Best Practices for Conducting Comparative Analyses in ANDAs

Andrew J. Fine, PharmD, BCPS
Commander, U.S. Public Health Service
Senior Advisor
Division of Clinical Review, Office of Safety & Clinical Evaluation
Office of Generic Drugs
CDER | U.S. FDA

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Provide key principles for conducting comparative analyses
- Review user-interface considerations for specific categories of products
- Discuss tips for user interface assessment during product development

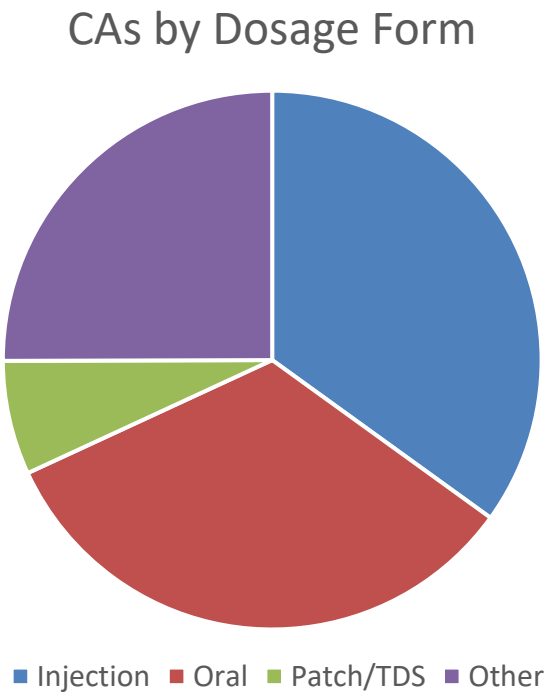
Comparative Analyses in ANDAs

- **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 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)

Regulatory Framework

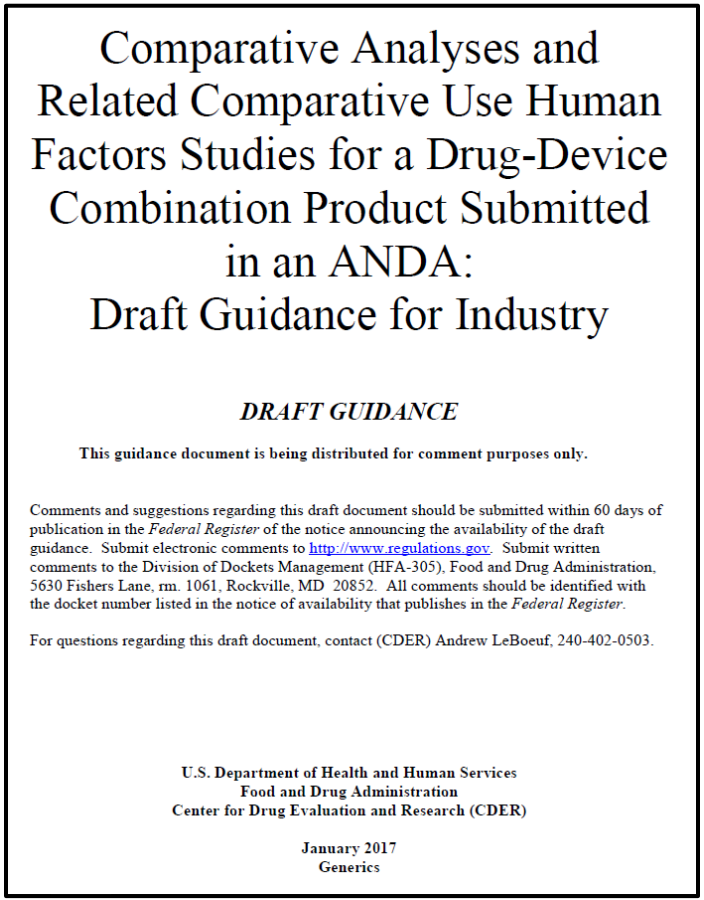
- Comparison of the proposed user interface of the generic drug-device combination product compared to the user interface of the RLD.
- All relevant determinations of sameness under section 505(j) are made with respect to the RLD.
- When RLD information is unavailable, performing the comparison to the RLD is challenging but still required.

