DOSAGE FORM AND FUNCTION:

Bioavailability and Bioequivalence Implications for Topical Dermatological Products

AAPS Workshop on Locally Acting Drug Products: Bioequivalence Challenges and Opportunities
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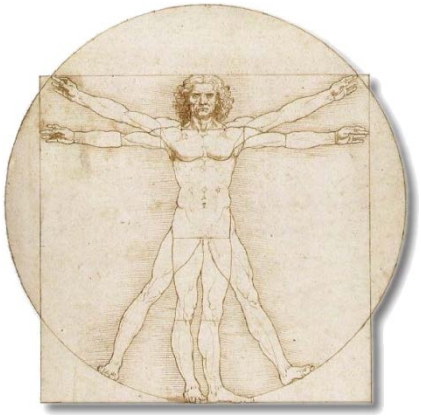
- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

Form Follows Function

*"It is the pervading law of all things organic and inorganic… that **form ever follows function**."*

- Louis Henry Sullivan, 1896
  (American architect)
- Attributed to Marcus Vitruvius Pollio's De Architectura
  (Ancient Roman architect & engineer)



Leonardo Da Vinci's Vitruvian Man

Dosage Forms

- Why do we have specialized dosage forms?
  - Tablets, capsules, and others for oral administration
  - Suppositories for rectal administration
  - Solutions for intravenous administration
  - Inhalers for inhalational administration
  - Semisolids or patches for topical administration

Dosage Forms and their Functions

- How does each dosage form suit its functions?
  - Oral dosage forms are swallowed and may dissolve
  - Rectal dosage forms are inserted and may melt
  - Injectable dosage forms provide rapid bioavailability
  - Inhaled dosage forms control drug dispersions
  - Topical dosage forms partition drugs into skin
- Dosage forms are suited to specific functions
- A generic product must serve the same functions
- A generic must be an equivalent dosage form

AT-Coded Therapeutic Equivalents

- Pharmaceutical Equivalence (PE)
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength

Recommended Studies: Acceptable comparative physicochemical characterization of the test and reference listed drug (RLD) formulations of the product to establish that the test product is pharmaceutically equivalent[1] to the RLD with identical strength.

- Examples of Product-Specific BE Recommendations
  - **Draft Guidance on Triamcinolone Acetonide** *(Topical Ointment)*
  - **Draft Guidance on Triamcinolone Acetonide** *(Topical Cream)*
  - **Draft Guidance on Crotamiton** *(Topical Cream)*
  - **Draft Guidance on Crotamiton** *(Topical Lotion)*

Solution-Based Topical Drug Products

- "Less complex" solution-based topical products
  - In vitro comparative physicochemical characterization mitigates the risk of potential failure modes that may impact bioequivalence

  - Examples of Product-Specific BE Recommendations
    - **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 Product-Specific BE Recommendations
    - **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 Product-Specific BE Recommendations
    - **Draft Guidance on Mesalamine** *(Rectal Suppository)*

    "…in vitro evidence that the test and RLD products have the same final physicochemical characteristics, to include differential scanning calorimetry, viscosity, melting point, and density."

    NOTE: An in vivo BE study with PK endpoints is still recommended

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

    "i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2). ii. Acceptable comparative physicochemical characterization of the test and RLD formulations. iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD formulations."

    NOTE: A clinical endpoint BE study is recommended as an alternative

Semisolid Topical Drug Products

- "Complex" semisolid topical products
  - Example of a Product-Specific BE Recommendation
    - **Draft Guidance on Benzyl Alcohol** *(Topical Lotion)*

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

    ii. Equivalent comparative physicochemical and microstructural (Q3) 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..."

Complex Topical Drug Products

- As the complexity of a dosage form increases so do the potential failure modes for bioequivalence
- How can product quality characterizations, appropriate to the complexity of the drug product, be aligned with efficient bioequivalence assessments to ensure therapeutic equivalence?
- Could this facilitate the availability of high quality, affordable topical drug products to the public?

Office of Generic Drugs

- The mission of the Office of Generic Drugs is to make **high quality**, **affordable** medicines **available** to the public.
- Key initiatives to support the mission
  - High Quality generics (**product quality characterization**)
  - Availability of generics (**efficient bioequivalence standards**)
- How can regulatory science positively impact both these initiatives?

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

- What are the impacts of "efficient" standards?

