Complex Product Workshop

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November 6, 2019
Generic + Biosimilar Medicines Conference
North Bethesda, MD

Workshop Disclaimer

- The opinions and conclusions expressed in this workshop are the viewpoints of the speaker(s) and do not necessarily reflect the official position of the U.S. Food and Drug Administration.

Complex Generic Products in GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables, implantable drugs
- Complex drug-device combination products
  - Transdermals, metered dose inhalers (MDIs)
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

GDUFA: Generic Drug User Fee Amendments

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Product Workshop Logistics

1:30 PM – Salon B/D

Introduction	Markham Luke
Podium Keynote	Rob Lionberger
Pre-ANDA – Interacting with FDA	Kris Andre

1:55 PM - Breakout Session Descriptions by Session Leads

2:25 PM – End Main Room Session – Go to Breakouts

Workshop Logistics 2

2:30 PM—Breakout Sessions – Hands-on Role Play for Pre-ANDA

- Group 1 – Salon B/D – Liposomal Ophthalmologic Suspension
- Group 2 – Salon A – Orally Inhaled Drug-Device Combination Product
- Group 3 – Brookside – Topical Dermatologic Cream

Each session will include

a) Crafting a meeting package – what to include
b) How to write good questions to ask FDA
c) Simulated pre-ANDA meeting

4:25 PM—End of Breakout Sessions

Workshop Logistics 3

4:30 PM – Salon B/D

Report back from each of the Breakout Sessions

5:00 PM – Closing Remarks – Rob Lionberger and Jeff Jiang

Course Evaluations

End of Workshop

Acknowledgements

- Sam Raney, Lei Zhang
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- Our FDA Faculty for the Complex Product Workshop
  - Robert Lionberger, Kris Andre
  - Jeff Jiang, Darby Kozak, Bing Cai, Andrew Babiskin
  - Bryan Newman, Sneha Dhapare, Ross Walenga, Dhaval Gaglani, Bhagwant Rege
  - Priyanka Ghosh, Eleftheria Tzakalozou, Pahala Simamora

Robert A. Lionberger, PhD

Director

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Office of Generic Drugs (OGD), CDER, FDA, HHS

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GDUFA II: Pre-ANDA Meetings for Complex Generic Products

Kris Andre
Associate Director for Regulatory Affairs
Office of Research and Standards
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Pre-ANDA Program Goals

- Clarify regulatory expectations for prospective applicants early in product development
- Assist applicants to develop more complete submissions
- Promote a more efficient and effective ANDA assessment process
- Reduce the number of review cycles required to obtain ANDA approval, particularly for ***complex*** products

Complex Products

Complex active pharmaceutical ingredient (API)	• Any drug product containing a complex API, regardless of administration routes and dosage forms. e.g., Conjugated Estrogen Tablet, Glatiramer Acetate Injection
Complex routes of delivery	• Any non-solution drug product with a non-systemic site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action) e.g., Cyclosporine Emulsion, Acyclovir Cream
Complex dosage forms/formu-lations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation e.g., Doxorubicin HCl Liposomes, Leuprolide Acetate for Depot Suspension
Complex drug-device combinations	• Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption e.g., Epinephrine Injection (autoinjector)
Other products	• Any solid oral opioid drug products with FDA approved labeling for that show properties (and thus gaining their labeling) to meaningfully deter drug abuse e.g., Hydrocodone Bitartrate ER Tablet

Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, Clinical Pharmacology & Therapeutics (CPT), 2019, Vol.105(4), p.878-885

GDUFA II Meetings: Before ANDA Submission

Product Development (PDEV)

- Scientific exchange to discuss specific issues or questions (e.g., a proposed study design, alternative approach, or additional study expectations)
- Targeted advice regarding ongoing ANDA development program

Pre-submission (PSUB)

- Discuss and explain content and format of the ANDA to be submitted
- Advice to enable efficient review and improve chances of first cycle approval
- Does ***not*** include substantive review of summary data or study reports
- ANDA is anticipated to be submitted ~6 months of meeting date

GDUFA II Meetings: After ANDA Submission

Mid-Review-Cycle Meeting (MRCM)

- For applicants with prior PDEV and/or PSUB meetings
- Generally within 30 days after the mid-point
- Update on status of review and next steps