Comparative Analyses (CA) Submitted to OGD Since 2017



- Categories of drug-device combination products
  - Injectable
  - Oral
  - Topical/Transdermal
  - Other

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)

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Generics

Key Definitions

- External critical design attributes:
  - Features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product
- Critical tasks may be considered as:
  - 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

General Recommendations

Consider and include all components with which end-users interact when conducting comparative analyses

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

Physical Comparison

- Include visual, auditory, tactile examination of the physical features of the RLD delivery device constituent part
  - such as size, shape, color, texture, weight, thickness, sound
- Compare features to those of the proposed generic 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 delivery device constituent part of the RLD to those of proposed generic combination product
  - include clear, detailed, and color photographs
- Identify and provide adequate justification for all differences in delivery device constituent parts

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 end-users need to perform to use the drug product

  -From opening the packaging to disposing of the product (e.g., disposing of transdermal products)

Labeling Comparison

- Use current version of RLD label
- Ensure that labeling, including Instructions for Use (IFU) and images, accurately describes proposed generic combination product
- Verify that labeling, including IFU, accurately describes all tasks necessary for proposed product
  - Includes tasks that differ from RLD

Assessment of Identified Differences

Consider any identified differences in the context of the *overall risk profile* of the product

- No Differences
- 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

Assessment of Identified Differences: Considerations

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

Assessment of Identified Differences: Considerations

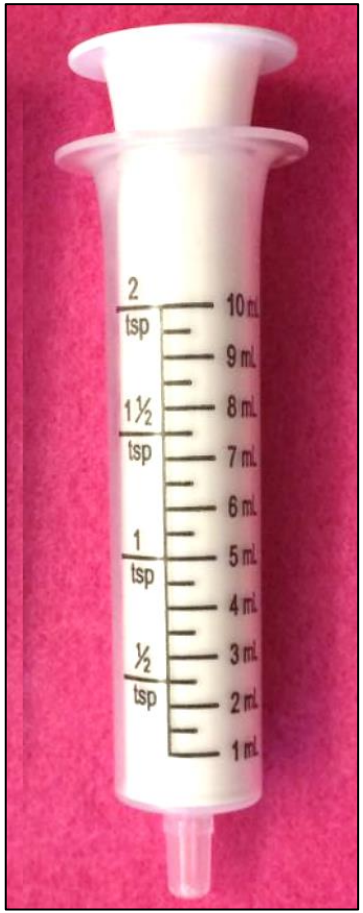
Context of use

- Urgency of use: Emergency vs. non-emergency
- Frequency of use: Single use vs. repeated use
- End-user: Patients, caregivers, healthcare professionals
- Environment of use:
  - Clinical: hospital, clinic
  - Nonclinical: home, school, etc.
- Patient population:
  - Dexterity issues (rheumatologic, neuromuscular disorder)
  - Incapacitated (naloxone HCl)

Common Deficiencies in Oral Dosing Syringe for Drug-device Combination Products

Incorrect Orientation of Dose Marking

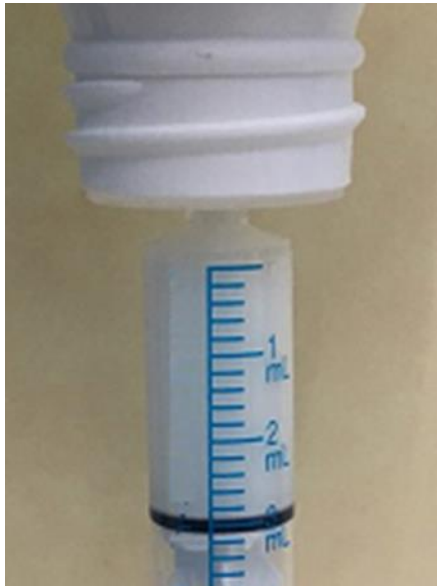
Note: Instructions for Use for RLD directs end-users to invert bottle to withdraw the dose



