Approach to a Comparative Analysis When the RLD is Unavailable

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day (1), Session (2): (Drug-Device Combination Products with a Focus on Devices)

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Learning Objectives

- ***Review the importance of comparing a proposed product to the Reference Listed Drug (RLD)***
- ***Discuss the general approach to conducting Comparative Analyses when the RLD is not available***
- ***Review an example of how to approach Comparative Analyses with a discontinued RLD***

Generic Drug Products

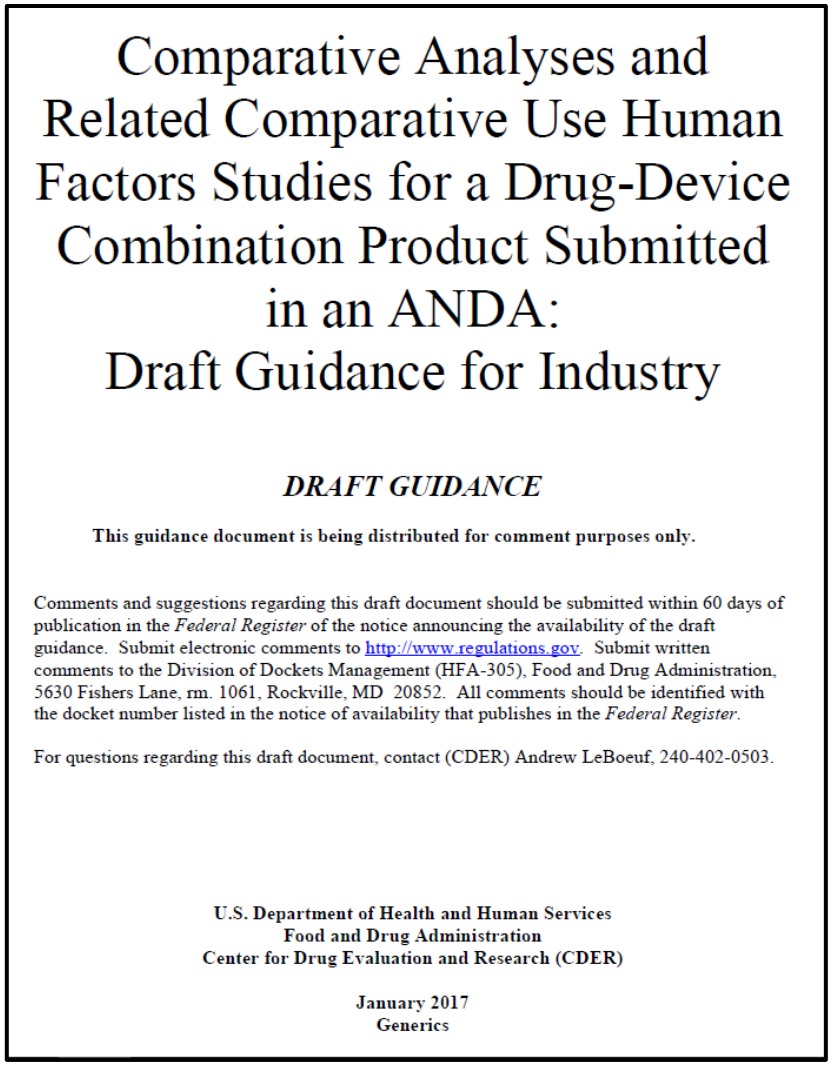
- **Therapeutic equivalence**
  "*. . .* can be expected to have the *same clinical effect and safety profile* when administered to patients under the *conditions specified in the labeling.*"
- **Same expectations** apply for generic drug-device combination products
  - FDA considers whether end-users can use the generic combination product when it is substituted for the reference listed drug (RLD) without the intervention of the healthcare professional 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)

FDA Draft Guidance "Comparative Analyses and Related Coparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA"
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/comparative-analyses-and-related-comparative-use-human-factors-studies-drug-device-combination

Conducting Comparative Analyses

- Compare the proposed user interface of the generic drug-device combination product to the user interface of the **RLD**
- When RLD information is unavailable, performing the comparison to the **RLD** is challenging but still required

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Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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

Challenges When RLD is Unavailable

- Labeling Comparison
  - RLD was discontinued many years ago, no IFU
- Physical Comparison
  - Discontinued, no samples available
- Comparative Task Analysis
  - Proposed container closure is different than RLD