FDA will grant a PDEV or PSUB meeting for a complex product, if:

- No PSG available
- Proposing an alternative BE approach to the PSG
  - Change in study type (e.g., in vitro instead of in vivo approach)
- Meeting package is complete
- Questions could not be adequately addressed through a controlled correspondence (CC)
- A meeting would significantly improve ANDA review efficiency

Depending on available resources, FDA may grant if, in FDA's judgment:

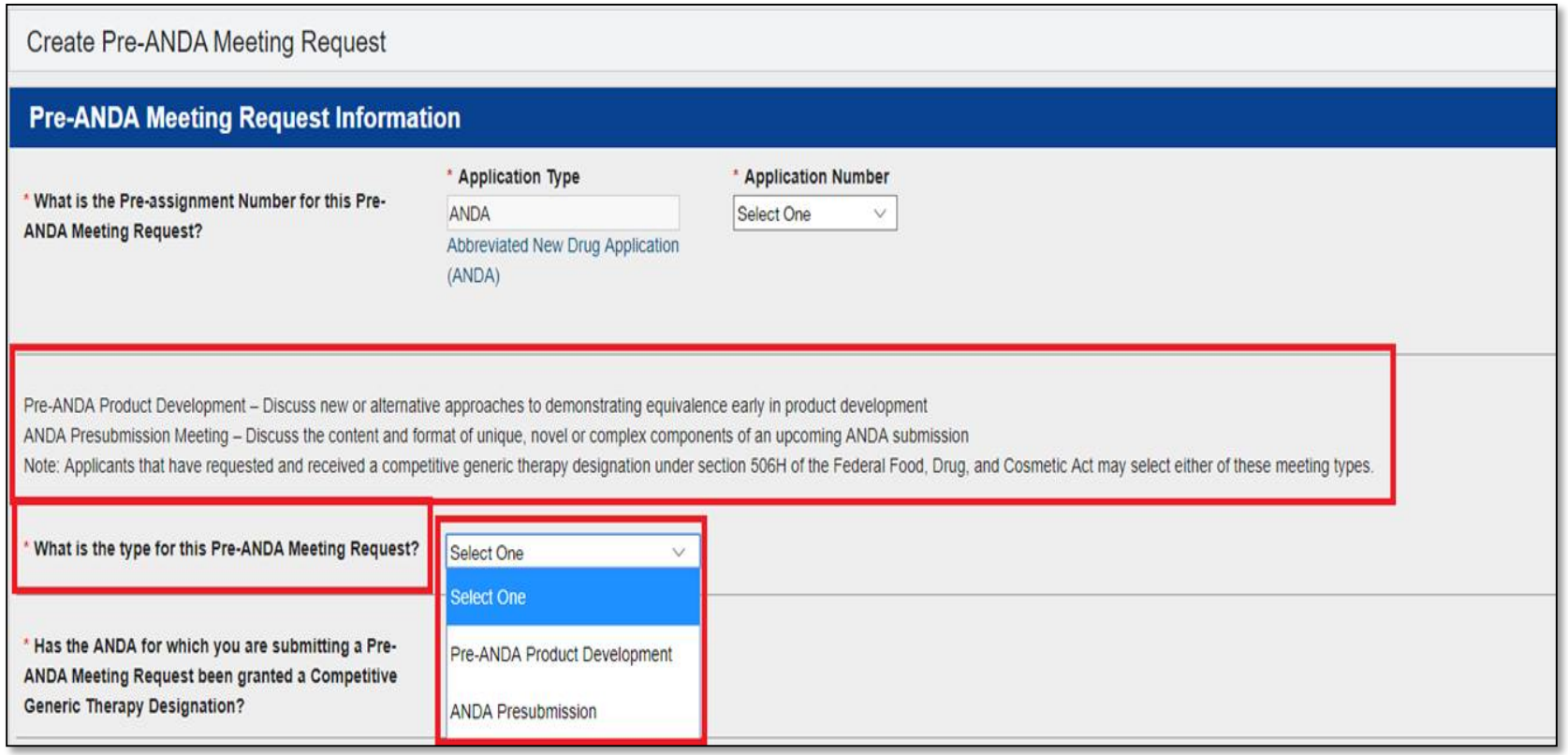
- Concerns complex product development issues
- Meeting package is complete
- Questions could not be adequately addressed through a CC, and
- A meeting would significantly improve ANDA review efficiency

