Part 2: Comparative Analyses Update

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Learning Objectives

- Review the comparative analyses (CA) process
- Provide key principles for conducting comparative analyses
- Discuss tips for user interface assessment during product development

Generic Drug-Device Combination Products

- **Therapeutic equivalence**

  "**.** . . 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 reference listed drug (RLD) without the intervention of the healthcare professional or without additional training prior to the use of the generic combination product
- Generic and RLD products do not need to be identical as long as the differences do not preclude approval under an abbreviated new drug application (ANDA)

Comparative Analyses Process

Key Players

OGD Division of Therapeutic Performance I (DTP I)

- Lead for pre-ANDA CA assessments

OGD Division of Clinical Review (DCR)

- Lead for ANDA and post-approval CA assessments

OSE Division of Medication Error Prevention and Analysis I and II (DMEPA)

- Lead for CUHF* study and protocol assessments

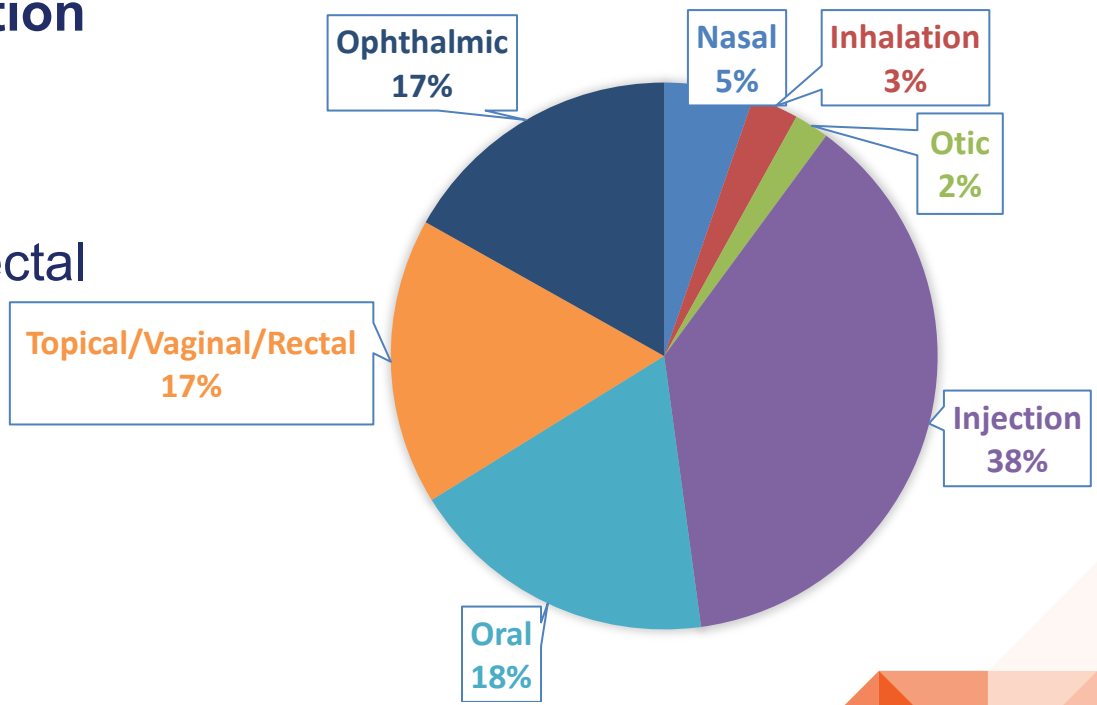
Office of Biostatistics, Division of Biometrics VIII

- Statistical lead for CUHF study assessments

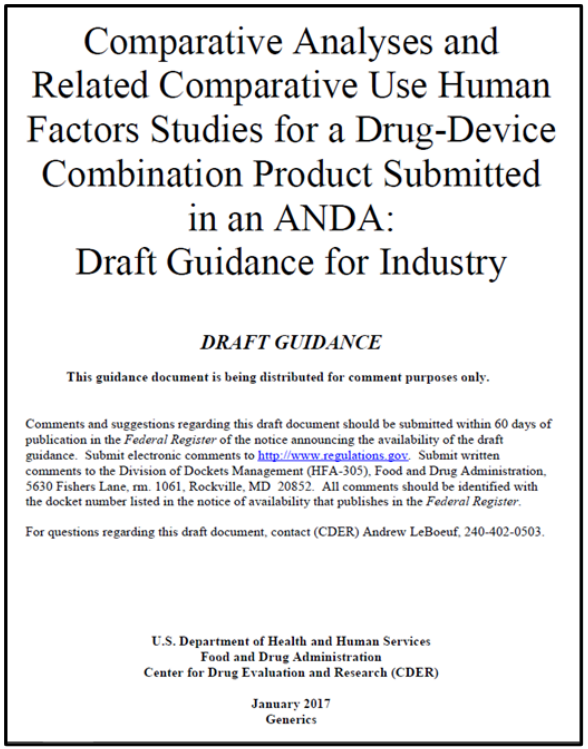
*CUHF-Comparative Use Human Factors

ANDA Submissions with Comparative Analyses

- **Route of Administration**
  - Injection
  - Oral
  - Topical/Vaginal/Rectal
  - Ophthalmic
  - Nasal
  - Inhalation
  - Otic



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Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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