Overall Drug Products [1]

- **89%** of prescriptions dispensed in 2015 were for generics
- $1.46 trillion saved in healthcare costs 2006-2015

Topical Drug Products [2]

- Clinical endpoint BE studies have helped make generics available for only **23.9%** of RLDs
- In vivo vasoconstrictor BE studies helped make generic glucocorticoids available for another **13.8%** of RLDs
- Total % of topical products with generics ➔ **37.7%**

[1] GPhA 2016 Generic Drug Savings & Access in the United States Report
[2] Office of Generic Drugs Topical & Transdermal Products Database

Complex Dosage Forms

- Complex compositions of matter in the product
  - Immiscible mixtures of several “inactive” ingredients
- Complex states of matter in the product
  - Partially dissolved, partially dispersed drug(s)
- Complex arrangements of matter in the product
  - Multiple phases/components in the drug product
- Complex drug diffusion within the dosage form
  - Potentially complex and dynamic distribution of drug(s)
- Complex drug/device-patient interactions
  - Potentially altered bioavailability at target site of action

Linking Quality to Clinical Efficacy

- Product quality characterization can describe:
  - The composition of the drug product
  - The phase states and 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

Linking Q3 to Specific Failure Modes

- Differences in any of numerous physicochemical properties may alter product performance
- For example, pH alone can influence
  - Ionization state of the drug
  - Polymorphic form of the drug
  - Particle size distribution of the drug
  - Stability of the drug in the drug product
  - Solubility of the drug in phases of the formulation
  - Distribution of drug in the product microstructures
  - Ratio of dissolved to undissolved drug
  - Dosage form properties and metamorphosis in vivo
  - Drug deposition/release/delivery and bioavailability
  - Patient use considerations and perceptions of quality

Failure Modes Related to pH (Q3)

- Do we have appropriate tools to measure pH?
  - What does it mean to measure the bulk pH of a cream?
  - Is it important to independently measure the pH of the aqueous component of an emulsion?
  - Does it matter what kind of probe/technology is used?
  - How might these measures of pH change following application to the skin?
  - Is the formulation adequately buffered, if pH is critical?

Dosage Form pH may Change on Skin

- Change in product pH after 1hr on skin in vivo

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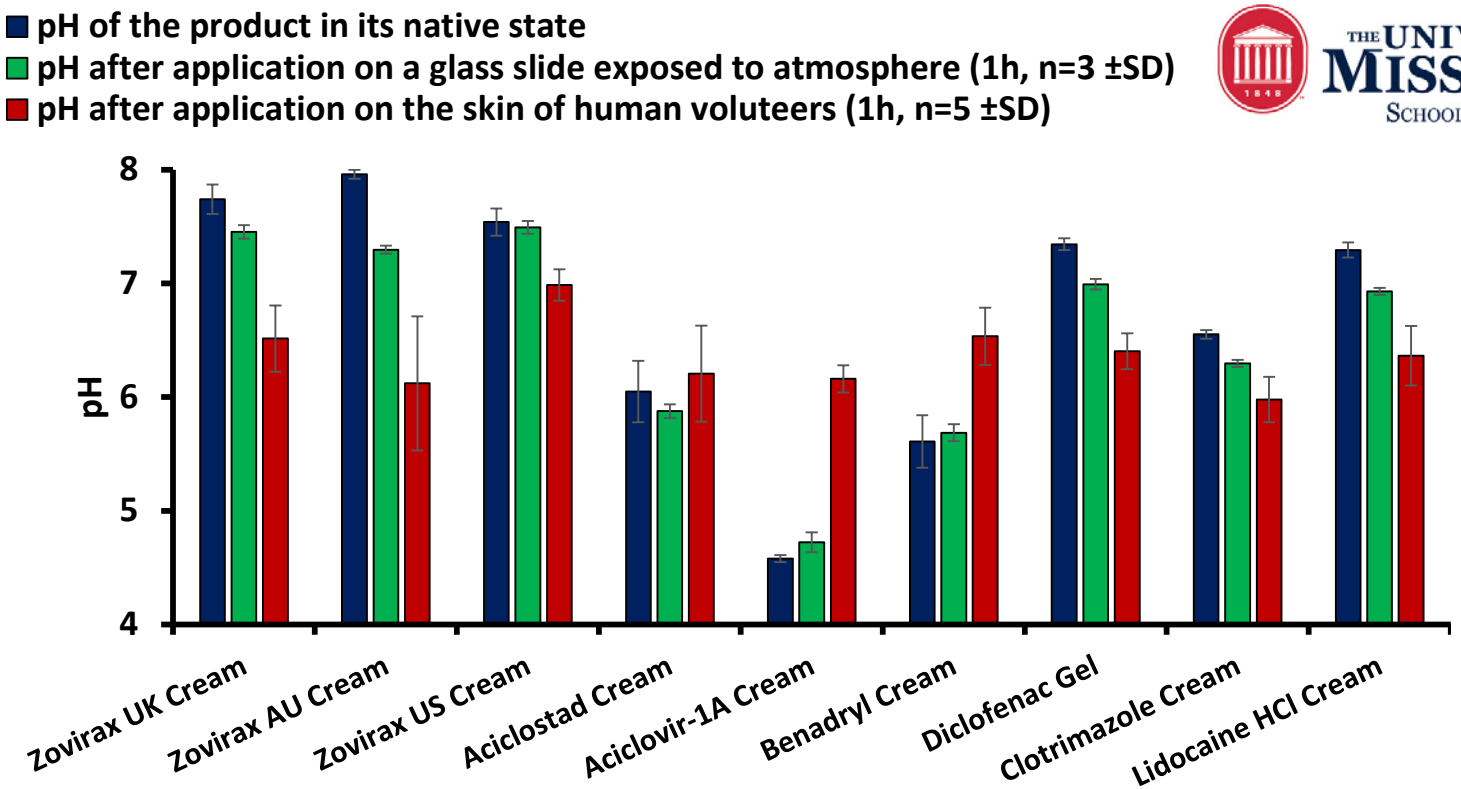