Submitting Your Meeting Request

- Obtain a pre-assigned ANDA number

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

- Submit via the CDER Direct NextGen Collaboration Portal



Submitting Your Meeting Request

- Meeting package for PDEV
  - Provide specific proposals and questions supported by appropriate data and scientific justification
- Meeting package for PSUB
  - Outline the unique, novel, or complex aspects of your upcoming submission
  - If you have specific questions, provide appropriate background material and data related to those questions

Meeting Package Format and Content

- Refer to the draft Guidance for Industry (October 2017)
  - *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*
- Each question is followed by a corresponding justification, rationale or data to support discussion as applicable
- List of questions grouped by discipline (e.g., BE, CMC, etc.)
- Each question clearly numbered (e.g., 1,2,3 without sub-questions)

Meeting Request Evaluation

- Parallel assessments of the meeting request by Office of Generic Drugs (OGD) and Office of Pharmaceutical Quality (OPQ)
  - Assessment team reviews the product details, contents and submitted questions
  - OGD and OPQ coordinate to provide a unified response

My Meeting Was Granted

- Typically granted as face-to face meeting, though the applicant can request a written response or teleconference
- Written responses and teleconferences still qualify you for a mid-review-cycle meeting
- A project manager from the Office of Research and Standards (ORS) is assigned as the point of contact

Pre-ANDA Meeting Package Assessment

- FDA staff will review the meeting package, request consults and send information requests (if needed)
- Information Requests (IR)
  - Sent to prospective applicant through the portal
  - FDA strives to send early in the process, but can be sent at any point
  - Applicant responds to the IR through the portal
- Preliminary responses are based upon the Agency's current thinking and knowledge
  - May change with available data or research, etc.

Preliminary Responses

- Preliminary written responses from the FDA will be sent via the portal approximately 5 days before your scheduled meeting
- Your opportunity to focus your meeting
  - Submit presentation materials (not required)
  - Submit a revised agenda
  - Submit these items through the portal at least 48 hours prior to scheduled meeting
- Should NOT generate the submission of new questions
- You can cancel your meeting if you feel the preliminary responses adequately address your questions
  - Still be eligible for a MRCM

Meeting Day

- Meetings are typically 1 hour
- Discussion should be focused on clarification of the Agency's preliminary written responses
- Meeting participants discuss the data, questions, and the responses provided to assist the prospective ANDA applicant's complex product development program
- **FDA will not address or discuss new data or questions not presented in the original meeting package**

Post-Meeting

- If prospective ANDA applicants would like the FDA to consider their meeting summary:
  - Submit within 7 calendar days of the meeting via the portal
- FDA will issue official minutes within 30 calendar days of the meeting

Competitive Generic Therapy

- New pathway for drugs with “inadequate generic competition”

- Eligible for PDEV and PSUB meetings
  - Includes both complex and non-complex products
  - Provide documentation of Competitive Generic Therapy (CGT) designation with meeting request
  - Does **not** provide for an expedited meeting timeline

- FDA will consider the following, among other factors, to determine whether to grant or deny a meeting request with CGT:
  - Complexity of developing an ANDA for a specific drug
  - Potential public health impact (e.g., severity of the condition treated, size of impacted patient population)
  - Impact on FDA resources and other workload commitments

U.S. FOOD & DRUG ADMINISTRATION

Breakout Session 1: Liposomal Ophthalmologic Suspension

Bing Cai, PhD.

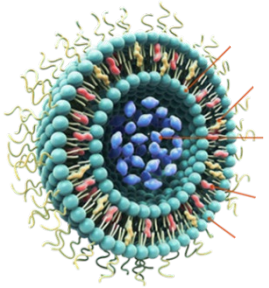
(Office of Lifecycle Drug Products | Office of Pharmaceutical Quality)

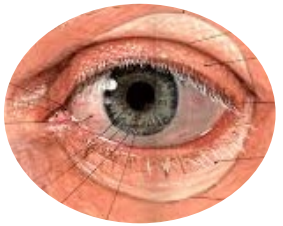
Darby Kozak, PhD.

