Product Development Considerations for Generic Topical Products

Complex Generic Drug Product Development Workshop

Session 5: Complex Route of Delivery/Dosage Forms
Topical (Dermatological) and Transdermal
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This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Generic Topical Product Development

Approaches for establishing bioequivalence (BE)

- Understand the drug product to identify the potential regulatory pathways
  - Waiver of in vivo studies (for topical solutions)
  - Pharmacodynamic studies (vasoconstrictor (VC) studies)
  - Comparative clinical endpoint studies
  - In vitro product characterization (and pharmacokinetic (PK) studies)
    - Identify potential failure modes for BE associated with the drug substance
    - Identify potential failure modes for BE associated with the dosage form
    - Understand the mechanism and/or site of action
    - Provide evidence to mitigate the BE risks related the points above

Failure Modes (BE) – Drug Substance

Is the Drug Substance **Dissolved** in the Formulation?

- Isomers of the drug
- pKa(s) of the drug
- pH of the formulation

Is the Drug Substance **Suspended** in the Formulation?

In addition to the potential failure modes identified on the left….

- Polymorphic forms of the drug
- Particle size distribution of the drug (and crystalline habit)

Failure Modes (BE) – Dosage Form

Is the Formulation a **Single Phase** System? *e.g. solution, gel*

- Excipient differences
- Viscosity/Rheology
- pH

Is the Formulation a **Multi Phase** System? *e.g. lotion, cream*

In addition to the potential failure modes identified on the left….

- Phases and arrangement of matter
- Distribution/localization of drug

Remember: The packaging configuration may impact bioavailability

Mechanism and/or Site of Action

Is the Mechanism/Site of Action **Well Understood?**

- Acyclovir Topical Cream
- Benzyl Alcohol Topical Solution

An in vitro characterization based approach may be recommended

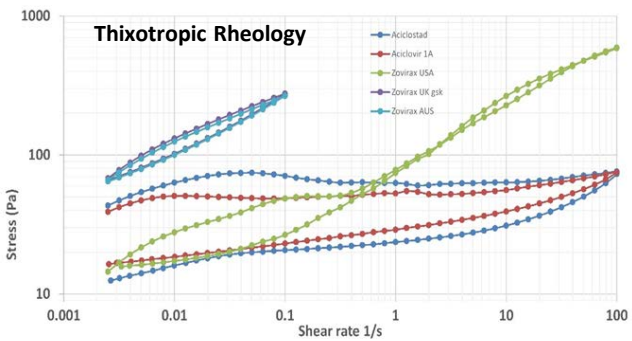
Is the Mechanism/Site of Action **Not Well Understood?**

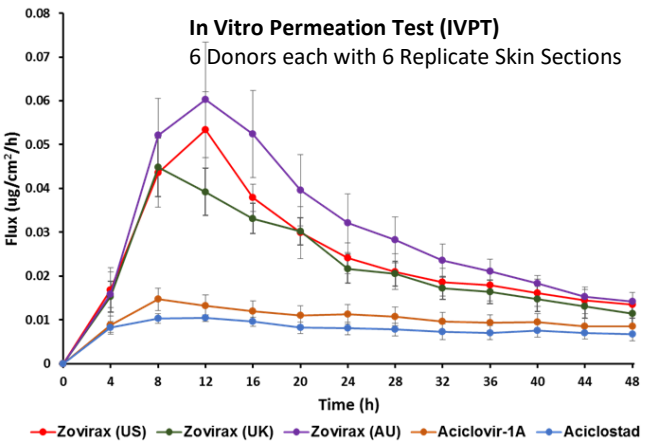
- Dapsone Topical Gel
- Ivermectin Topical Cream

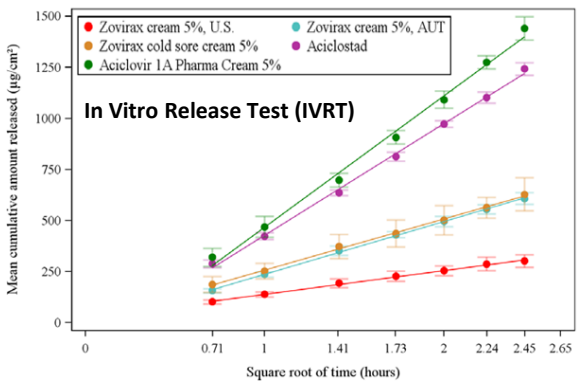
If the mechanism and/or site of action may be (partially) systemic, an in vivo PK study may also be recommended

