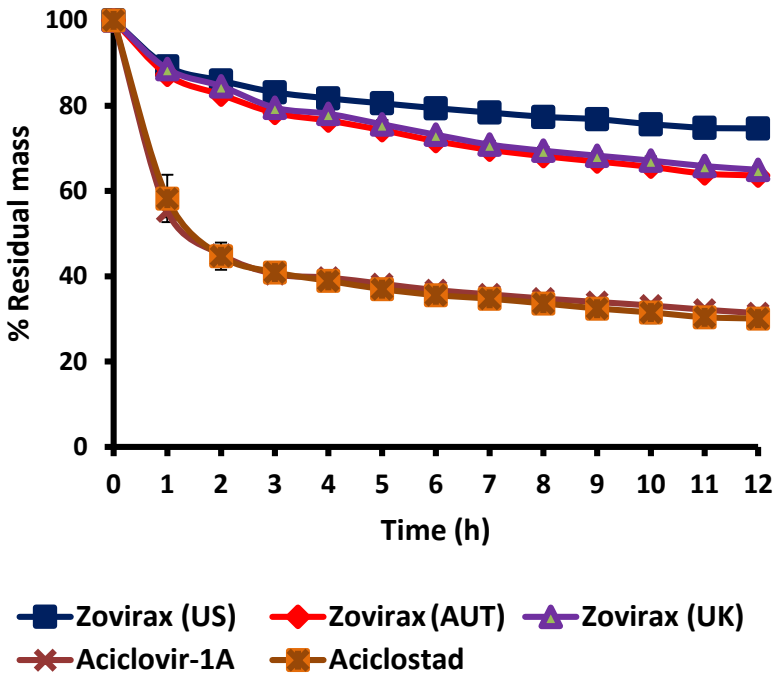
Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

  Prof. Narasimha Murthy FDA Award U01-FD005223



Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Data provided courtesy of Prof. Narasimha Murthy

Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

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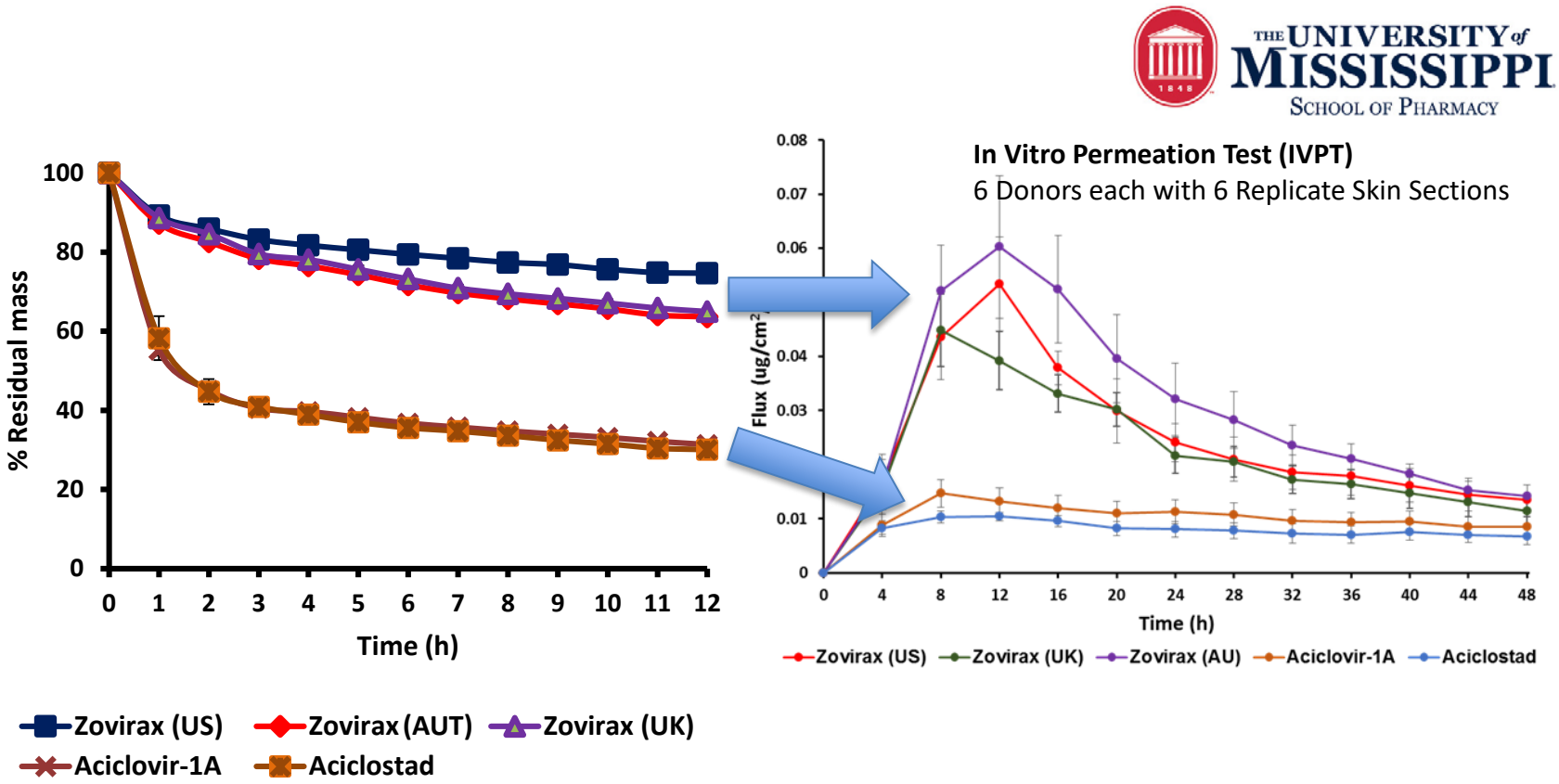

Data provided courtesy of Prof. Narasimha Murthy

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**

What to Do About It

- **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**

What to Do About It

- Advancing **Efficient** Bioequivalence Standards

  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?

[3] FDA Office of Generic Drugs Topical & Transdermal Products Database

Developing Rational BE Standards

- **A <u>Modular</u> 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 <u>Scalable</u> Framework for BE Evaluation**
  - **In Vivo** systemic PK studies may be appropriate
  - **In Silico** computational modeling may be useful

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)[5] are developed to be appropriate to the nature and complexity of the relevant drug product

[5] Product-Specific Guidances for Generic Drug Development Website: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

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*
    - **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)*
      - *Q1/Q2 sameness of the test and RLD formulations*
      - *The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization…*
      - *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*
      - *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)*
      - *Equivalent comparative qualitative and quantitative (Q1/Q2) characterization.*
      - *Equivalent comparative physicochemical and microstructural characterization of comparable pH, specific gravity, emulsion globule size distribution …and viscosity profiles...*
      - *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...*
      - *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)*
      - *Q1/Q2 sameness*
      - *Comparative physicochemical characterization (Q3 similarity)*
      - *IVRT equivalence*
      - *in vitro BE study with local (cutaneous) PK endpoints (IVPT)*
      - *In vivo BE study with systemic (plasma) PK endpoints*

Future Directions

- 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) *Comparative physicochemical characterization (Q3 similarity)?*
3) *IVRT equivalence?*
4) *In vitro BE study with local (cutaneous) PK endpoints (IVPT)?*
5) *In vivo BE study with local (cutaneous) PK endpoints?*
6) *In vivo BE study with systemic (plasma) PK endpoints?*
7) *Physiologically-based PK (PBPK) modeling and simulation?*

Conclusions (What To Do)

- 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 (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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