(Office of Research & Standards | Office of Generic Drugs)

Andrew Babiskin, PhD.

(Office of Research & Standards | Office of Generic Drugs)



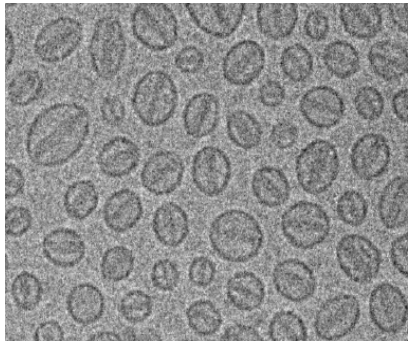


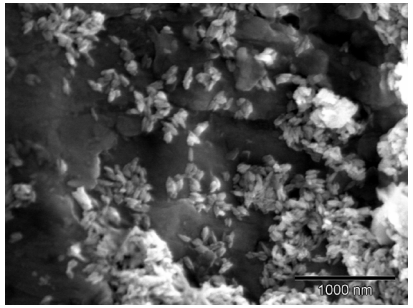
Challenges in Developing Complex Liposomal and Ophthalmic Products

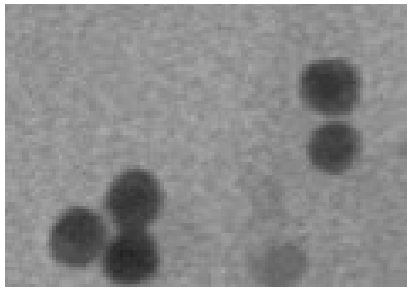
- Formulation Complexity
  - Permissible generic formulation composition
  - Identifying and characterizing critical quality attributes of complex formulations
  - Identifying and justifying appropriate product characterization techniques
- Bioequivalence (BE) Study Complexity
  - In vivo study design
    - Design on appropriate comparative clinical endpoint BE study
    - Sampling for comparative aqueous humor pharmacokinetic study
  - In vitro studies
  - Modeling and simulation to support a BE approach

Formulation and Quality Considerations

- Regulatory
  - Drug substance
  - Excipients (e.g., Q1/Q2)
  - Container closure system
- Assessing Critical Quality Attributes (CQA)
  - Formulation and manufacturing
  - Testing and specifications
- Pre-ANDA Meeting Requests
  - Where do they fit in?
  - What are common issues?

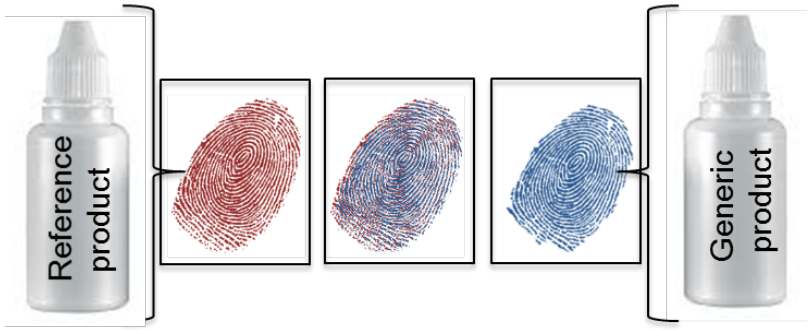




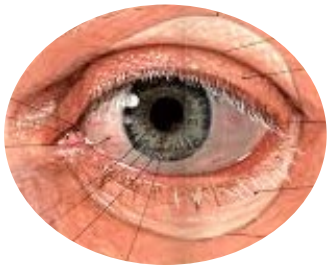


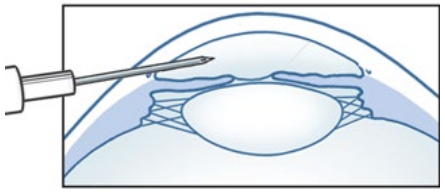
Establishing BE:

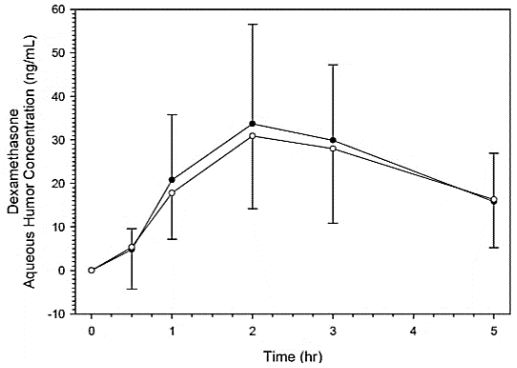
In Vitro Testing:



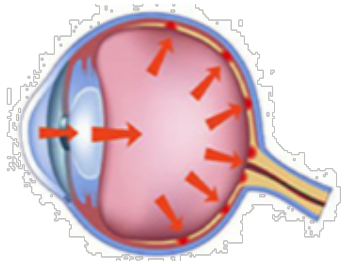
Comparative Aqueous Humor PK:

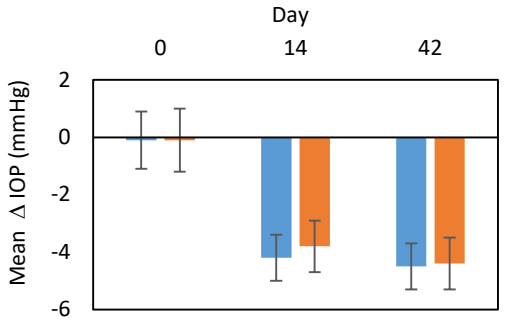






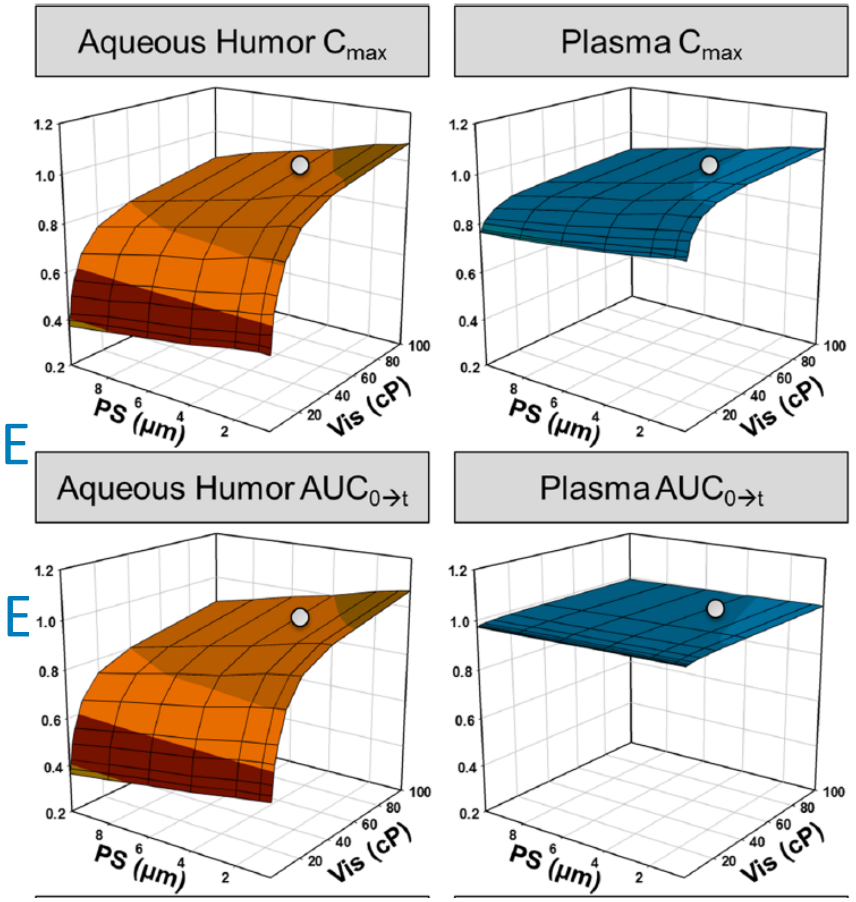
Comparative Clinical Endpoint:





Use of Modeling and Simulation

- Support CQA and proposed BE approach
  - Predict in vivo performance based on product CQAs
  - Support CQA space that gives rise to BE products
  - Design and power more appropriate BE studies



A Hypothetical Product:
FLOXASOME (lipofloxacin ophthalmic liposome) 0.5%

- Locally-acting ophthalmic liposomal drug product for post operative prophylactic treatment of bacterial endophthalmitis.