Assessing Product Quality (Q3)

- Examples of Tests to Characterize Q3
  - pH
  - Appearance
  - Polymorphic form(s) of the drug
  - Particle size distribution and crystal habit of the drug
  - Micrographs of phase states in the drug product
  - Rheological behavior of the drug product
  - Solvent (water) activity of the drug product
  - Release rate of the drug from the drug product
  - Metamorphosis of the drug product on the skin
  - Influence of the drug product dispenser

Q3 and Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

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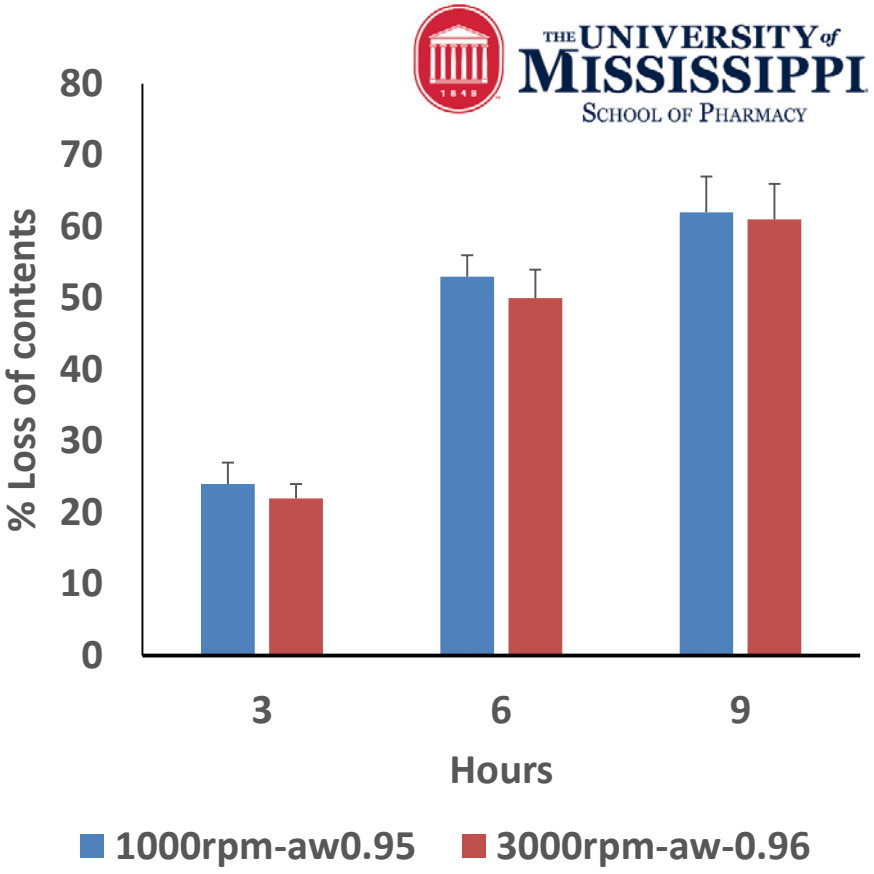
Ingredients	Quantity (%w/w)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69
Total	100
Manufacturing Conditions	**Solvent Activity (a_w)**
1000 RPM (20 min)	0.950± 0.004
3000 RPM (20 min)	0.961 ± 0.006



Q3 and Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

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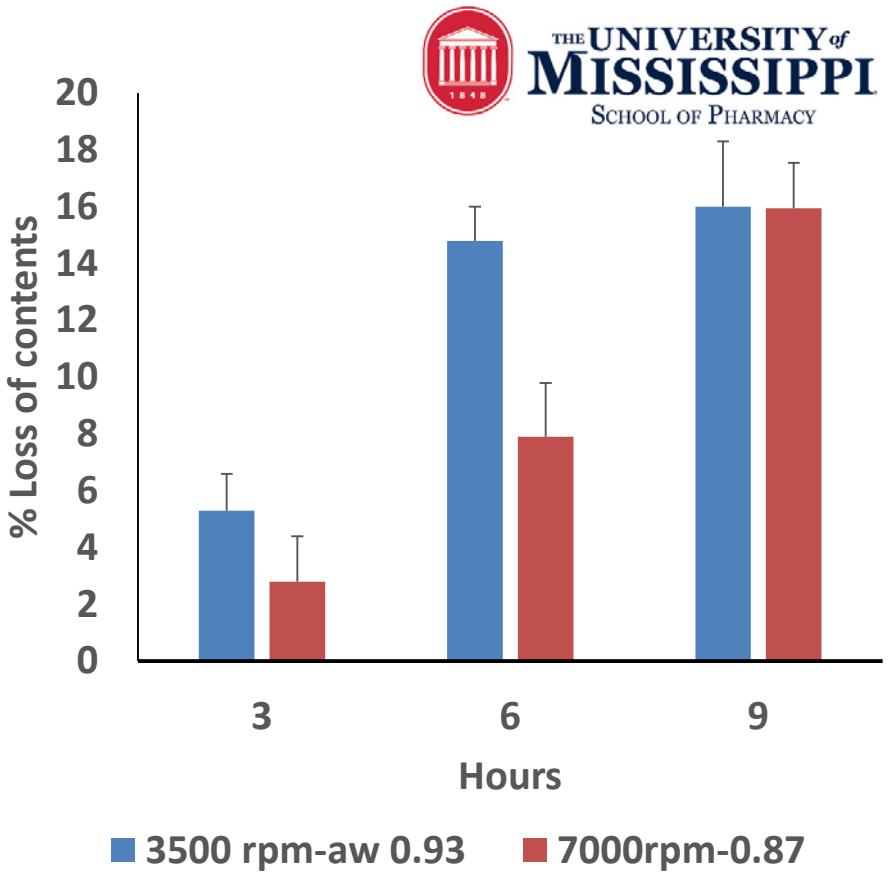
Ingredients	Quantity (%w/w)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100

