Topical Dermatological Drug Products

Complex Generic Drug Products (CGDPs) with a Locally-Acting Route of Delivery

Flight Simulator Workshop: Learning How to Develop CGDPs

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Topical Dermatological Products

Examples:

- Solutions
- Powders
- Gels
- Ointments
- Lotions
- Creams
- Aerosols/Foams

Generic Topical Drug Product Development

Considerations:

- Establish Quality Target Product Profile (QTPP)
- Comprehensive testing of RLD product
  - Multiple lots (fresh and aged lots)
  - Mean value and variability of quality attributes
- Identify Critical Quality Attributes (CQAs)
  - Derived from QTPP
  - Associated with API, excipients, intermediates (in-process materials) and drug product
- Conduct risk-based approach to product development
  - Excipient selection
  - Identify and rank the risks (input materials, process, equipment) with potential to have an impact on product quality
  - Linking material attributes and process parameters to drug product
  - Risk mitigation
  - Product understanding
- Selection of appropriate manufacturing process
  - Process robustness
- Develop control strategy
  - Ensuring product of required quality will be produced consistently

Generic Topical Drug Product Development

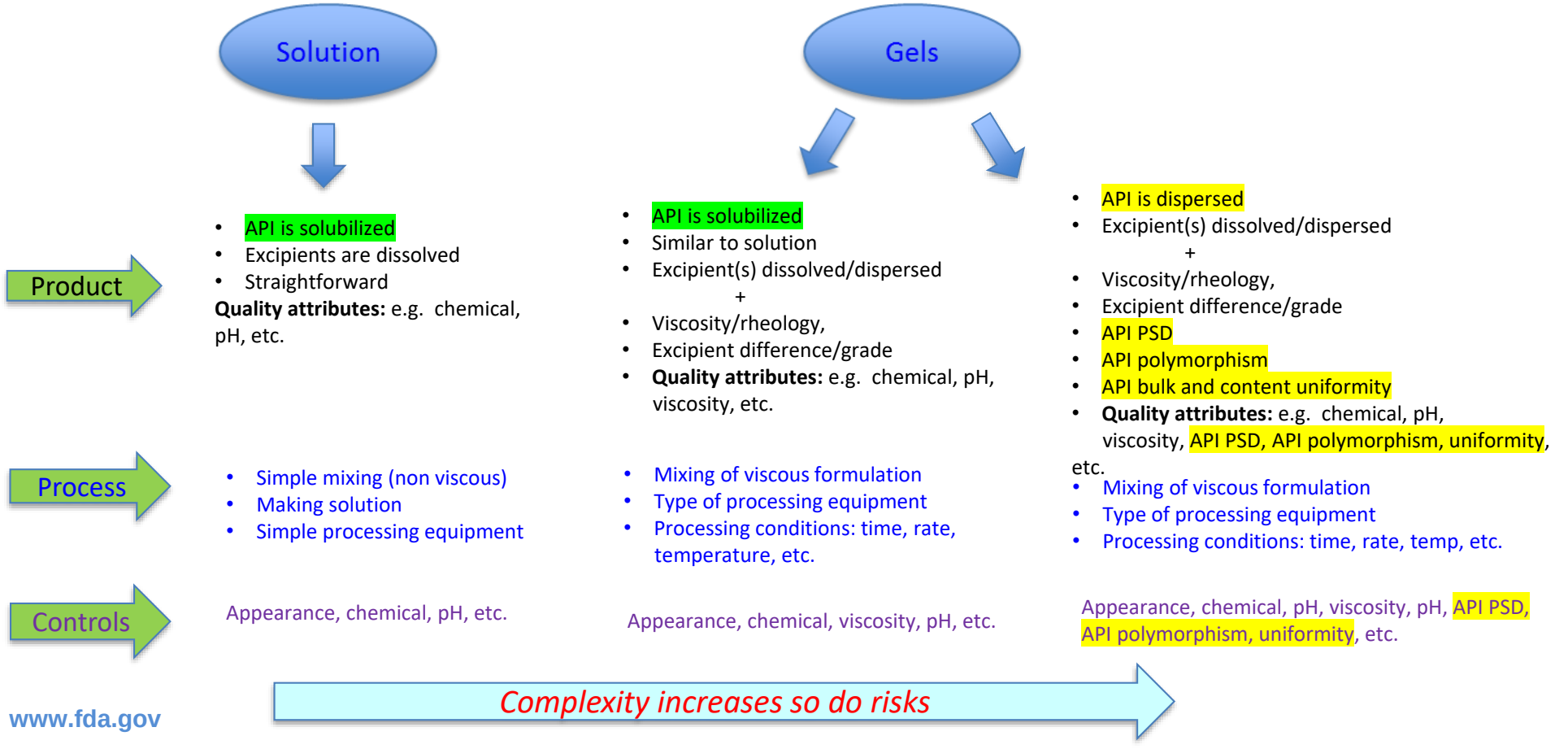
Quality Target Product Profile (QTPP)

