GDUFA RESEARCH AND REGULATORY INITIATIVES FOR COMPLEX TOPICAL PRODUCTS

4th Annual Symposium on Development of Generics & 505(b)(2)
Achieving Access to Complex Drug Products:
Integrating Scientific and Regulatory Expectations

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Disclaimer

- The views expressed in this presentation do not reflect the official policies of the FDA, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

GDUFA

- Generic Drug User Fee Amendments (GDUFA)[1]
  - Enacted by Congress in 2012 (GDUFA I)
  - Intended to ensure that patients have access to safe, high-quality, and affordable generic drug products
  - Intended to bring greater predictability and timeliness to the review of generic drug applications

[1] Source: *Generic Drug User Fee Amendments* accessible on www.fda.gov at https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

GDUFA II

- Generic Drug User Fee Amendments (GDUFA)[2]
  - Reauthorized by Congress in 2017 (GDUFA II)
  - Includes a Pre-ANDA program to facilitate approval of "complex" generic products, help applicants develop more complete submissions, and make ANDA review more efficient.
  - Also includes enhancements regarding controlled correspondence, regulatory science, safety determination letters, and the Inactive Ingredient Database.

[2] Sources: *Generic Drug User Fee Amendments* accessible on www.fda.gov at https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm559570.htm, and https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm568916.htm

What is a "Complex" Drug Product

- Complex Drug Products are defined[3] as those with:
  - **Complex active ingredients**
    - peptides, polymeric compounds, complex mixtures of APIs, etc.
  - **Complex formulations**
    - liposomes, colloids
  - **Complex routes of delivery**
    - locally acting drugs
  - **Complex dosage forms**
    - transdermals, metered dose inhalers, extended release injectables, etc.
  - **Complex drug-device combination products**
    - auto injectors, metered dose inhalers
  - **Other products where complexity or uncertainty concerning the approval pathway** or possible alternative approach would benefit from early scientific engagement

[3] Source: *GDUFA II Commitment Letter* accessible on www.fda.gov at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Topical Generic Products

- Topical products can be “complex” in multiple ways
  - Complex formulation:
    - e.g., a foam, gel, cream, etc.
  - Complex route of delivery:
    - e.g., locally acting; topical dermatological
  - Complex dosage form:
    - e.g., a topical patch
  - Complex drug-device combination products:
    - e.g., a topical solution in a metered dose pump

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 (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 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 PSG
    - **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 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

Product Understanding

- 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 skin
  - 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

Process Understanding

- 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?

Complex Product Failure Modes

- 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

Complex Product Characterization

- Examples of Product Characterization Tests
  - 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

Pharmacokinetic (PK) Studies

- How can relevant PK-based approaches provide evidence to support the bioequivalence of complex topical drug products?
  - In Vitro Permeation Tests (IVPT)
  - In Vivo Dermal Microdialysis/Microperfusion
  - In Vivo PK Studies in the Systemic Circulation
  - In Silico Modeling of Local and Systemic PK

Developing Complex Generics

- How can complex generic product developers
  - ensure that complex generic drug products are of high quality
  - bring greater predictability and timeliness to the review of generic drug applications
- Complex generic product developers can
  - Demonstrate a comprehensive understanding of the product complexities and manufacturing issues
  - Provide information that mitigates risks of potential failure modes for therapeutic equivalence
  - Initiate pre-ANDA communication with the FDA during product and program development, if necessary