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



Q3 and Dosage Form Metamorphosis

- 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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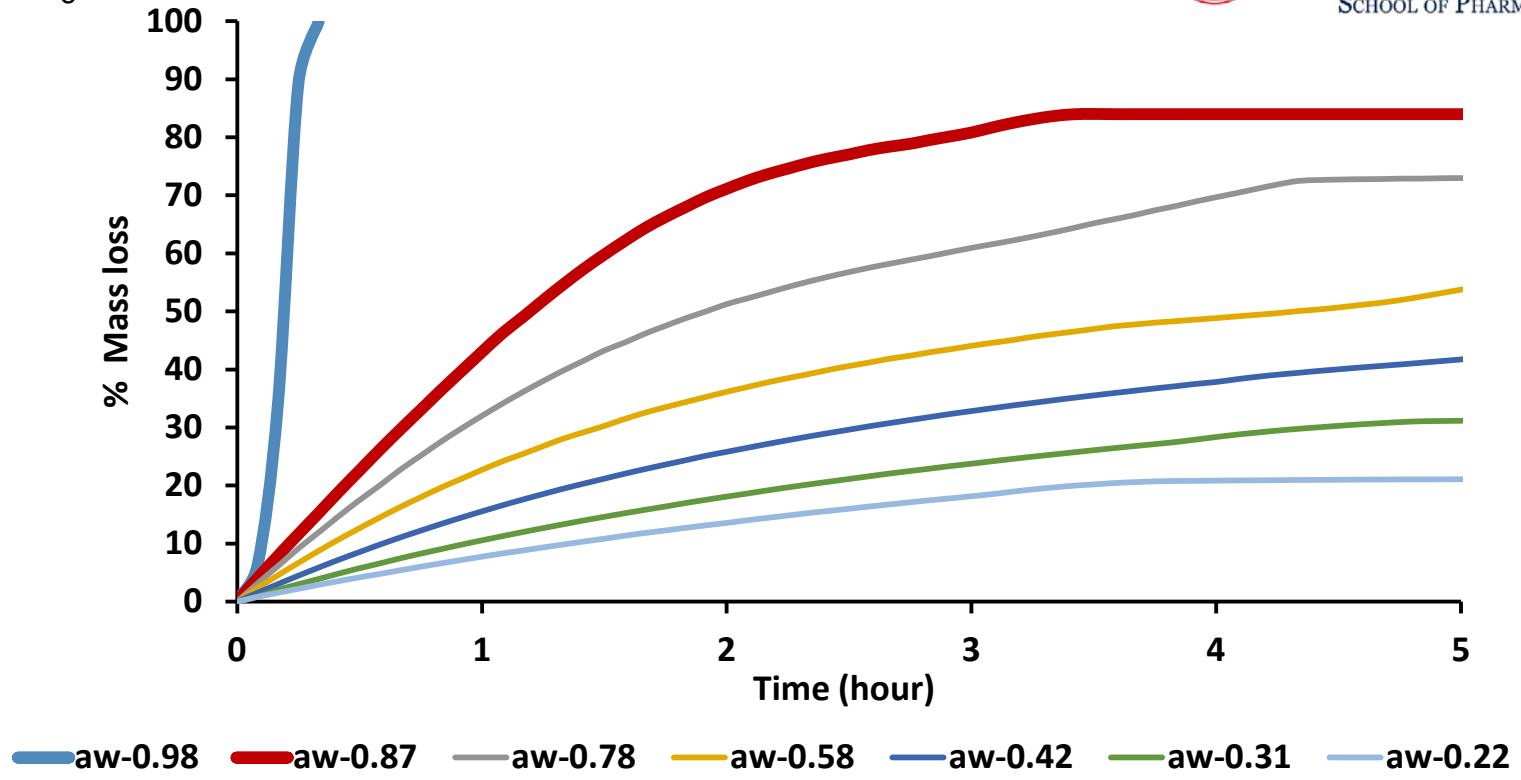

