# Overview of Regulatory and User-Interface Considerations, and the Role of Comparative Analyses, in Developing a Generic Drug-Device Combination Product in an ANDA

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# Disclaimer

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

# Outline

- General Overview of Combination Products
- Regulatory Considerations for Drug-Device Combination Products Submitted in an ANDA
- Comparative Analyses for a Drug-Device Combination Product Submitted in an ANDA
- ANDA Considerations for OINDPs
- Product Development Considerations for OINDPs

# What is a combination product?

- A “combination product” is:
  - A product comprised of two or more different types of medical products (e.g., drug and device, drug and biological product, device and biological product, or all three together)

# What is a combination product?

- Combination products are not a “drug”, a “device”, or a “biological product.” They are their own, distinct type of product
- Combination products are subject to multiple sets of regulatory requirements (e.g., cGMPs, post-market safety reporting)
- Combination products are assigned to a “Lead Center” having primary responsibility for their review
- Coordination between Centers is important to effective, efficient, consistent regulation of combination products

# Types of combination products

## Types of Combination Products

| | "Single-entity" | "Co-packaged" |
|---|---|---|
| **Description** | Chemically or physically combined constituent parts | Constituent parts packaged together |
| **Examples** | • Drug-eluting stent<br>• Prefilled syringe<br>• Transdermal patch<br>• Bone void fillers with drugs | • First-aid or surgical kit<br>• Syringe packaged with vial of drug<br>• Drug + prefilled diluent, reconstitution/ transfer device, fillable cartridge and wearable patch |
| **Reference** | 21 CFR 3.2(e)(1) | 21 CFR 3.2(e)(2) |

# Types of combination products

- There is another type of combination product, which includes constituent parts that are packaged separately, but specifically labeled for use with one another to achieve the intended therapeutic effect

# What is not a combination product?

- A combination product is not:
  - A product comprised of only two or more of the *same* type of medical product
  - A medical product combined only with a non-medical product (e.g., drug product co-packaged with food product)
- Examples:
  - Drugs combined only with each other, such as fixed dose combination drugs
  - Kits of just devices, just drugs, or just biological products

# Primary Mode of Action

- Combination products have multiple “modes of action” (see 21 CFR 3.2(k))
- There are three potential modes of action for a combination product:
  - Drug
  - Device
  - Biological product

# Primary Mode of Action

- Combination products are assigned to a “Lead Center” having primary responsibility for their review
  - Will consult with non-Lead Center via Inter-Center Consult process, where appropriate

- Lead Center is based on:
  - The “primary mode of action” (PMOA): Constituent that provides the greatest contribution to the product’s intended effects

# Combination Products Submitted in ANDAs

# General Framework for ANDAs

- Approval of generic drug starts with a listed drug – generally an innovator product approved under 505(c)
- ANDA relies on FDA's finding of safety and effectiveness for listed drug
- Requires demonstration of "sameness" of a number of characteristics + additional information to permit reliance on the reference listed drug (RLD)
- In the context of combination products, applicants should generally seek approval of a presentation approved for the RLD

# NDA vs. ANDA Review Process

**Brand Name Drug**

**NDA Requirements**

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Animal Studies
7. Clinical Studies
8. Bioavailability

**Generic Drug**

**ANDA Requirements**

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Bioequivalence

# Generic Drug Product Substitutability

In relation to the RLD, generic products are expected to be:

- **Pharmaceutically Equivalent**

  The same active ingredient, dosage form, strength, route of administration and meet the same compendial standards (strength, quality, purity, and identity)

- **Bioequivalent**

  No significant difference in the rate and extent of absorption of the active ingredient at the site of action