Approach to Conducting Comparative Analyses

Comparative Analyses

Identify and provide an adequate justification for all differences regarding the:

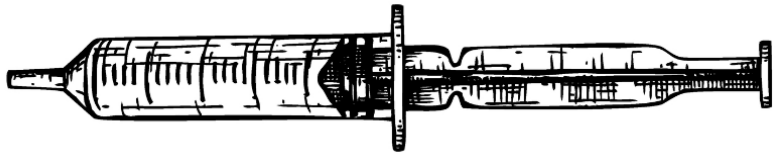
- Labeling Comparison
  - Side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD
- Physical Comparison
  - Visual, auditory, tactile examination of the physical 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
  - Comparative task analysis is assessed between the RLD and the proposed generic drug-device combination product

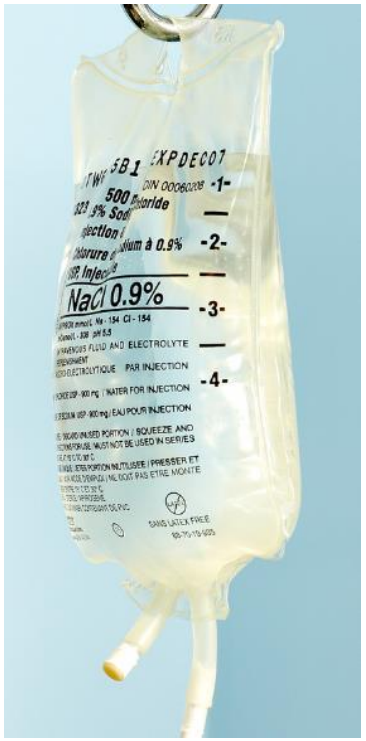
Labeling Comparison

- Use current version of RLD label
- Labeling comparison should focus on instructions for use (IFU) and sections related to user interface.
  - Drugs@FDA
  - If RLD labeling cannot be located, submitting a controlled correspondence (CC) is another option
  - All approved RLD labeling is available from FDA's Division of Freedom of Information

Physical Comparison

- Information from labelling
  - Images or sketches
  - Physical descriptions
- Documents supporting RLD approval
- Promotional Materials from RLD Sponsor*
- General knowledge of common container closures





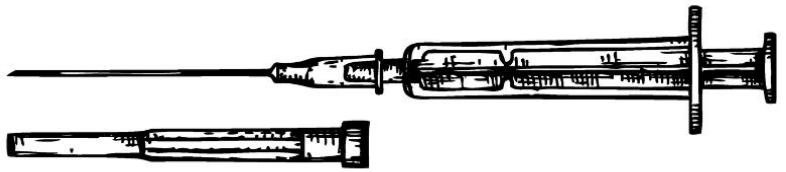
*must be for the U.S. marketed product

Comparative Task Analysis

- Most tasks can be determined from
  - Overall container closure
    - E.g., general knowledge of a glass vial or oral dosing syringe/cup
  - Additional details of container closure description in the RLD label
    - E.g., presence of a dust cap
- If the proposed container closure is different from the RLD, tasks described should reflect those differences.

Supportive Information

- The primary comparison must be conducted between the proposed generic product and its **RLD**
- Currently marketed products may be used as supportive information
  - E.g., RLD was a single dose glass vial, proposed and all other approved and marketed products are single dose prefilled syringes



Atrovent (ipratropium bromide) Nasal Solution 0.03%

Example

Atrovent (ipratropium bromide) Nasal Solution 0.03%

- Approved 10/20/1995
- Indicated for symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children, 6 years and older.
- Discontinued in 2018, not for reasons of safety or effectiveness

Labeling Comparison

- Label available at Drugs@FDA

Supplements

CSV | Excel | Print

Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
05/11/2015	SUPPL-14	Manufacturing (CMC)		Label is not available on this site.
01/05/2015	SUPPL-13	Manufacturing (CMC)		Label is not available on this site.
02/02/2011	SUPPL-11	Labeling-Package Insert	Letter (PDF)	Label is not available on this site.
12/04/2007	SUPPL-7	Labeling	Label (PDF) Letter (PDF)	
05/23/2003	SUPPL-4	Labeling	Label (PDF) Letter (PDF)	
01/27/2000	SUPPL-2	Manufacturing (CMC)		Label is not available on this site.
08/18/1999	SUPPL-3	Manufacturing (CMC)-Control		Label is not available on this site.
04/01/1998	SUPPL-1	Efficacy-New Indication	Letter (PDF)	Label is not available on this site.

