An FDA Perspective on the Comparative Analyses of Critical Material, Quality, and Design Attributes for Topical, Transdermal, Rectal, and Vaginal Drug-Device Combination Products

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Outline

- Considerations from FDA's draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017)
- Considerations for the user interface of rectal and vaginal drug products
- Considerations for the drug formulation
- Considerations for transdermal and topical delivery systems (TDS)
- Hypothetical device examples

Types of Threshold Analyses

- *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017)

Labeling comparison

Side-by-side, line-by-line comparison of the full prescribing information, instructions for use (IFU), and descriptions of the delivery device constituent parts for the test and reference products

Comparative task analysis

Comparison of the manual and intellectual activities for end-users interacting with the test and reference products to characterize the potential for use error

Physical comparison of the delivery device constituent part

Visual and tactile examination of the physical features of the test and reference products

Outcomes of Threshold Analyses

No design differences

- Additional data and/or information is likely not necessary to support the approval of an ANDA

Minor design differences

- May be considered acceptable based on provided data and information (e.g., data collected through threshold analyses)

Other design differences

- Recommend modifying the design of the user interface to minimize these differences
- May request a comparative use human factors study

User Interface Considerations

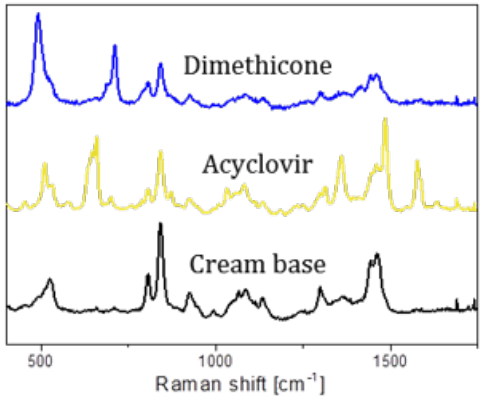
- General considerations
  - What is the indication and conditions of use of the product?
  - Who is the end-user?
  - What is the potential for use error? What is the impact of the use error?
- Differences in critical design attributes
  - Does this difference impact:
    - How the end-user handles the device?
    - The administration of the drug formulation?
    - The safety to the patient?
    - The substitutability of device for the reference product?
- The classification of a difference as a “minor design difference” or “other design differences” is product-specific

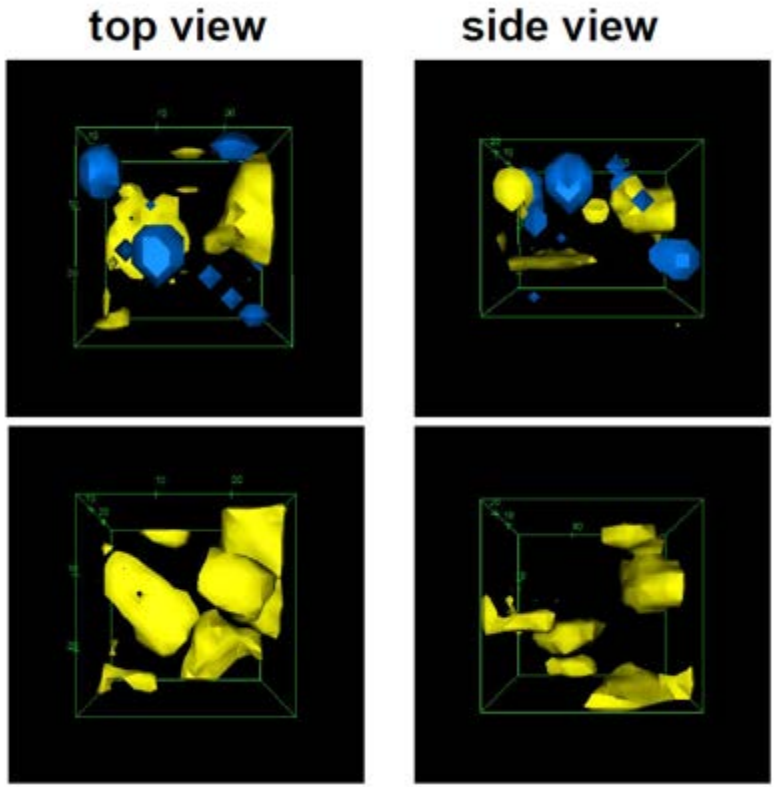
Conducting Comparative Analyses

- Identify the external critical design attributes and critical tasks
  - Review the IFU of the reference product
  - Evaluate all tasks that need to be performed to use the product
  - Identify the tasks that are critical to use the product
  - Identify the features of the device that are used in the critical tasks
- Compare the IFUs *(labeling comparison)*
- Compare the critical tasks by following the IFUs *(comparative task analysis)*
- Compare the physical attributes *(physical comparison of the device)*
- Classify the identified differences between the devices as “minor design differences” or “other design differences”