- Information regarding RLD product
- Sources: Labeling, literature, patent, etc.
- Information collected:
  - Dosage form
  - Strength
  - Active and inactive ingredients
  - Dose and administration
  - Container closure system
  - Storage conditions
  - Shelf life, etc.

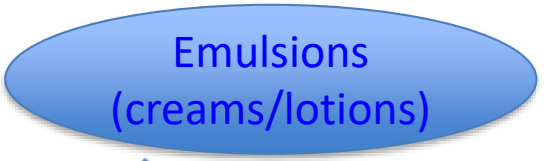
Example for hypothetical generic cream USP, N%

QTPP Element	Target	Justification
Dosage form	Cream	Pharmaceutical equivalence requirement: Same dosage form
Route of administration	Topical	Pharmaceutical equivalence requirement: Same route administration
Dosage strength	N% w/w	Pharmaceutical equivalence requirement: Same strength
Stability	At least 24-month shelf-life at room temperature.	Equivalent to or better than RLD shelf-life, pharmaceutical equivalence requirement.
Drug product quality attributes	Physical Attributes: rheological behavior, drug particle size, oil globule size, pH, in vitro release test	Pharmaceutical equivalence requirement: Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality)
	Identification	
	Assay	
	Homogeneity and Tube Uniformity	
	Degradation products/Residual Solvent	
	Preservatives Content	
	Microbial Limits	
Container closure system	Identical primary packaging to RLD	Match RLD and for patient acceptability
Package Integrity	No failure	Needed for stability, clinical effectiveness and safety
Administration	Concurrence with RLD labeling	Information provided in the RLD labeling

Single/Multi Phase System (e.g., solution, gels)



Multi Phase System (Emulsions)



Product

- API is solubilized
- Excipient(s) dissolved/dispersed
  +
- Viscosity/rheology,
- Excipient difference/grade
- Globule size
- **Quality attributes:** e.g. chemical, pH, viscosity, globule size, etc.

Process

- Mixing of viscous formulation
- Type of processing equipment - emulsification
- Processing conditions: time, rate, temperature, etc.
- Impact of processing conditions on the quality attributes/product quality?

Controls

Appearance, chemical, viscosity, pH, globule size, etc.

- API is dispersed
- Excipient(s) dissolved/dispersed
  +
- Viscosity/rheology,
- Excipient difference/grade
- API PSD
- API polymorphism
- API bulk and content uniformity
- Globule size
- **Quality attributes:** e.g. chemical, pH, viscosity, API PSD, API polymorphism, uniformity, globule size, etc.

- Mixing of viscous formulation
- Type of processing equipment - emulsification
- Processing conditions: time, rate, temp, etc.
- Impact of processing conditions on the quality attributes/product quality?

Appearance, chemical, pH, viscosity, pH, API PSD, API polymorphism, uniformity, globule size, etc.

Complexity increases so do risks

Risks - Drug Substance

What would you do if ….

API is solubilized in the formulation

- Quality attributes
  - Physical attributes? - None/Low
  - Chemical attributes:
    - Assay
    - Related substances

- API
- Preservatives
- Anti-oxidant
- Chelator
- etc.

API is dispersed in the formulation

- Quality attributes
  - Physical attributes? - Yes
    - e.g. Polymorphism, Particle size, Crystal habits, etc.
    - Should be evaluated in the drug product
  - Chemical attributes:
    - same as identified on the left

Risks – Dosage Forms

What would you do if ….