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



Inadequate Contrast

Note: There should be adequate contrast between the drug product and device

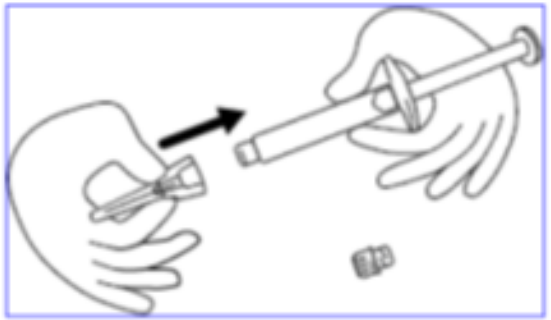
*Depictions are hypothetical and for illustrative purposes only

Avoid Common Deficiencies in Oral Dosing Devices

- *Examples: co-packaged dosing cups, oral syringes, and oral droppers*
- Minimize 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

Complex Issues and Common Deficiencies with Injectable Products

Prefilled Syringes



- Healthcare or patient administered
- Multiple routes of administration
  - SQ, IV, IM, Other
- Preassembled with needle or user must attach needle
- RLD is also prefilled syringe or ampule vial for injection
- Usually least complicated injectable combination product

Injection Kits

- Usually healthcare professional administered
- Assembly and reconstitution often required by healthcare professional
- Emergency or non-emergency use

Prefilled Syringe Case Study

- Prefilled syringe for emergency use
- After connecting needle, self-injected by patient
- Applicant proposes needle safety guard not present in RLD
- ***Other design difference***: may potentially affect an external critical design attribute that involves administration (clinical use and performance) when substituted for the RLD

RLD

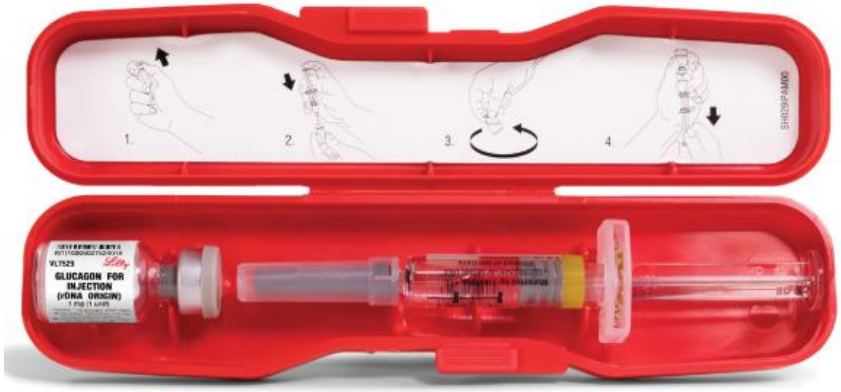
Generic (hypothetical)

https://www.bd.com/en-us/offerings/capabilities/syringes-and-needles/safety-syringes-and-needles/safety-needles/bd-eclipse-needle

Injection Kit Case Study

- Emergency use product, administered by patient or caregiver
- Critical Tasks:
  - Remove needle cover
  - Insert needle into vial
  - Remove needle, reconstitute solution
  - Insert same syringe to withdraw liquid

RLD Injection Kit



- ***Other Design Difference:*** Difference in external critical design attributes impacting a critical task (e.g., significantly shorter plunger length may make it be more difficult to grasp flange to withdraw drug prior to injection)

https://www.lillyglucagon.com/taking-glucagon/glucagon-kits-for-emergencies

Other Common Deficiencies (Injectable products)

- Instructions for use (labeling) does not accurately represent proposed test product
- Images in labeling do not accurately represent proposed test product
- Dose/measurement markings don’t correspond to dose recommended in prescribing information

Comparative Analyses Tips

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 “to-be-marketed” generic combination product in comparative analyses

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

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
  - 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

Challenge Question #1

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

A. True

B. False

Challenge Question #2

When assessing differences between your proposed product and the RLD, Applicants should consider the context of use that includes:

A. Urgency of use
B. Frequency of use
C. Environment of use
D. Patient population
E. All of the above

Summary

- Refer to the Draft Comparative Analyses Guidance for recommendations
- All design differences should be identified, adequately analyzed, and scientifically justified
- Focus on potential differences in the critical tasks between the RLD and generic combination product
- Consider context of use of the product
- Engage early with FDA during combination product development
- Submit controlled correspondence for product development specific questions (refer to Guidance)
- Proposed complex products may be eligible for FDA advice via pre-ANDA meetings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