Best Practices for Conducting Comparative Analyses for Combination Products in ANDAs

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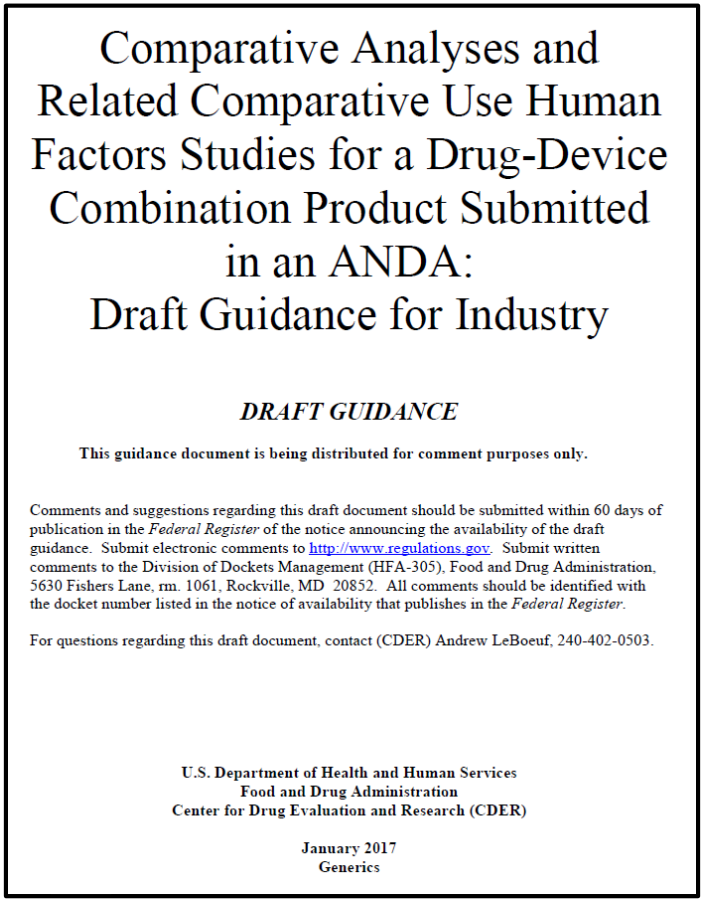
Outline

- Provide recommendations for conducting comparative (threshold) analyses
- Review user-interface considerations for specific categories of drug-device combination products
- Discuss considerations and tips during development of drug-device combination products

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

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Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

Comparative Analyses

1. Labeling Comparison

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

2. 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

3. Comparative Task Analysis

Comparative task analysis is assessed between the RLD and the proposed generic drug-device combination product

Comparative Analyses

- This presentation will focus on best practices in conducting comparative analyses submitted in an ANDA
- Refer to the **Additional Resources** section at the end of this presentation for previous FDA presentations about the guidance including general information

General Recommendations

- Identify and provide adequate justification for **ALL** user interface differences in comparative analyses
- Focus on potential differences in external critical design attributes and the critical tasks between the RLD and generic drug-device combination product
- Consider context of use, end-users, environments of use, patient population
  - Context of use: emergency vs. non-emergency
  - 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) or incapacitated (naloxone hydrochloride)

General Recommendations

- Consider and include all components with which end-users interact when conducting comparative analyses
  1. Labeling Comparison
     - Full prescribing information, Instructions for Use, and descriptions of the delivery device
  2. Physical Comparison
     - Integrated device and/or supplied dispensing devices, disposal units, etc.
  3. Comparative Task Analysis
     - All steps that need to be performed starting from opening the packaging to disposing of the product

General Recommendations

- Design differences are product specific and must be analyzed within the context of **comparison to RLD**

  Example: color change of specific part
- Use to-be-marketed generic combination product in comparative analyses
- Ensure samples of generic combination product and RLD provided to FDA match those products depicted in comparative analyses
- Submit comparative analyses report in Section 5.3.5.4 of Original ANDA submission

Recommendations for Conducting Comparative (Threshold) Analyses

Labeling Comparison

- Use current version of RLD label in comparative analyses
- Ensure that labeling, including Instructions for Use and images, accurately describes proposed generic combination product
- Verify that labeling, including Instructions for Use, accurately describes all tasks necessary for proposed product

Labeling Comparison

- Generic drug product labeling generally must be the same as the RLD
  - Certain limited exceptions* – evaluated on case by case basis
  - Note: changes in labeling such as “think alternative way is better” is unlikely to be adequate justification
- All differences in labeling comparison should be identified and adequate justification should be provided in comparative analyses

Why?

>50% of comparative analyses that were assessed as “not acceptable” contained deficiencies related to labeling comparison

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

Physical Comparison

- Include visual, auditory, tactile examination of the physical features of the RLD

  Example: size, shape, color, texture, resistance, weight, thickness, sound

- Compare them to those of the delivery device constituent part for the proposed generic combination product
- Components with which end-users **do not** interact **should not** be included in physical comparison
  - Example: internal design mechanism

Physical Comparison

- Provide information comparing physical features of the RLD to those of the delivery device constituent part of the proposed generic combination product

  Example: Include clear, detailed, and color photographs

- Identify and provide adequate justification for all differences in delivery device constituent parts

Why?