Developing Complex Generics

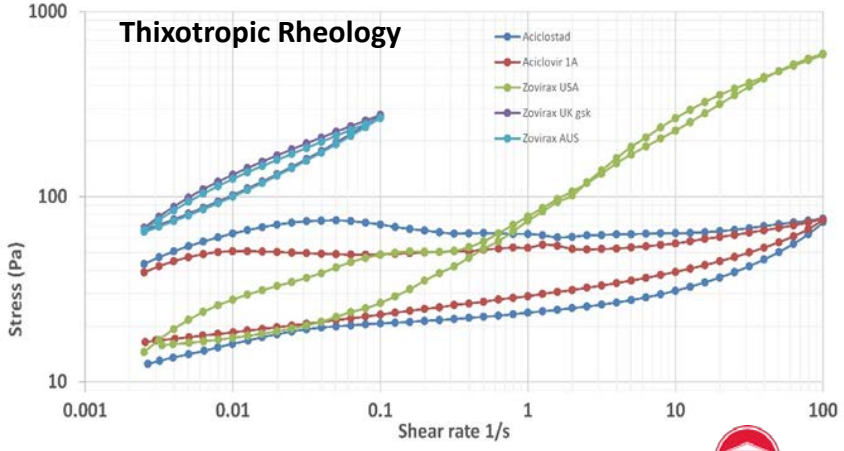
- How can the FDA
  - ensure that complex generic drug products are of high quality
  - bring greater predictability and timeliness to the review of generic drug applications
- The FDA can
  - Develop science-based regulatory standards that address product complexities and manufacturing issues
  - Develop guidance indicating what evidence would be acceptable to support a demonstration of BE
  - Initiate pre-ANDA communication with Industry during product and program development, as appropriate

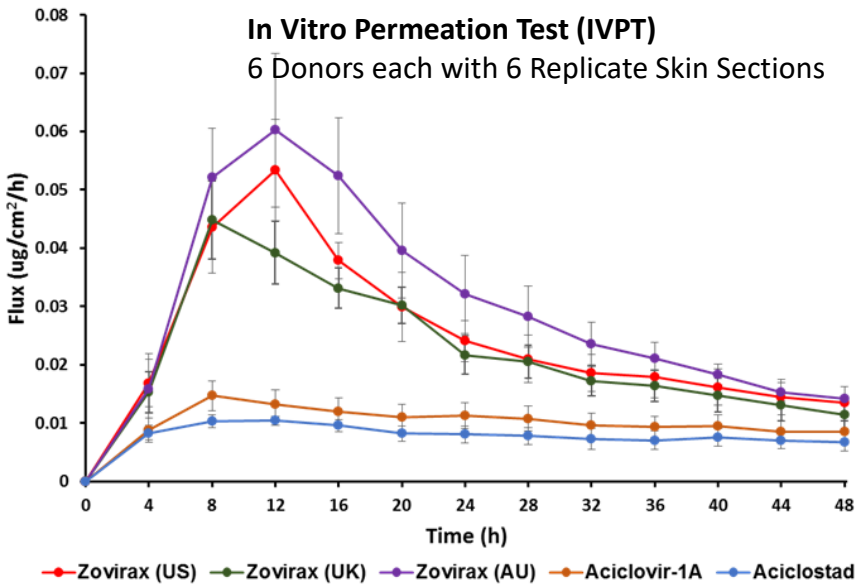
Regulatory Science Research

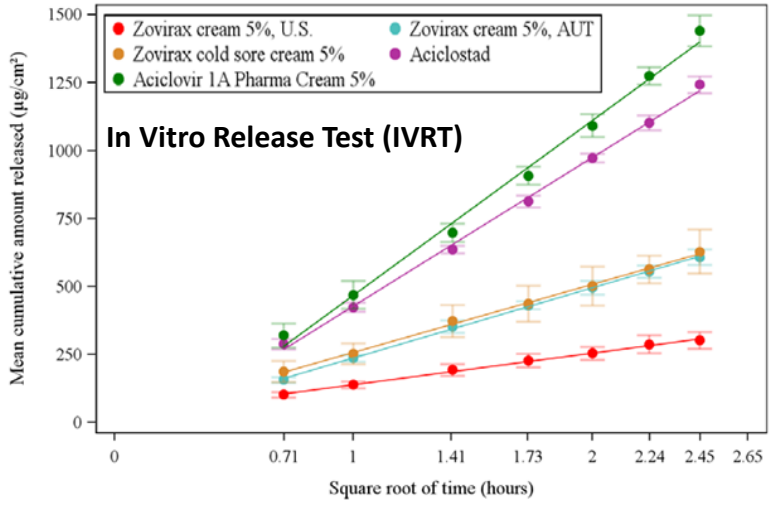
- **Product Quality Characterization**
  - FDA/CDER/OTS/DPQR (USA) — Physicochemical Tests
  - University of Mississippi (USA) — Physicochemical Tests
  - University of South Australia (and Germany) — Physicochemical Tests
- **In Vitro Release Test (IVRT)**
  - FDA/CDER/OTS/DPQR (USA) — IVRT
  - Joanneum Research (Austria) — IVRT
- **Cutaneous PK: In Vitro Permeation Test (IVPT)**
  - University of Mississippi (USA) — IVPT
  - University of Maryland (USA) — IVPT
  - University of South Australia — IVPT
- **Cutaneous PK: In Vivo Methods**
  - Joanneum Research (Austria) — dermal Open Flow Microperfusion (dOFM)
  - University of Maryland (U.K.) — Tape Stripping