- Breakout Session:
  - What to pay attention to in the label
  - Formulation assessment and CQA characterization considerations
  - In vitro and in vivo BE study design considerations
  - Utilizing the pre-ANDA meeting process

U.S. FOOD & DRUG ADMINISTRATION

Session 2: Orally Inhaled and Nasal Drug Products (OINDPs)

Bryan Newman, PhD.
FDA/CDER/OGD/ORS/DTP
Sneha Dhapare, PhD.
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Ross Walenga, PhD.
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Kairui Feng, PhD.
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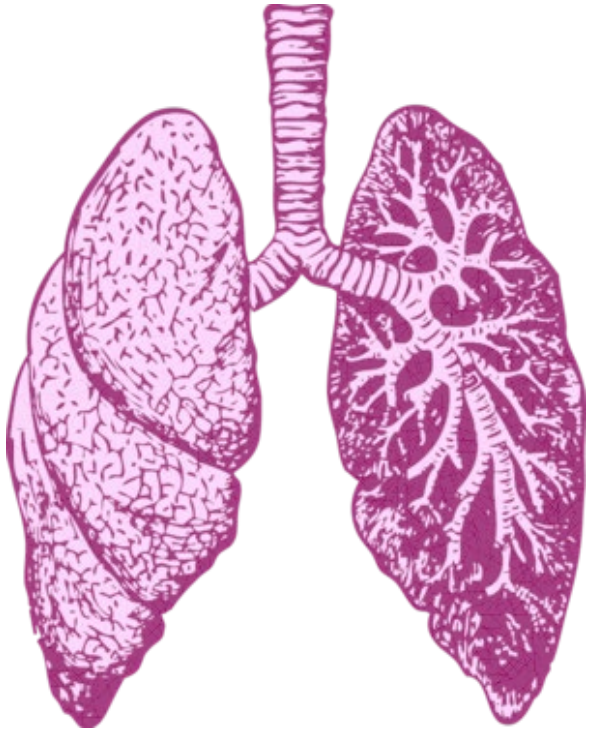
FDA/CDER/OPQ/OLDP



Challenges in Developing Locally-Acting Generic OINDPs

- Patient-associated complexity
  - Respiratory tract diseases - asthma, chronic obstructive pulmonary disease (COPD), rhinitis
  - Regional distribution and site of action
- Device-associated complexity
  - Drug-device combination products
  - Device design
  - User interface
- Formulation-associated complexity
  - Physicochemical properties
  - Types and amounts of inactive ingredients

Establishing BE with OINDPs: Aggregate Weight-of-Evidence Approach

OINDP Device Considerations

- Assessing device substitutability
- Comparative Analyses

OINDP Quality Considerations

- Sources of variability in OINDP development
  - Drug substance
  - Excipients
  - Container closure system
- Assessing OINDP Critical Quality Attributes

- Pre-ANDA Meeting Requests
  - Where do fit in?
  - What are common issues?

Hypothetical OINDP: Breatheatol

- MDI drug product containing a corticosteroid

- Breakout Session:
  - What to pay attention to in the label
  - Formulation assessments
  - Device assessments and substitutability
  - In Vitro/In Vivo BE
  - Utilizing the pre-ANDA meeting request process for generic OINDP development

BIOEQUIVALENCE OF GENERIC TOPICAL DERMATOLOGICAL DRUG PRODUCTS

Generic + Biosimilar Medicines Conference/ Complex Product Workshop
Session 3: Topical Dermatologic Cream
November 06, 2019

Priyanka Ghosh, PhD; Markham C. Luke, MD PhD; and Eleftheria Tsakalozou, PhD
Office of Research and Standards
Office of Generic Drugs |CDER | U.S. FDA
Pahala Simamora, PhD
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality |CDER | U.S. FDA

TOPICAL DERMATOLOGICAL DRUG PRODUCTS

PSGs for Topical Dermatological Products

Potential ways to establish bioequivalence (BE) for complex topicals:

- Comparative clinical endpoint BE studies
  - Clinical endpoint (CE)
  - Pharmacodynamic endpoint (e.g., vasoconstrictor (VC) studies)
- *Efficient* characterization-based BE studies (e.g., in vitro)
  - in vitro
  - in vivo pharmacokinetic (PK) studies

PSG: Product-Specific Guidance

Generic Topical Product Development

- Other Methodologies of Interest
  - **In Vivo** Cutaneous PK Studies
    - ✓ Dermal Open Flow Microperfusion (dOFM)
    - ✓ Dermal Microdialysis (dMD)
    - ✓ Epidermal and/or Dermal Pharmacokinetic Tomography

PSGs for Topical Dermatological Products

A Modular and Scalable Approach to BE Evaluation

- Sameness of inactive ingredient components and quantitative composition, e.g., qualitative **(Q1)** and quantitative **(Q2)** sameness
- **Q3** (Physical & Structural Characterization) as relevant to the nature of the product
- **IVRT** (In Vitro Release Test)
- **IVPT** (In Vitro Permeation Test) or another bio-relevant assay may be appropriate for some products
- In vivo systemic **PK** studies may be appropriate for some products

PSGs for Topical Dermatological Products

- Formulation
  - What do we mean by no difference in inactive ingredients

1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole topical gel, 0.75% the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*[1], the bioequivalence of the test product with respect to the reference product may be established using the in vitro option if the criteria below are also satisfied.

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
- Additional performance tests (e.g. IVPT) may be required

Note: The packaging configuration itself 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

Regulatory Utility of Dermal PBPK Models

Generic drug approval

- Support alternative BE approaches
  - Comparative clinical endpoint BE studies may not be sensitive to formulation differences
  - BE assessment for Q1/Q2 formulations leveraging in vitro testing
- Define a “safe space” for formulation attributes
  - Risk assessments on the impact of product attributes on in vivo drug product performance
- Extrapolate BE assessments from healthy to diseased subpopulations

Source: 2018 SBIA OGD Complex Generic Drug Product Workshop

Regulatory Utility of Pharmacometric Approaches

How can pharmacometric approaches be leveraged?

- For designing an adequately powered comparative CE BE study

- To justify:
  - A shorter duration comparative CE BE study
  - Appropriate timepoints for comparative CE BE study
  - A pharmacodynamic endpoint in lieu of a CE

- Propose different endpoint, e.g., area under effect curve (AUEC), maximum effect (E_{max}) in place of fixed time point comparison

Generic Topical Product Development

- If a PSG is available
  - Follow the recommendation in the PSG to establish BE
  - Submit a pre-ANDA meeting request when you propose an alternative BE approach
  - Submit controlled correspondence (CC) for questions related to appropriateness of a formulation for a specific BE approach, etc.

- If PSG is Unavailable

  Steps toward the development of a generic topical product
  - Identify the reference product
  - Identify the studies proposed to support a demonstration of BE appropriate to the complexity of the dosage form
  - Submit a pre-ANDA meeting request with specific questions to obtain the Agency's feedback

Outline for Breakout Session

- Product label for the (hypothetical) reference product
  - Components and composition
  - Dosage and administration
  - Indication
  - Mechanism/site of action
  - Other key information to consider for the product development and BE strategy
- Considerations related to formulation of the test product
  - Examine and compare potential product formulations
- Considerations related to BE strategy
  - Including PBPK-based approaches
- Considerations related to Q3 characterization and the packaging configurations

Acknowledgements

Office of Research and Standards

- Sam Raney, PhD
- Tannaz Ramezanli, PharmD, PhD
- Andrew Babiskin, PhD
- Liang Zhao, PhD
- Lei Zhang, PhD
- Robert Lionberger, PhD

Office of Pharmaceutical Quality

Office of Lifecycle Drug Products

- Pahala Simamora, PhD
- Richard Chang, PhD
- Bing Cai, PhD

Go to Breakouts

(Maximum of 40 persons per breakout – 5 minutes transit time)

- Group 1 – Salon B/D – Liposomal Ophthalmologic Suspension (STAY HERE)
- Group 2 – Salon A – Orally Inhaled Drug-Device Combo Product
- Group 3 – Brookside – Topical Dermatologic Cream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