>70% of all comparative analyses that were assessed as “not acceptable” contained deficiencies related to differences in physical comparison

Comparative Task Analysis

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

  Example: opening the packaging to disposing of the product

- Critical tasks may be considered as:
  - For example, 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

User-Interface Considerations for Specific Categories of Drug-Device Combination Products

Combination Products

- Examples of categories of drug-device combination products
  - Oral
  - Transdermal
  - Injectable
  - Inhaled
- Engage early with FDA during product development via controlled correspondence and pre-ANDA processes

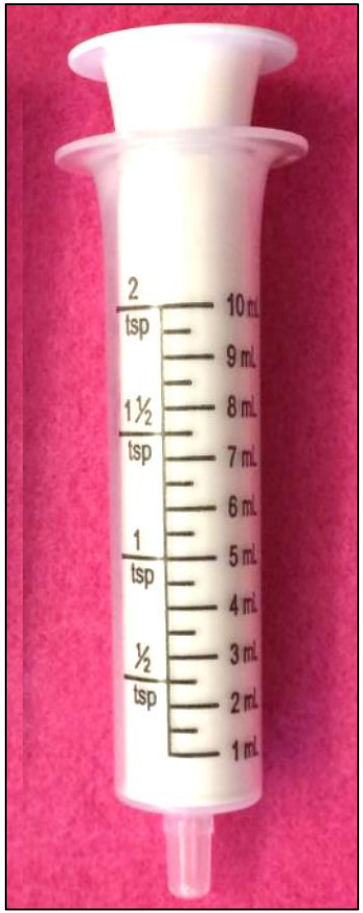
Oral Combination Products

- *Examples: co-packaged dosing cups, oral syringes, and oral droppers*
- Consider minimizing differences from RLD in dispensing devices
  - Remove extraneous markings (measurements)
  - Ensure correct orientation of markings
  - Remove trailing zeros
  - Ensure dispensing device can measure exact dose(s) that are recommended in label

Incorrect Orientation

Note: Instructions for Use for RLD directs end-users to invert bottle to withdraw the dose

*Depictions are hypothetical and for illustrative purposes only



Extraneous Markings

Note: Syringe contains measure markings that are not referred to in the RLD's labeled dosage directions

*Depictions are hypothetical and for illustrative purposes only

Oral Combination Products

- Ensure sample dispensing devices provided to FDA match those products used in comparative analyses
- Guidance for Industry: Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (May 2011)

Why?

>45% of comparative analyses for oral drug-device combination products submitted in an ANDA were assessed as “not acceptable”

Transdermal Combination Products

- *Examples: patches and films*
- Consider minimizing differences from RLD in:
  - size and shape of transdermal combination product
  - imprinted label on transdermal combination product
- Include disposal unit (if applicable) in comparative analyses

Injectable Combination Products

- *Examples: prefilled syringes, injection kits, and autoinjectors*
- Consider context of use, end-users, environments of use, patient population
- Design the user interface to minimize differences from the RLD
  - Needles, safety devices, connectors

Inhaled Combination Products

- *Examples: metered dose inhalers and dry powder inhalers*
- Context of use: rescue vs. controller
- Avoid adding new critical tasks or design features not present in the RLD

Considerations and Tips During Development of Drug-Device Combination Products

Tips for Combination Product Development

- 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
- Early and frequent communication with FDA is highly encouraged through:
  - Controlled correspondence
  - Pre-ANDA meeting request

Tips for Combination Product Development

- 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
  - Include your proposal of additional information or data to assess the acceptability of differences identified in the user interface
  - Submit specific questions with your proposal

Summary

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

Additional Resources

- Witzmann, Kimberly. “Comparative Analysis: Device and User Interface Considerations” CDER Small Business & Industry Assistance (SBIA) REdl Complex Generic Drug Product Development Workshop. College Park, MD. September 26, 2019. PowerPoint presentation. Retrieved from https://sbiaevents.com/cgp2019/

- Bercu, Lisa. “Overview of Drug-Device Combination and What Constitutes Complex Drug-Device Combination” CDER Small Business & Industry Assistance (SBIA) REdl Complex Generic Drug Product Development Workshop. College Park, MD. September 26, 2019. PowerPoint presentation. Retrieved from https://sbiaevents.com/cgp2019/

Additional Resources (continued)

- Lin, Michelle. “Overview of Comparative Analyses (Clinical Perspective)” CDER Small Business & Industry Assistance (SBIA) REdl Complex Generic Drug Product Development Workshop. College Park, MD. September 26, 2019. PowerPoint presentation. Retrieved from https://sbiaevents.com/cgp2019/

- Fine, Andrew. “Comparative Analyses: Focus on Injectable Drug-Device Combination Products ” CDER Small Business & Industry Assistance (SBIA) REdl Complex Generic Drug Product Development Workshop. College Park, MD. September 26, 2019. PowerPoint presentation. Retrieved from https://sbiaevents.com/cgp2019/

Additional Resources (continued)

- LeBoeuf, Andrew and Kimberly Witzmann. “Developing generic drug-device combination products: Regulatory considerations for user-interface and the role of comparative analyses” CDER Small Business & Industry Assistance (SBIA) REdl Complex Generic Drug Product Development Workshop. White Oak, MD. September 13, 2018. PowerPoint presentation. Retrieved from https://sbiaevents.com/complex-generics-2018/

- U.S. Department of Health and Human Services. Food and Drug Administration. Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry. January 2017. Retrieved from https://www.fda.gov/media/102349/download

Additional Resources (continued)

- U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors. April 2016. Retrieved from https://www.fda.gov/media/84903/download

- U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry: Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products. May 2011. Retrieved from https://www.fda.gov/media/78087/download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