Drug Formulation Considerations

- Impact of the device on:
  - Formulation composition
  - Microstructure of the drug formulation



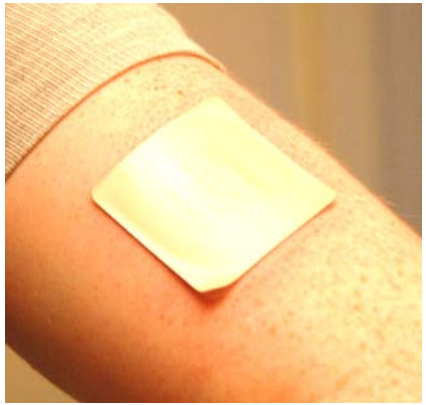


Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs (FDA Grant U01-FD005226)

TDS Product Considerations

- TDS products have unique considerations related to the device, as they are worn on the body for an extended period of time.

TDS design attribute	Considerations
Size	Anatomical placement
	Patient compliance
Shape	Performance (adhesion)
	Addition of new orientation
Orientation	Performance (adhesion)
Components	Aesthetic/patient compliance
	Safety (e.g., metal backing)
Disposal method	Safety



Hypothetical Vaginal Cream

RLD: Kelchazole vaginal cream, 2%

- Indication: Treatment of bacterial infection

• Oil-in-water emulsion	Consider: • Potential changes to the drug formulation microstructure
• Available in a tube that is co-packaged with three applicators	Consider: • Dimensions of applicators • Material of applicators
• Dosage and administration: Administer one applicator of drug product twice daily (morning and night) for 3 days	Consider: • Who is using the product • Re-use of the applicator

RLD: Reference listed drug

Hypothetical Vaginal Cream

RLD: Kelchazole vaginal cream, 2%

1. Screw applicator onto tube.
2. Fill applicator to designated fill line. → Consider:
   - Readability of the fill line
3. Insert applicator into vagina.
4. Press plunger to dispense cream. → Consider:
   - Force to depress plunger
5. Clean applicator after use.

Hypothetical Rectal Gel

RLD: Megadiol rectal gel, 1%

• Indication: Treatment of seizure activity for patients ages 2-7 years	Consider: • Condition of use • Intended patient population
• Packaged in a pre-filled syringe capable of delivering 6 different unit doses	Consider: • Steps to adjust the dose • Location of the dose window
• Dosage and administration: For inpatient use. Administered by a healthcare professional during a seizure	Consider: • Who is the end-user
• Single phase hydroalcoholic gel	Consider: • Potential for evaporation of volatile components

Hypothetical Rectal Gel

RLD: Megadiol rectal gel, 1%

1. Adjust the dose on the syringe.	Consider: • Who is adjusting the dose
2. Remove cap off of the syringe tip.	Consider: • Force to remove cap • Color of cap
3. Insert syringe tip into the rectum.	Consider: • Safety features
4. Depress the plunger.	Consider: • Force to depress plunger
5. Discard the syringe.	

Receiving Feedback on a Test Device

- Pathways
  - Controlled correspondence (CC)
    - Response in 60 days for standard CCs
    - Response in 120 days for complex CCs
  - Pre-abbreviated new drug application (pre-ANDA) product development meeting request
    - Response in 120 days for pre-ANDA meetings
- Information to submit
  - Samples of the test and reference devices
  - Complete comparative threshold analyses
  - Specific question(s) based on the outcome of the comparative threshold analyses

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/controlled-correspondence-related-generic-drug-development-draft-guidance-industry
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry

Conclusions

- When developing a generic drug-device combination product, the impact of the device on the drug formulation should be considered.
- When designing your test device, it is important to consider aspects such as the conditions of use, end-user, and critical tasks of the reference device.
- When assessing the differences between a test and reference device, consider whether an end-user can substitute the proposed generic product for the reference product without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.
- To receive feedback on a proposed test device, you can submit a CC or pre-ANDA product development meeting request to the Office of Generic Drugs.

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