Acyclovir Cream, 5% In Vitro Studies

	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

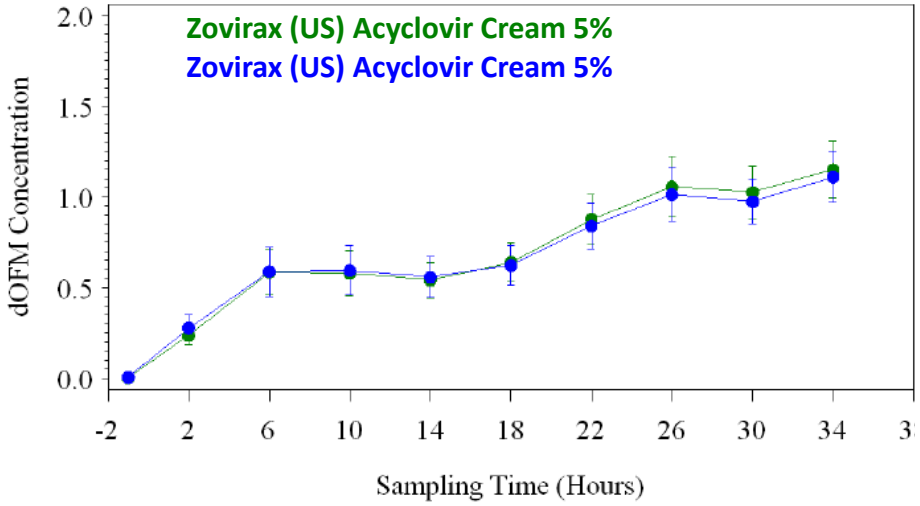


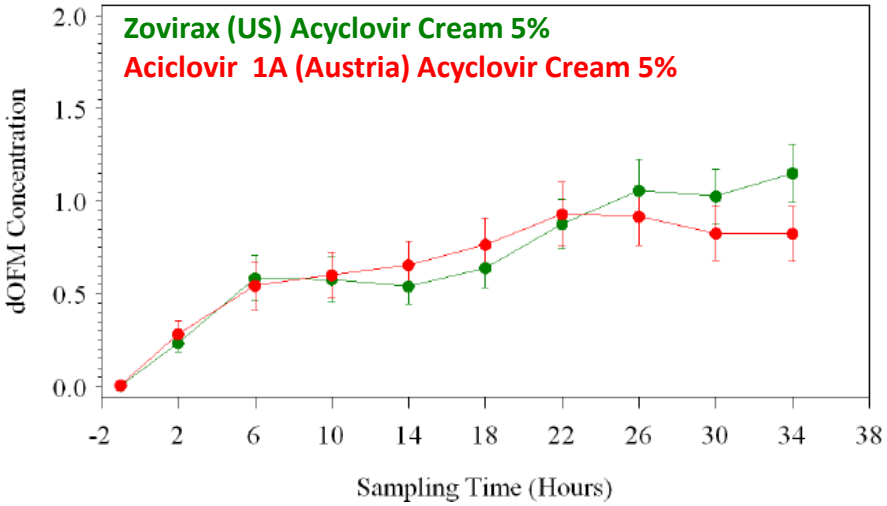




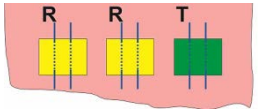
Acyclovir Cream, 5% In Vivo Studies

- Dermal Pharmacokinetics by dOFM (20 subjects)





Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]



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Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

Developing Guidance

- Translation of the Science to a PSG
  - Draft Guidance on Acyclovir (Acyclovir Cream, 5%)

    "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"*

Pre-ANDA Communications

- Pre-ANDA Meeting Requests
  - **Product Development Meetings**
    - For situations involving the development of a complex generic product with no PSG published, or where an alternative BE approach is proposed for a complex generic product with a PSG
    - The prospective applicant submits a complete meeting package, including a data package and specific proposals for product development
    - For situations where a controlled correspondence would not adequately address the prospective applicant's questions
    - For situations where a product development meeting would significantly improve ANDA review efficiency (e.g., ultimately decrease the number of review cycles for an application)

Pre-ANDA Communications

- Pre-ANDA Meeting Requests
  - **Pre-Submission Meetings**
    - To discuss and explain the format and content of the ANDA to be submitted for a complex generic product
    - Not a substantive review of summary data or full study reports, but FDA can identify items or information that should be clarified prior to submission of the ANDA
    - Not to determine whether the ANDA is acceptable for filing
    - Anticipated to occur approximately 6 months prior to submission of the ANDA

Pre-ANDA Communications

- Pre-ANDA Meeting Requests
  - **Mid-Review Cycle Meetings**
    - An opportunity for FDA to provide the applicant with an update on the status of the review, discuss issues identified during review, and convey possible deficiencies to the applicant
    - Held only during the first review cycle with applicants that have participated in a prior product development or pre-submission meeting
    - Will generally take place 30 days after the mid-point of the review cycle

Conclusions

- FDA has directed regulatory science research to:
  - Develop in vitro and in vivo product characterization tools for industry to use during generic product development
  - Support the development of more efficient BE standards, including numerous PSGs
- FDA has enhanced ANDA review infrastructure to:
  - Improve communication between prospective applicants and the FDA during generic product development, prior to submission, and during ANDA review
  - Improve predictability and timeliness of ANDA reviews
  - Improve patient access to high quality generic products

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- Frank Sinner, PhD

Public Workshop

FDA U.S. FOOD & DRUG ADMINISTRATION

Demonstrating Equivalence of Generic Complex Drug Substances and Formulations

Advances in Characterization and In Vitro Testing

Public workshop highlighting GDUFA funded research on generic complex drug substances and products:

- Emulsions
- Polymers
- Liposomes
- Peptides
- Long-acting injectables
- Implants
- Suspensions
- Natural source products

When?

October 6 2017
8:00 am – 4:00pm

Where?

FDA White Oak Campus
10903 New Hampshire Ave
Building 31 Conference Center
Great Room 1503 B + C
Silver Spring, MD 20993

Register

www.fda.gov/drugs/newsevents/ucm552461.htm

FREE **Public Workshop: October 20th, 2017**

➔ ***8:00 AM – 4:30 PM*** ***in person*** *or* ***via webcast***

Topical Dermatological Generic Drug Products:

Overcoming Barriers to Development and Improving Patient Access

- ✓ **Presentations by academic experts on the latest regulatory science research results**
- ✓ **Presentations by FDA review divisions discussing ANDA review considerations**
- ✓ **Presentation of prepared public comments as well as a forum for open public comments and dialogue with FDA**

Register at https://www.fda.gov/Drugs/NewsEvents/ucm557252.htm

Webcast at https://collaboration.fda.gov/ogddermaldrug/

FREE **Public Workshop: October 20th, 2017**

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