Ophthalmic Drug-Device Combination Products – Comparative Analyses

Shinae Kim, PhD
Pharmacokineticist
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Objectives

By the end of this presentation, you will be able to:

- Understand the comparative analyses framework for ophthalmic Drug-Device Combination Products (DDCPs) user interface assessment
- Apply best practices for evaluating user interface differences in generic DDCPs
- Categorize user interface differences using FDA guidance
- Utilize pre-ANDA consultation opportunities to enhance submission quality

Key Definitions

- Drug-Device Combination Product (DDCP):
  - Therapeutic and diagnostic products combining drug and device constituent parts (21 CFR 3.2(e))
  - DDCP contains a drug constituent part and device constituent part(s).
- User interface:[1]
  - All components of the product with which a user interacts
  - Includes device constituent parts and any associated controls, displays, product labeling, and packaging
- Critical task:[2]
  - A user task that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised care
- External critical design attribute: [1]
  - A feature that directly affects how users perform a critical task that is necessary in order to use or administer the drug product

1. Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry | FDA
2. Application of Human Factors Engineering Principles for Combination Products: Questions and Answers | FDA

Regulatory Classification of Ophthalmic DDCPs

21 CFR § 800.10(c)

(c) Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles, which are regulated as medical devices unless packaged with the drugs with which they are to be used, should be packaged so as to maintain sterility until the package is opened and be labeled, on or within the retail package, so as to afford adequate directions and necessary warnings to minimize the hazard of injury resulting from contamination during use.

- When packaged with an ophthalmic drug product, classified as a combination product (see § 3.2(e))
- **Eye drops** administered via droppers are classified as **DDCPs**, due to the dropper's role in determining dose delivery.

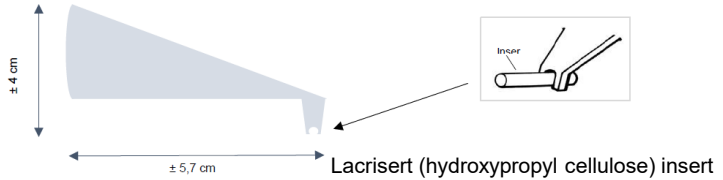
Ophthalmic DDCP Presentations

Dropper /dispenser (most common):

- Prefilled drug delivery device (Type 2 DDCP)
- Single-dose vial with a dropper tip
- Multi-dose bottle with dropper tip

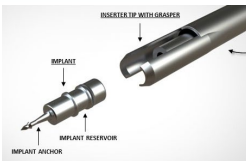
Inserts/implants

- Case-by-case
- Applicator typically serves as device constituent.

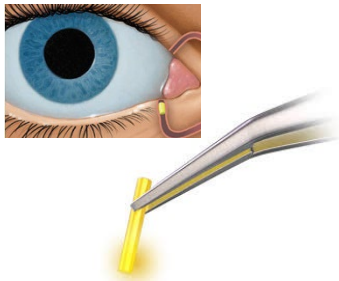


Lacrisert (hydroxypropyl cellulose) insert

Durysta (Bimatoprost) implant



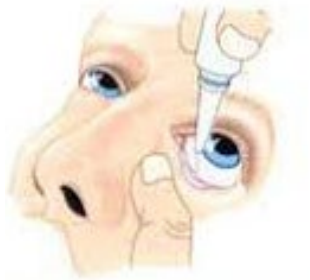
Idose TR (travoprost) intracameral implant



Dextenza (dexamethasone) insert

Non-DDCP Example: Understanding the Distinction

- Example: TobraDex ointment
  - Supplied in a tube with a polyethylene tip and cap
  - A small amount (~1/2 inch) of drug is applied to the "V" pocket between the eyeball and lower lid
  - The tip aids in applying the ointment to the "V" pocket but does not meter the delivered dose
  - The tube, including the tip, functions as a container closure system and not as a device constituent



