Comparing Device User Interfaces and Seeking Advice in the Pre-ANDA Period

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Learning Objectives

- Discuss how to seek advice regarding generic combination products.
- Understand principles for conducting comparative analyses.
- Identify factors that inform categorization of user interface differences.

Drug-Device Combination Product

- Defined in 21 CFR 3.2(e)
- Drug constituent part and device constituent part(s).
  - CDER regulates when drug product is primary mode of action
- Drug and device constituent parts may be integrated, co-packaged, or cross-labeled.
- For ANDAs, combination products have simple or complex device constituents.

Development of Complex Generic Products

Complex products are:

1. Products with complex active ingredients, formulations, routes of delivery, or dosage forms.

2. Complex drug-device combination products.

3. Other products where complexity or uncertainty would benefit from early scientific engagement.

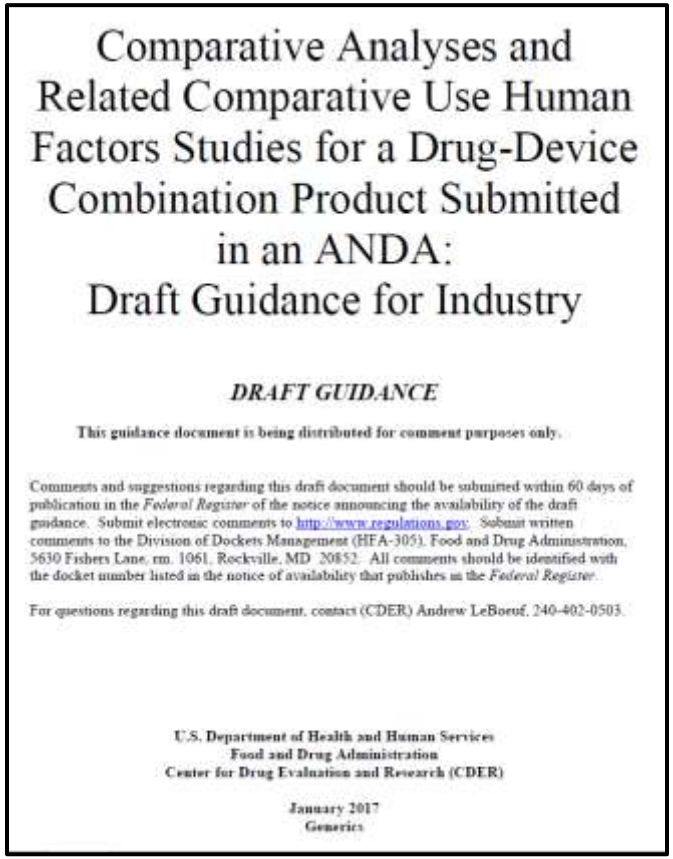
Therapeutic Equivalence and Generic Substitutability

- Generic product expected to have the same clinical effect and same safety profile as RLD when administered to patients under the use conditions specified in the labeling.
- Generic product does not need to be identical to its RLD in all respects.

Generic Combination Product Substitutability

- User Interface:
  - Includes all components of the product with which a user interacts:
    - Delivery device constituent of combination product
    - Any associated controls and displays
    - Product labeling and packaging
- Similarity of proposed generic and RLD device user interfaces evaluated through comparative analyses.

Draft Comparative Analyses Guidance



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Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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.

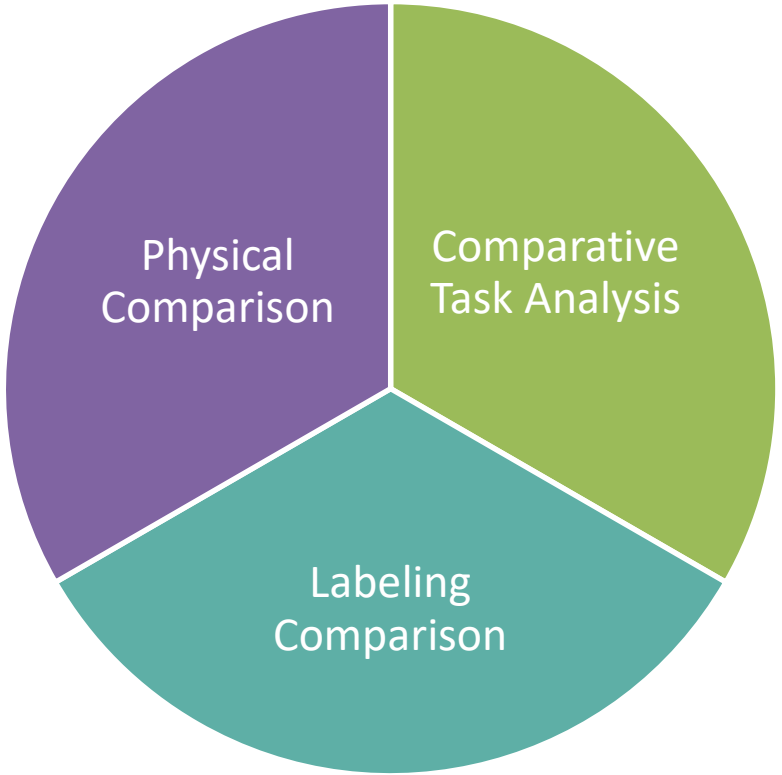
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

Access at:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/comparative-analyses-and-related-comparative-use-human-factors-studies-drug-device-combination

Comparative Analyses (CA)

- Tool for comparative device user interface evaluation
- Three analyses for comparing device user interface of the proposed generic combination product to the user interface of the RLD.