Q3 and Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

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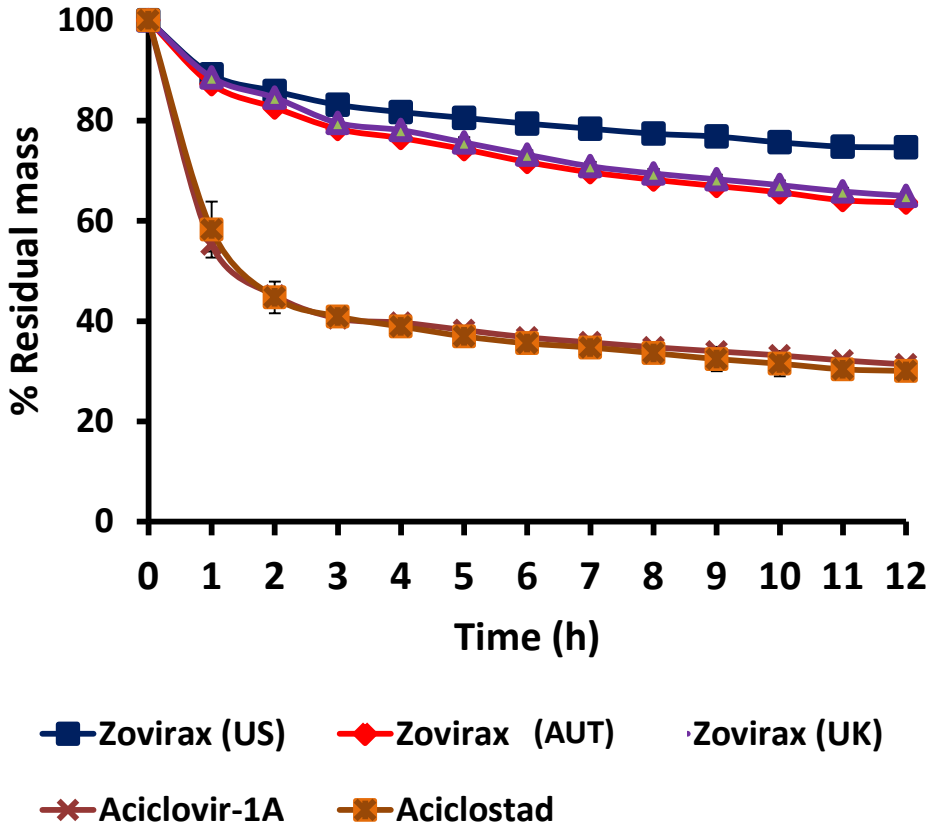

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Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Q3

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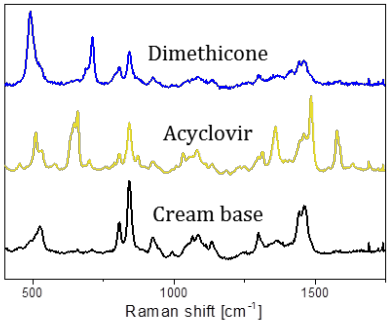

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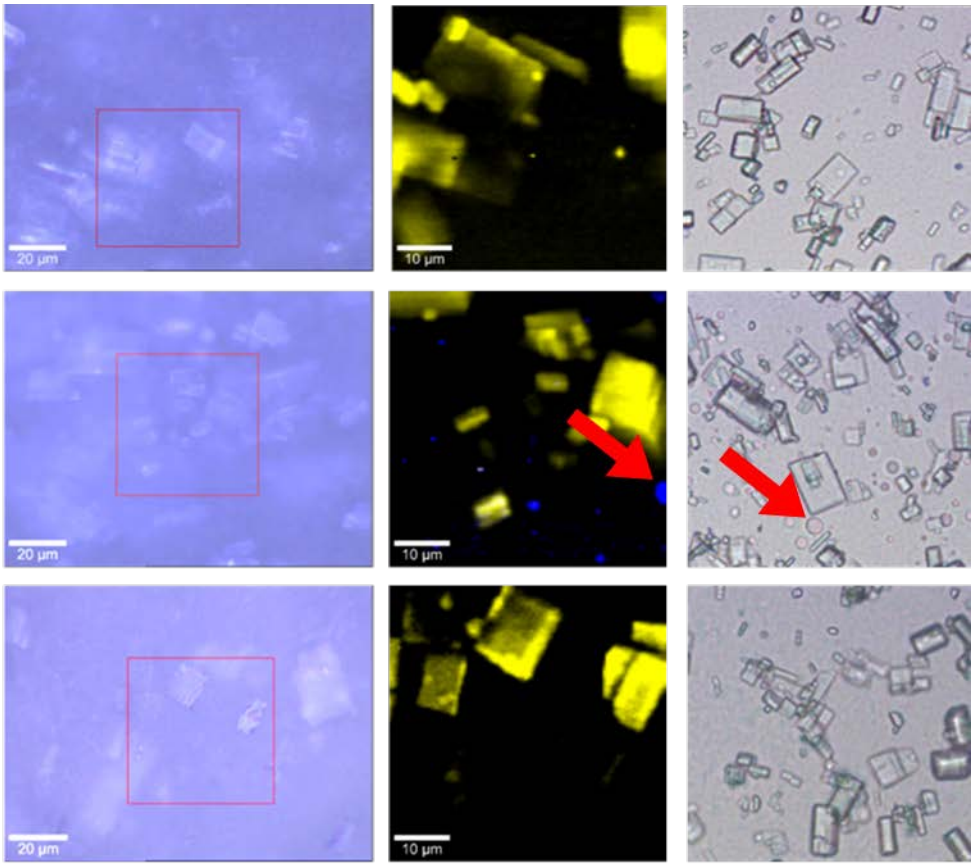
Zovirax® UK
Tube

Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)



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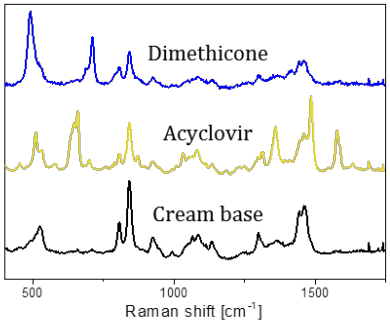

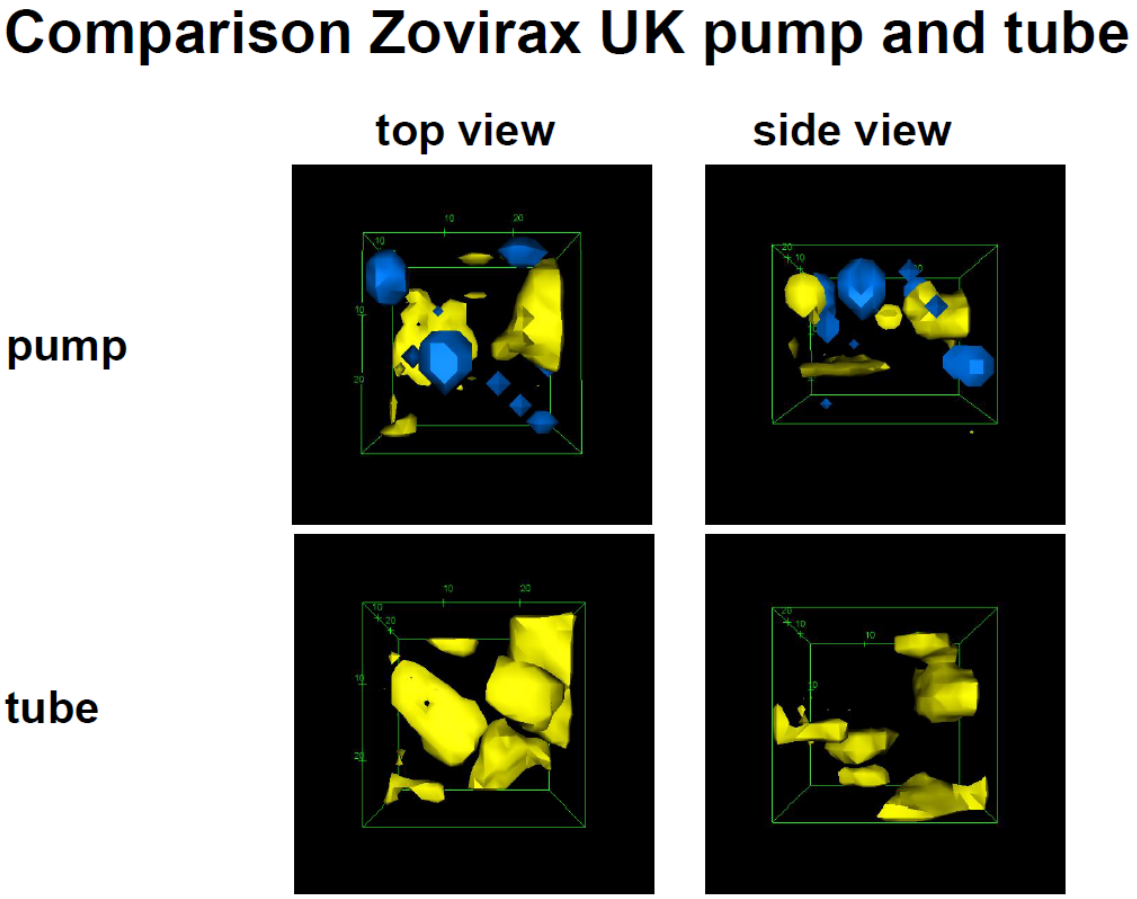

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Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Q3