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Labels for NDA 020393

Labeling Comparison

- Full product labeling available on Drugs@FDA, dated 12/4/2007
- Labeling Supplement 11 dated 2/2/2011
- All updates after the latest provided label are included in the Supplement 11 letter
  - Can be noted in the comparative analyses review

Physical Comparison

- Off market for about 4 years
- Physical samples are difficult to obtain
- Information from the labeling:
  - No actual images in label
  - Physical description in the “How Supplied” Section
  - IFU

Physical Comparison

- How Supplied

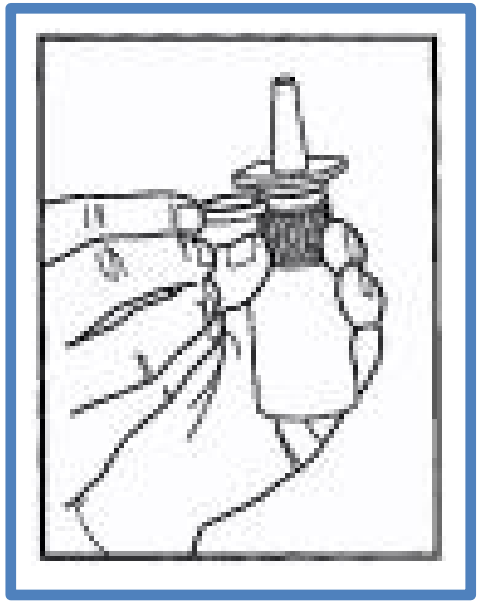
Atrovent® (ipratropium bromide) Nasal Spray 0.03% is supplied in a white high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a green safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains 31.1 g of product formulation, 345 sprays, each delivering 21 mcg of ipratropium bromide per spray (70 µL), or 28 days of therapy at the maximum recommended dose (two sprays per nostril three times a day) (NDC 0597-0081-30).

- IFU

To Use:

1. Remove the clear plastic dust cap and the green safety clip from the nasal spray pump (Figure 1). The safety clip prevents the accidental discharge of the spray in your pocket or purse.

Figure 1



Task Comparison

- Standard nasal spray bottle design
  - "How Supplied" section provides a description
  - IFU sketched images provide overall appearance
- IFU outlines steps to use bottle

Supportive Information

- Six currently marketed ipratropium bromide nasal spray products in Orange Book
  - Examine for IFU, common physical features, etc.

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	A076156	SPRAY, METERED	NASAL	0.021MG/SPRAY	AB			APOTEX INC
RX	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	A076025	SPRAY, METERED	NASAL	0.021MG/SPRAY	AB			BAUSCH HEALTH US LLC
RX	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	A076664	SPRAY, METERED	NASAL	0.021MG/SPRAY	AB		RS	HIKMA PHARMACEUTICALS USA INC
RX	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	A076155	SPRAY, METERED	NASAL	0.042MG/SPRAY	AB			APOTEX INC
RX	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	A076103	SPRAY, METERED	NASAL	0.042MG/SPRAY	AB			BAUSCH HEALTH US LLC
RX	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	A076598	SPRAY, METERED	NASAL	0.042MG/SPRAY	AB		RS	HIKMA PHARMACEUTICALS USA INC

Summary

- All Comparative Analyses must compare the proposed generic product to the RLD
- When RLD samples cannot be obtained, use all available information including:
  - RLD label
  - RLD descriptions from approval package
  - General knowledge of common container closures such as glass vials and nasal spray bottles

Challenge Questions

Question #1

True or False?

Proposed Drug/Device Combination Product X is a prefilled syringe. The RLD, a glass vial, was discontinued 20 years ago. The Comparative Analyses must be conducted using the current RS, a prefilled syringe.

False

Question #2

True or False?

Many of the tasks to use a device can often be determined from the RLD description, images in the RLD IFU, and images or descriptions in the documents to support RLD approval.

True

On Your Next Comparative Analyses

- Compare the proposed product with the RLD for all three parts of the Comparative Analysis (Labeling, Physical, and Task Analysis)
- Use all available public information to find descriptions, sketches, and images to inform your analysis
- Where able, design the generic product to minimize differences in user interface and critical tasks as compared to the RLD
- Engage early with FDA during product development via controlled correspondence and pre-ANDA pathways for further guidance if necessary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