Dosage form is a **single phase** system

- Examples: solution, simple gel and simple ointment
- Quality attributes:
  - Physical attributes due to API – None/Low
  - Uniformity – None/Low
  - Physical attributes due to formulation, e.g.
    - Viscosity/rheology
    - Excipient differences or grade
    - pH
  - Chemical attributes
    - Assay
    - Related substances

- API
- Preservatives
- Anti-oxidant
- Chelator
- etc.

Dosage form is a **multiple phase** system

- Examples: gel, ointment and emulsions (creams & lotions)
- Quality attributes:
  - Physical attributes due to API
    - None/Low (if API is solubilized)
    - Yes (if API is dispersed)
  - Uniformity – Yes
  - Physical attributes due to formulation, e.g.
    - Viscosity/rheology
    - Excipient differences or grade
    - pH
    - Globule size
    - Specific gravity
  - Chemical attributes
    - Same as identified on the left

Generic Topical Product Development

Approaches for establishing BE for complex topical products:

- Understand the drug product to identify the potential regulatory pathways
  - Pharmacodynamic studies (vasoconstrictor (VC) studies)
  - Comparative clinical endpoint studies
  - In vitro product characterization
  - In vitro product characterization and pharmacokinetic (PK) studies

BE Recommendations for Topical Products

- Approaches for establishing BE for generic topical dermatological products are based on the complexity of the dosage form and the drug product.
- 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

Failure Modes (BE) – Dosage Form

What would you do if ….

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

- Excipient differences
- Viscosity/Rheology
- pH

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

What would you do if ….

The Mechanism/Site of Action **Well Understood?**

- An in vitro characterization based approach may be recommended
  - Acyclovir Topical Cream
  - Benzyl Alcohol Topical Solution

The Mechanism/Site of Action **Not Well Understood?**

- If the mechanism and/or site of action may be (partially) systemic, an in vivo PK study may also be recommended
  - Dapsone Topical Gel
  - Ivermectin Topical Cream

What would you do When….

The PSG is Unavailable

Steps toward the development of a generic topical 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

You request pre-ANDA meeting with the Agency

- Submit details about the proposed formulation(s) for the generic product
- Submit a clear outline of the proposed BE approach and any supporting information
- Submit the information to support the feasibility of any novel techniques
- Submit information about all proposed product packaging configurations

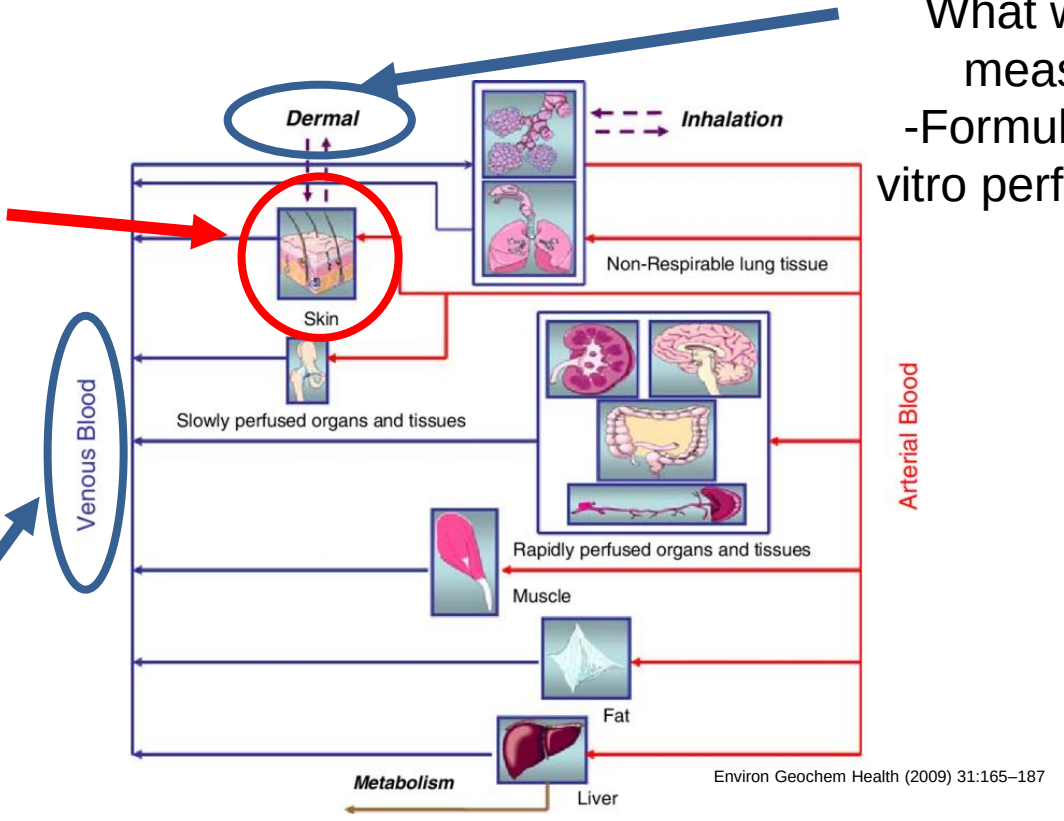
For additional information, please see the draft guidance for industry, Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf

Physiologically Based PK (PBPK) Modeling

Dermal PBPK modeling relates what we want to know to what we can measure

What we would like to know:
-local drug concentrations

What we can measure:
-Systemic drug exposure



Environ Geochem Health (2009) 31:165–187

What we can measure:
-Formulation in vitro performance

Source: 2018 SBIA-ORS Complex Generic Drug Product Workshop

Regulatory Utility of Dermal PBPK Models

Utilize dermal PBPK modeling in:

- Product-specific guidance development
- Generic drug approval
  - Support alternative approaches for demonstrating bioequivalence (BE)
    - Comparative clinical endpoint BE studies may not be sensitive to formulation differences
    - In vitro testing for BE assessment for Q1/Q2 formulations
  - Define a safe space for critical attributes of dermatological products
    - Risk assessments on the impact of critical quality product attributes on in vivo drug product performance
  - Extrapolate BE assessments from healthy to diseased subpopulations

Source: 2018 SBIA-ORS Complex Generic Drug Product Workshop

Developing Reliable Dermal PBPK Models…

Dermal PBPK modeling is a powerful approach that can be used to

- explore relationships between systemic and local drug exposure
- predict in vivo performance of dermatological drug products when only product critical quality attributes are available
- conduct risk assessment on the impact of product critical quality attributes on the in vivo drug product performance of reference and test drug products

Source: 2018 SBIA-ORS Complex Generic Drug Product Workshop

What would you do if ….

Your Q3 attribute of your Q1/Q2 formulation deviates from the RLD or exhibits greater variability than the RLD?

- Can you establish that the deviation or additional variability will not impact local and/or systemic bioavailability?
- A mechanistic PBPK approach can explore of the impact of quality attributes on bioavailability

What would you do if ….

You want to use in vivo systemic PK as a pivotal approach to establishing bioequivalence?

- Can you establish that there is a correlation between some measures of systemic exposure and local bioavailability, particularly at the site of action?

- If local concentrations cannot be measured/not available, a dermal PBPK approach can be used to predict local concentrations for establishment of the correlation

Pharmacometric Approaches

How Can Pharmacometric Approaches Be Leveraged in Generic Product Development?

- For designing adequately powered comparative clinical endpoint (CE) bioequivalence (BE) study

- Justify:
  - Shorter duration comparative CE BE study
  - Appropriate timepoints for comparative CE BE study
  - Pharmacodynamic endpoint in lieu of CE

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

What would you do if ….

You have developed a MODEL to support approval of your generic product?

- The pre-ANDA product development meeting is a good venue to discuss your model and its application with OGD prior to ANDA submission

- Example of discussion topics:
  - How model performance/predictability will be assessed?
  - How the model will be verified (including model assumptions, limitations, optimization/refinement)
  - How virtual bioequivalence studies will be conducted? How will the two products (test vs. reference) be defined in the model?

- Acceptability of your approach will be determined at the time of ANDA review

- For PBPK modeling reports, refer to the 2018 Guidance for Industry – PBPK Analysis – Format and Content:
  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

Summary

- A good Pre-ANDA Product Development meeting package
  - Should clearly characterize the complexity of the drug product
  - Should contain the formulation composition of the test product
  - Provide clear and concise information about how the proposed approach can systematically mitigate concerns related to potential failure modes for BE
  - Should contain sufficient data and rationale to support the questions
  - If modeling involved, should contain a clear presentation of how the model will be used and how the model will be verified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