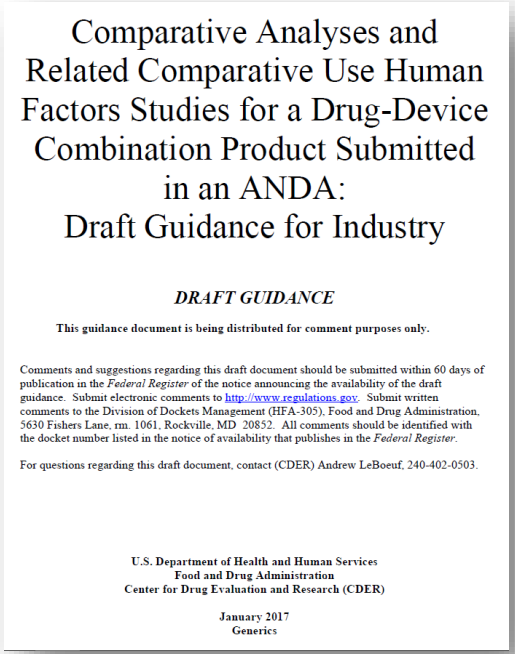
- Important Notes:
  - This example does not mean all ophthalmic ointments are non-DDCP products
  - Submit a controlled correspondence if you need clarification on your product's DDCP classification

Therapeutic Equivalence Framework

- Therapeutic equivalence:
  - A generic drug product must be therapeutically equivalent to its RLD, which means it ". . . can be expected to have the **same clinical effect and safety profile** when administered to patients under the conditions specified in the labeling."
  - Same expectations apply for generic drug-device combination products
  - FDA considers whether end-users can use the generic combination product when it is substituted for the RLD without intervention of a healthcare professional and/or without additional training prior to use of the generic combination product
- Note: Generic and RLD products **do not** need to be identical as long as the differences do not preclude approval under an ANDA

Comparative Analyses (CA) Overview

- ***Physical comparison*** *between RLD and generic device constituent parts:* FDA recommends that the potential applicant of the proposed generic combination product acquire the RLD to examine and compare (e.g., visual and tactile examination) the physical features of the user interfaces of the RLD and proposed generic products.
- ***Comparative task analysis:*** FDA recommends that potential applicants conduct a comparative task analysis between the RLD and the proposed generic combination product.
- ***Labeling comparison:*** FDA recommends a side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD.



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA:
Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Generics

https://www.fda.gov/media/102349/download

Physical Comparison

- Visual, auditory, tactile examination of the physical features of the proposed generic to the RLD.
  - Size, shape, color/transparency, feedback, texture, sound, thickness, font size/shape
- Include all components necessary to delivery drug (e.g., packaging, connectors) and external design features
- Include side-by-side clear, detailed, and color photographs.
- Clearly identify, characterize, and provide justification for differences noted.

Comparative Task Analysis

- Analyze and compare step-by-step use processes
  - Identify steps that end-users need to perform to use the product
    - From opening the packaging to disposing of the product (e.g., disposing of transdermal products)
- Highlight differences in tasks that arise due to difference in user interface design. Note if differences may impact an existing critical task or give rise to a new critical task.
- Clearly identify, characterize, and provide justification for differences noted.
- Task comparison should be focused on tasks rather than labeling.

Labeling Comparison

- Use current version of RLD label
  - For Pre-ANDA CA evaluations:
    - Focuses on the instructions for use (IFU).
  - For the ANDA:
    - Side-by-side, line-by-line, figure-by-figure comparison of all labeling components
- Generic product labeling should be the same as that of the RLD, except for permissible differences described at 21 CFR 314.94(a)(8)(iv).
- Permissible differences in user interface generally fall within the scope of permissible differences in labeling.

Outcomes from CA

Each comparison has an outcome:

- **No Design Difference**
- **Minor Design Difference:**
  - If the difference in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD do not affect an external critical design attribute.
- **Other Design Difference:**
  - If any aspect of the comparative analyses suggests that difference in the design of the user interface of a proposed combination product as compared to the RLD may impact an external critical design attribute that involves administration of the product.
- Consider any identified differences in the **context of the overall risk profile** of the product.