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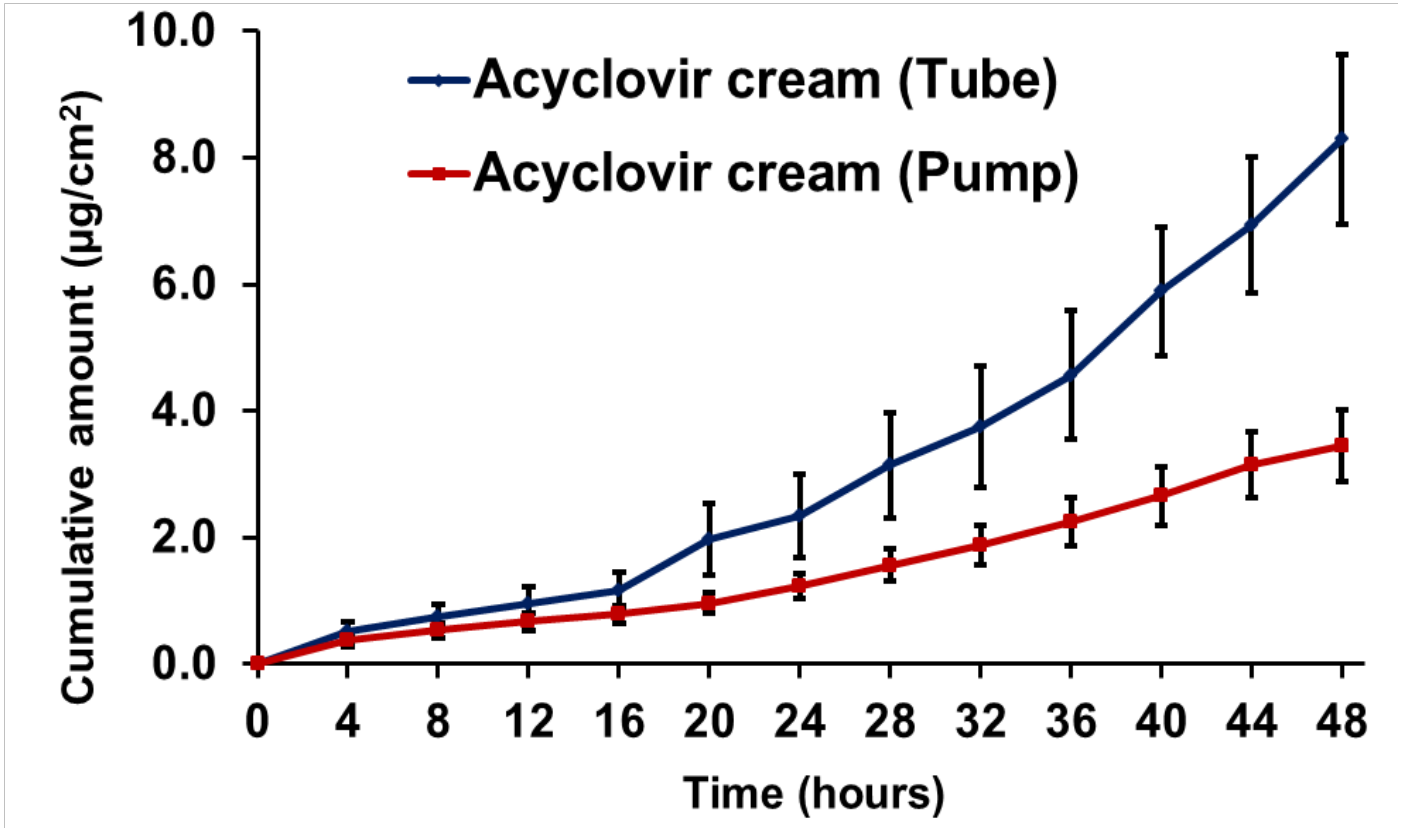
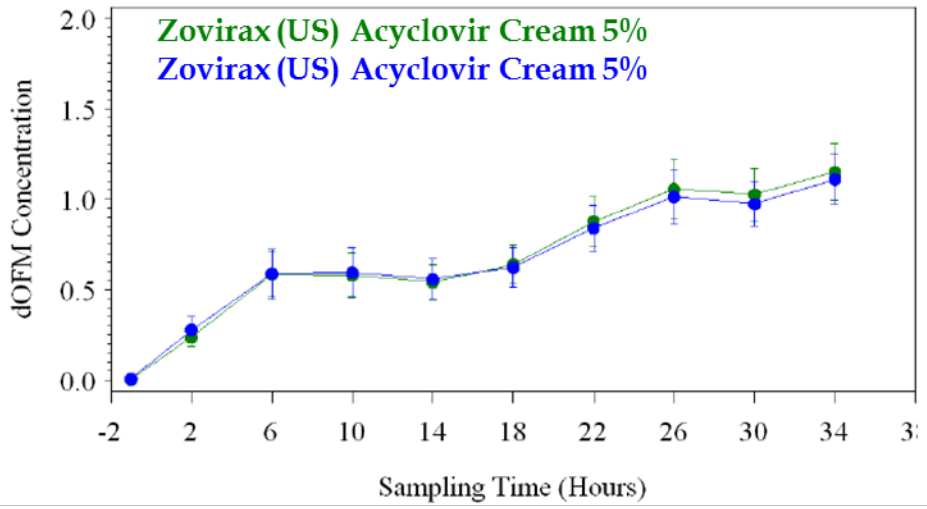