- **Therapeutically Equivalent**

  Approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

# Historical Policy

## Citizen Petitions

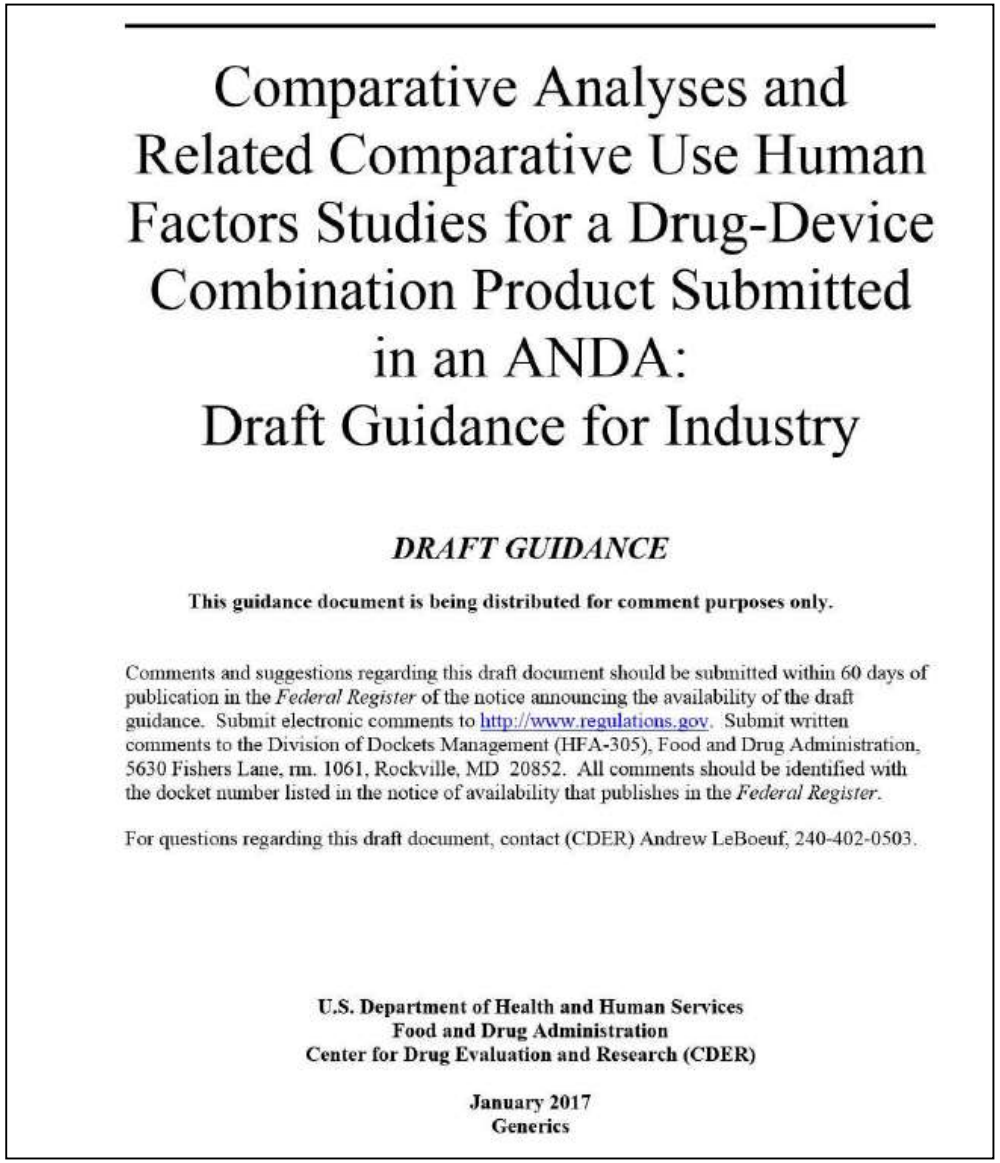
- FDA Response to King Pharmaceuticals (Jul. 29, 2009) (Docket No. FDA-2007-P-0128/Docket No. FDA-2009-P-0040)
  - Auto-injectors/Imitrex (Sumatriptan succinate)

- FDA Response to Dey Pharma L.P. (May 27, 2010) (Docket No. FDA-2009-P-0578)
  - EpiPen/Emergency-use auto-injectors

# General Principles

- Considerations include, but are not limited to:
  - Performance characteristics
    - Review of a generic combination product is informed by the general framework for ANDAs, but also takes into consideration the performance of the device constituent and its interaction and impact on the delivery of  the drug constituent
  - User Interface

# 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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# Draft Guidance – Key Takeaways

- FDA does not expect that the design of the user interface for a generic drug-device combination product be identical to the design of the user interface for its RLD
- Differences in the design of the user interface should be adequately analyzed, scientifically justified, and not otherwise preclude approval under an ANDA
- FDA intends to assess whether an end-user can use the generic combination product when it is substituted for the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product

# Draft Guidance – Key Takeaways

- Certain labeling differences to reflect differences in design of a proposed generic drug-device combination product may be permitted and will be evaluated on a case-by-case basis
- Baseline assessment for any identified differences occurs during comparative analyses and will determine whether additional information and/or data is warranted
  - Comparative Use Human Factors Studies