Getting Pre-ANDA Feedback: Device Evaluation

1. Controlled Correspondence

- To seek information about a specific element of product development
- Standard (Level 1 under GDUFA III): 60 calendar day review timeline
- Complex (Level 2 under GDUFA III): 120 calendar day review timeline

2. Product Development Meeting

- To discuss specific scientific issues or questions that involve multiple disciplines
- 120 calendar day review timeline
- Generally available for complex products

Pre-ANDA Device User Interface Assessment

- FDA provides feedback about whether:
  - A proposed device may be appropriate for an ANDA submission referencing a particular reference listed drug (RLD).
  - There are user interface differences that may require justification with additional data/information (“other design differences”).
- FDA may request clarification through an information request.

Device Evaluation Submission Materials

- 3 to 5 samples of proposed generic.
  - State if device is prototype
  - Identify planned differences for to-be-marketed version
- At least 1 sample of the reference listed drug (RLD).
- Comprehensive comparative analyses (CA) report.
- Specific questions about the CA that you want answered

CA: 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
- External design mechanisms and features.
- Clearly identify, characterize, and provide justification for differences noted.

CA: Comparative Task Analysis

Analyze and compare step-by-step processes for drug administration.

1. Identify steps that end-users need to perform to use the product.
2. Note and analyze any differences.
3. Task comparison should be focused on device tasks rather than labeling.

Example Comparative Task Analysis.

RLD Tasks	T device as compared to RLD
Priming the inhaler: 1. Remove inhaler from its package 2. Remove the dust cap from the mouthpiece 3. Check that the dose counter shows a black dot in the window	**Minor difference** *T device shows a "black star" in dose counter prior to priming, not black dot.* *Difference is not expected to impact user's ability to execute priming task or to understand when priming has occurred.*

CA: Labeling Comparison

- For the ANDA:
  - Side-by-side, line-by-line, figure-by-figure comparison of all labeling components
- For Pre-ANDA device evaluations:
  - Focuses on the instructions for use (IFU).
- 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).
- Labeling differences that stem from permissible differences in design between the user interface for the proposed generic combination product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA.

Outcomes from CA

- Each comparison has an outcome:
  - No Difference
  - Minor Design Difference
  - Other Design Difference
- Consider any identified differences in the context of the *overall risk profile* of the product.

Challenge Question #1

Which of the following statements is NOT true?

A. Generic combination products must be identical to the RLD in all respects.

B. Labeling comparisons assessed in pre-ANDA submissions focus on the instructions for use.

C. The device user interface is a consideration for generic substitutability.

D. The device user interface includes all components the end-user interacts with.

Identification of Minor vs. Other Differences

- **Minor** design difference
  - A difference in the user interface of proposed generic product, in comparison to RLD user interface, that does not affect an external critical design attribute.
- **Other** design difference
  - An aspect of the comparative analyses that suggests differences in the design of the user interface of a proposed generic product, as compared to the RLD user interface, may impact an external critical design attribute that involves administration of the product.

Minor Design Differences

- Some examples include, but are not limited to:
  - Differences in color scheme that would not result in confusion
  - Minor differences in dimensions that do not impact end-user use
  - Proposed generic drug name substitution on device in lieu of RLD name
  - Some changes in dose counter font size/style/color and/or background color that do not make reading the dose counter more difficult.
- Assessed on an ANDA-specific basis

Other Design Differences

- Some examples include, but are not limited to:
  - Addition of a new task required to administer the proposed generic
  - Change in cleaning procedure that results in different requirements for disassembly of generic
  - Generic injection pen requires a manual push to deliver the drug, whereas the RLD drug injection has automated drug delivery after pushing the dose button.
- Assessed on an ANDA-specific basis
- “Other” design differences may increase risk to end-user or require additional instruction from health care provider.

Considerations for Assessing Differences

1. Urgency of Use: Emergency vs. Non-Emergency.
2. Frequency of Use: Single vs. Repeat.
3. End-Users: Patient and caregiver groups vs. healthcare providers.
4. Environment of Use: Clinical setting vs. home use.
5. Patient Population: Age, Range of motion, Fine motor coordination.

Consider these factors for <u>all</u> tasks (e.g., priming, cleaning procedures, storage).

Example of End-User Considerations

- Emergency inhalers used by pediatric patients.

vs.

- Maintenance inhaler used by adults.

Options to Address "Other" Design Differences

- Modifying design of user interface to minimize differences
  - Human factors-based risk evaluations should be part of the iterative drug-device combination product development process.
- Provide additional data/information such as:
  - A comparative use human factors (CUHF) study, another type of in vivo study, an in vitro study, or published literature.
  - Information should support/justify that the difference will not alter overall risk profile when generic substitution occurs.
  - Contact FDA via CC/product development meeting prior to conducting CUHF.

Ongoing Research

- Categorization of minor vs. other differences is a research focus
- FDA has funded and collaborated with external researchers to:
  - Support the categorization of differences in the design of the user interface
  - Explore in vitro or in vivo approaches to assess “other design differences” as alternatives to comparative use human factors (CUHF) studies.
- Future research may include conduct of FDA-designed CUHF studies to evaluate certain types of differences and impacts on user error rates.
  - Publication of outcomes will support the generic drug industry in designing CUHF studies.
  - Outcomes may revise FDA’s thinking about whether certain differences are “minor” or “other.”

Challenge Question #2

Which of the following statements is true?

A. Patient and caregivers may be accustomed to navigating differences in user interfaces more so than health care providers.

B. Firms should not communicate with FDA regarding their proposed generic product prior to ANDA submission.

C. Minor design differences are generally acceptable but should be identified and justified in comparative analyses.

D. FDA expects that end users can substitute generic products with additional training from a health care provider.

Summary

- Proposed generic combination product does not need to be identical to RLD in all respects.
- End-use scenario should be considered when assessing design differences as minor vs. other.
- Engage with FDA early to request feedback on the proposed generic combination product user interface.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