Physical comparison: Visual, auditory, tactile examination of the physical features (size, shape, feedback) of the RLD, compared to those of the delivery device constituent part of the proposed generic combination product

Comparative task analysis: Systematically analyze and compare the sequential activities required for the end-users to use the device and administer the drug product

Labeling comparison: Side-by-side, line-by-line comparison of the relevant sections of the prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD

Key Definitions

User Interface (UI)	• All components of the product with which a user interacts • Includes delivery device constituent part and any associated controls, displays, product labeling, and packaging
Critical Task	• 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	• A feature that directly affects how users perform a critical task that is necessary to use or administer the drug product

Physical Comparison

- Visual, auditory, tactile examination of the physical features of the proposed generic to the RLD

  Example: size, shape, color, resistance, sound

- Include all components necessary to deliver drug

  Example: packaging, connectors

- External design mechanisms and features
- Clearly identify, characterize, and provide justifications for differences noted

Comparative Task Analysis

- Systematically analyze and compare the sequential activities required for the end-users to use the generic drug product, and administer the drug product
- Include all steps which end-users need to perform to use the device

  Example: opening the packaging to disposing of the product

- 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

Labeling Comparison

- Use current version of RLD labeling
- Ensure that labeling, including Instructions for Use (IFU) and images, accurately describe the:
  - Proposed generic combination product
  - All tasks necessary to use the generic combination product
- Generic drug product labeling generally must be the same as the RLD
  - Certain limited exceptions* – evaluated on case-by-case basis
  - Evaluate labeling statements on the container label and carton labeling. These may include important elements that are intended to minimize medication errors or use errors
  - IFU differences, may reflect differences seen in a comparative task analysis

*As per 21 CFR 314.94(a)(8)(iv)

Outcomes from Comparative Analyses

- Each comparison has an outcome:
  - No Difference
  - Minor Design Difference
  - Other Design Difference

No Difference

- Outcome stating that there is no difference
- Provide explanation in the comparative analyses to support your assertion that there are no differences in design of your proposed user interface compared to the user interface of the RLD

Minor Design Difference

- Will not affect an external critical design attribute
  - **Example:** different color of the plunger rod for a prefilled syringe, and the color of the plunger rod is not critical to the correct use of the device
- If the FDA agrees that the design difference is a Minor Design Difference, then it would likely be acceptable

Other Design Difference

- If the design differences may impact an external critical design attribute that involves administration of the product
- When ***other design differences*** are identified, consider:
  - Re-designing the user interface to minimize differences from the RLD
  - Additional information and/or data to support the user interface design difference
    - The type of information/data will depend on the differences and risks being considered

Comparative Analyses Outcomes

- **Most deficiencies communicated and resolved within review cycle**
- **CA outcomes 2018-2023:**
  - 90% adequate
  - 10% “Other design differences-inadequate”

General Recommendations

- Identify and provide adequate justification for **ALL** differences in user interface in comparative analyses
- Focus on potential differences in the critical tasks between the RLD and generic drug-device combination product
- Consider context of use

General Recommendations

- **Context of use**
  - **Urgency of use**: Emergency vs. non-emergency
  - **Frequency of use**: Single use vs. repeat use
  - **End-users**: Lay users (patient and/or caregiver) vs. health care professionals
  - **Environments of use**: Non-clinical (homes, schools) vs. health care/clinical (inpatient hospital, outpatient clinics)
  - **Patient population**: Dexterity issues (rheumatologic or neuromuscular disorder)

Tips for Comparative Analyses

- Design differences are product specific and must be analyzed within the context of **comparison to RLD**
- If **RLD discontinued** and/or unavailable, we recommend submitting a controlled correspondence or pre-ANDA meeting request to discuss an alternative approach with the Agency
- Use the "**to-be-marketed**" generic combination product in comparative analyses

Tips for Comparative Analyses

- Engage early with FDA during product development via controlled correspondence and pre-ANDA processes
- Submit comparative analyses, samples of products, and specific questions in pre-ANDA communications request
- If an "**other design difference**" is present, recommend discussing early with FDA

Tips for Comparative Analyses

- Incorporate recommendations in **Draft Comparative Analyses Guidance** throughout combination product development
- Where able, design the generic product to minimize differences in user interface and critical tasks as compared to the **RLD**
- Perform comparative analyses throughout development program, especially if **changes** are made

Post-Approval Changes and Supplements

- **Change to device constituent part**
  - New oral dosing syringe to replace the approved dropper
  - Change from single dose vial to prefilled syringe
  - Change of the color of the dust cap of the inhalation device to match the revised RLD
- **Change to device constituent labeling**
  - To revise the graphics and the text of the instructions for use to be consistent with RLD updates
  - To represent the revised needle shield without other device changes

General Recommendations- Supplements

- Submit a CA Report with Supplements reflecting changes to the device and device-related labeling
  - Mention the CA report in Cover Letter and/or submitted in Module 5 (preferred)
  - Compare updated drug-device combination product to the RLD
- When in doubt:
  - Submit a CA report with changes
  - Consider Controlled Correspondence

Challenge Question #2

The Physical Comparison includes visual, auditory, tactile examination of the physical features of the proposed product compared to the RLD.

A. True.

B. False

Summary

- Refer to the Draft Comparative Analyses Guidance for recommendations
- All design differences should be identified, adequately analyzed, and scientifically justified
- Engage early with FDA during combination product development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