Research under GDUFA

	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		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		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

BE Standards for Generic Topical Products

- Potential failure modes for BE and therapeutic equivalence (TE) may increase as the product becomes more complex

- Product-Specific Guidances (PSGs) recommend studies appropriate to the nature and complexity of the drug product

Solution-Based Topical Products

Solution-based topical products

- Waivers for generic topical solutions that are Q1/Q2 the same as the RLD: *21 CFR 320.22(b)(3)*
- Product characterization is recommended to mitigate unique concerns

- **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…"

Q1- Qualitative (or component), Q2- Quantitative (or composition)
The solution-based topical products may not be eligible for the pre-ANDA program under GDUFA II

Solution-Based Topical Products

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 comparative clinical endpoint BE study

- **Draft Guidance on Minoxidil** *(Foam Aerosol)*
- **Draft Guidance on Clobetasol Propionate** *(Foam Aerosol)*

  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*

The solution-based topical products may not be eligible for the pre-ANDA program under GDUFA II

Semisolid Topical Products

Semisolid topical products

- **Draft Guidance on Acyclovir** *(Topical Ointment)*
  - *Q1/Q2 sameness of the generic and RLD formulations*
  - *Comparative physicochemical characterization of the generic and RLD products*
  - *Equivalent acyclovir release from the generic and RLD products evaluated by IVRT*

- **Draft Guidance on Silver Sulfadiazine** *(Topical Cream)*
  - *Q1/Q2 sameness of the generic 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 the generic and RLD products evaluated by IVRT*

Semisolid Topical Products

Semisolid topical products

Draft Guidance on Acyclovir *(Topical Cream)*

- *Q1/Q2 sameness of the generic and RLD formulations*
- *The generic and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization…*
- *The generic 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 generic and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT)… using an appropriately validated IVPT method*

Semisolid Topical Products

Semisolid topical products

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 Products

Semisolid topical products with multiple potential mechanisms/sites of action

Draft Guidance on Dapsone *(Topical Gels)*

Draft Guidance on Ivermectin *(Topical Cream)*

- *Q1/Q2 sameness*
- *Comparative physicochemical characterization (Q3 similarity)*
- *IVRT equivalence*
- *In vitro BE assessment with local (cutaneous) PK endpoints (IVPT)*
- *In vivo BE study with systemic (plasma) PK endpoints*

When a PSG is Unavailable

Steps toward the development of a proposed generic product

- Identify the reference listed drug (RLD)
- Identify the studies proposed to support a demonstration of BE appropriate to the complexity of the dosage form

The following information maybe helpful if FDA input is requested

- Details about the proposed formulation(s) for the generic product
- A clear outline of the proposed BE approach and any supporting information
- Information to support the feasibility of any novel techniques
- All proposed product packaging configurations

For additional information, please see the draft guidance for industry, Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf

Summary

- Topical dermatological products range from simple solutions to complex emulsions
- Approaches for establishing BE for generic topical dermatological products are based on the complexity of the drug product
- A good Pre-ANDA Product Development meeting package
  - Should clearly characterize the complexity of the drug product
  - Provide clear and concise information about how the proposed approach can systematically mitigate concerns related to potential failure modes for BE

References for GDUFA Research

- Research efforts have been expanded across all topical dermatological product classes
  - Gels, lotions, ointments, foams, etc.
  - Multiple drug substances and drug products
- Office of Generic Drugs FYs 2013 - 2017 Regulatory Science Research Report
- Workshop: Topical Dermatological Generic Drug Products: *Overcoming Barriers to Development and Improving Patient Access*

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FY 18 Funding Opportunities

- BE of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulation (U01) (RFA-FD-18-010)

- BE of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques (U01) (RFA-FD-18-012)

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