Addressing "Other" Design Differences

When other design differences are identified and need more evidence rather than justification:

- Consider **modifying design** of user interface to minimize differences
- Provide **additional data/information** such as:
  - A comparative use human factors study, an in vitro study, published literature, or alternative approaches.
  - Type of information/data will depend on the differences and risks being considered.
  - Information should support/justify that the difference will not alter overall risk profile when generic substitution occurs.
  - Recommend to contact FDA via Pre-ANDA communication meeting.

Considerations for Assessing Differences

- **Context of Use:**
  - **Urgency:** Emergency vs. routine use
  - **Frequency:** Single vs. repeated use
  - **Users:** Patients, caregivers, healthcare providers / Adults, pediatrics
  - **Environment:** Clinical vs. home use
- **Patient Population Factors:**
  - Dexterity limitations (i.e., range of motion, fine motor coordination)
  - Age-related considerations
  - Cognitive capabilities
  - Disease-specific impairments

Comparative Analyses: Best Practices

- Identify ALL user interface differences
- Classify ALL differences based on definitions in the guidance
- Provide clear justification for differences identified.
- Focus on potential differences in the critical tasks between the RLD and proposed generic drug-device combination products
  - Remember that **not every task is a critical task**
- Consider the product and its **context of use**
  - Same difference could be classified and assessed differently
  - Focus on individual RLD

Product-Specific Guidance Resources

- **FDA Product-Specific Guidances (PSGs):**
  - Current Agency thinking on generic development
  - RLD device characteristics to examine
  - Specific recommendations for complex products
- **Available Resources:**
  - Searchable database at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
  - Regular updates reflecting current science

Bimatoprost ophthalmic implant, NDA211911, PSG recommended May 2023

Additional information:

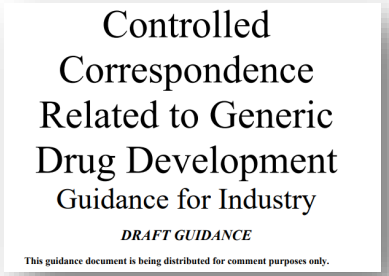
Device:
The reference listed drug (RLD) is presented as a preloaded, biodegradable, single-dose implant in a sterile, single-use applicator. The implant and the applicator are the device constituent parts. FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the Test (T) devices including:

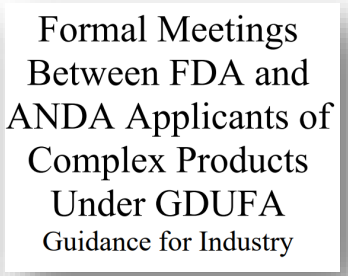
- Size of the biodegradable implant
- Preloaded, sterile, single-use applicator
- Needle features: silicone coating, gauge, and length
- Implant retention mechanism

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Pre-ANDA Program

- Goal is to clarify regulatory expectations for prospective applicants early in product development, assist applicants in developing more complete submissions, promote a more efficient and effective ANDA assessment process, and reduce the number of assessment cycles required to obtain ANDA approval.
- Potential applicants developing a complex DDCP are encouraged to submit CA and/or specific questions to FDA for review in Pre-ANDA Program.





Key Takeaways and Best Practices

- Success Strategies:
  - Start user interface assessment using CA early in development
  - Minimize differences when possible
  - Document thoroughly with clear justification / scientific evidence
  - Engage FDA early through Pre-ANDA programs (CC, pre-ANDA meeting)
- Remember:
  - Generic DDCPs are **not required to be identical** in user interface design to the RLD. FDA has accepted design differences in the user interface after being assessed to have no difference in clinical effect and safety profile from the RLD when used in accordance with the labeling.

Please contact shinae.kim@fda.hhs.gov with any questions. Thank you.