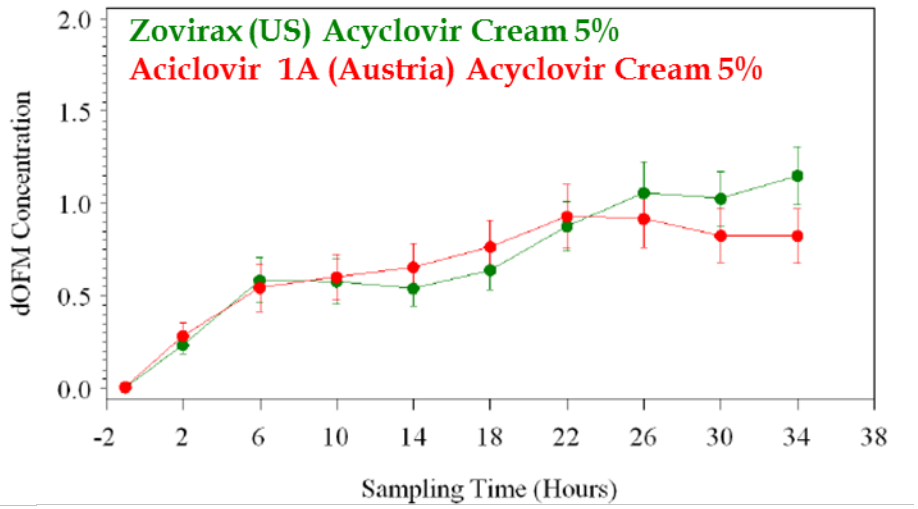
Cutaneous Pharmacokinetics

- Could cutaneous pharmacokinetic methods support the development of more efficient pathways for approval of topical drug products?
  - In Vitro Permeation Tests (IVPT)
  - In Vivo Dermal Microdialysis/Microperfusion

- Could such pathways facilitate the availability of affordable, high quality topical generic drug products?

In Vivo Cutaneous Pharmacokinetics





Comparison	PK endpoint	90 % confidence interval	*T*/*R* (point estimate)	Outcome
R_2 vs. R_1	$AUC_{0-36\ h}$	0.86–1.18	1.01	Positive BE result Confirmed
	C_{max}	0.86–1.21	1.02	R_2 is considered BE to R_1
T vs. R_1	$AUC_{0-36\ h}$	0.69–1.05	0.85	Negative BE result Confirmed
	C_{max}	0.61–1.02	0.79	T is not considered BE to R_1

AUC area under the curve, *BE* bioequivalence, C_{max} maximum plasma concentration, *PK* pharmacokinetic, *R* reference, *T* test product

Source: Bodenlenz M, Tiffner K, Raml R, Augustin T, Dragatin C, Birngruber T, Schimek D, Schwagerle G, Pieber TR, Raney, SG, Kanfer I, Sinner F (2016) *Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence*. Clinical Pharmacokinetics. DOI 10.1007/s40262-016-0442-z.

Failure Modes and Q3 Attributes

- For products across a range of complexity, consider how failure modes for product performance arise from and convolute among multiple quality attributes
- 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 qualities to characterize, what measurement techniques to use, and how to interpret the results

Impact of Product Quality on Patients

- Consider quality attributes that relate to
  - Storage, dispensing and re-dispensing
  - Dose application, maintenance and removal
  - Patient perceptions of quality and acceptability
  - Robustness of therapeutic effect in the real world
- Consider how the product quality changes during dose application and during subsequent metamorphosis
- Consider how the vehicle impacts the skin (hydrating or dehydrating effects, irritancy, burning sensation)
- Consider how product quality attributes at the limits of stability specifications impact these factors

When do Q3 Attributes Matter?

A suspension of particles and partially dissolved drug

- How critical is particle size distribution?
- How critical is the concentration of dissolved drug?
- How critical is the rate of metamorphosis on the latter?

A multi-phase emulsion with the drug predominantly dissolved in the oil phase

- How critical is globule size distribution?
- How does globule size distribution change in response to shear stresses of dose application?
- How does the microstructure, drug solubility, drug distribution, etc. change at different relevant temperatures?

Process Parameters can Impact Q3

- How critical is the composition of inactive ingredients?
- How critical is the grade of each inactive ingredient?
- How critical is the sequence of mixing?
- How critical are mixing rates and durations?
- How critical are temperatures and rates of change?
- How critical are the orifice diameters, tube lengths, pressures, etc. during transfer, holding, packaging?
- How critical is the inertness of the container closure system (e.g. are there adsorption/absorption issues)?
- How critical are the product dispensing stresses/forces?

Summary

- Consider the patient's needs and expectations
- Consider how to characterize the physicochemical properties and the complexity of the product
- Consider the relationship between quality attributes and potential failure modes, individually and collectively
- Consider dynamic ranges of conditions during formulation, manufacture, packaging, storage, dispensing, dosing, and metamorphosis in vivo
- Consider appropriate test methods for specific product qualities throughout Quality by Design (QbD) and as part of a program to fully characterize and control the product performance and therapeutic equivalence

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