# User Interface

Refers to all components of a product with which a user interacts, such as labels and packaging, the delivery device constituent part, and any associated controls and displays

# External Critical Design Attributes

Refers to those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product

# Drug-Device Combination Products






# Comparative Analyses

1. Labeling Comparison
2. Comparative Task Analysis
3. Physical Comparison of Delivery Device Constituent Part

# 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

# Sample Labeling Comparison

| IFU of Flovent® HFA | Proposed T product IFU |
|---|---|
| **Your FLOVENT HFA inhaler**<br>  <br><br>Figure A<br>  <br>Figure B<br>• The metal canister holds the medicine. **See Figure A.**<br>• The metal canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the plastic actuator. **See Figure B.**<br>• The counter starts at **124**. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at **000**.<br>• **Do not try to change the numbers or take the counter off the metal canister.** The counter cannot be reset, and it is permanently attached to the metal canister.<br>• The dark orange plastic actuator sprays the medicine from the metal canister. The plastic actuator has a protective cap that covers the mouthpiece. **See Figure A.** Keep the protective cap on the mouthpiece when the metal canister is not in use. The strap keeps the cap attached to the plastic actuator.<br>• **Do not** use the plastic actuator with a canister of medicine from any other inhaler.<br>• **Do not** use a FLOVENT HFA metal canister with an actuator from any other inhaler. | [YOUR PROPOSED LABEL HERE] |
| **Before using your FLOVENT HFA inhaler**<br>• The inhaler should be at room temperature before you use it.<br>• If a child needs help using the inhaler, an adult should help the child use the inhaler with or without a valved holding chamber, which may also be attached to a mask. The adult should follow the instructions that came with the valved holding chamber. An adult should watch a child use the inhaler to be sure it is used correctly. | [YOUR PROPOSED LABEL HERE] |
| **Priming your FLOVENT HFA inhaler**<br>  <br>Figure C<br>  <br>Figure D<br>• **Before you use FLOVENT HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it.**<br>• To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray the inhaler 1 time into the air away from your face. **See Figure C. Avoid spraying in eyes.**<br>• Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **120**. **See Figure D.**<br>• You must prime your inhaler again if you have not used it in more than 7 days or if you drop it. Take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from your face. | [YOUR PROPOSED LABEL HERE] |

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021433s033lbl.pdf

# Comparative Task Analysis

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

- Critical tasks are user tasks 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 medical care

# Physical Comparison of Delivery Device

- Visual and tactile examination of the physical features of the RLD
- Compare them to those of the delivery device constituent part for the proposed generic combination product
- Size, shape, visual or tactile feedback

# Assessment of Identified Differences

- Consider any identified differences between the user interface of a proposed generic combination product and its RLD in the context of the *overall risk profile* of the product
- **No Differences**
- **Minor Differences**
  - Guidance describes a design difference as minor if the differences 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 Differences**
  - FDA may not view a design difference as minor if any aspect of the threshold analyses suggests that differences in the design of the user interface of a proposed generic combination product as compared to the RLD *may* impact an external critical design attribute that involves administration of the product

# Assessment of Identified Differences

In instances when *other than minor* differences are identified:

- Consider re-design of the user interface to minimize differences from the RLD
- Potential need for additional information and/or data to support the ANDA submission

**Draft guidance recommends that potential applicants contact FDA through a pre-ANDA submission/controlled correspondence *before* conducting comparative use human factors studies**

# Generic OINDPs are Complex

- **Complex routes of delivery-** locally acting drugs
- **Complex drug-device combination products-** nasal sprays, metered dose inhalers, dry powder inhalers
- Other products where complexity or **uncertainty** concerning the approval pathway or possible **alternative approach** would benefit from early scientific engagement

GDUFA II commitment letter. http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

# Complex Generic Drug-Device Considerations

- Energy source
- System presentation
- Dose-metering principle
- Appearance
- External operating principles
- Cleaning
- Functionality, accuracy, robustness
- Dose counting mechanism
- Resistance

# Products Delivered to the Respiratory System

Factors influencing patient-product interactions and drug bioavailability include:

- dose percent deposited in the lungs vs. dose percent swallowed and absorbed from the GI tract
- local solubility/permeability
- receptor affinity
- deposition in central vs. peripheral parts of the pulmonary tree
- pulmonary residence time
- local clearance (mucociliary transport and RES uptake)
- device design
- effects of formulation differences on product performance

# Product Development Considerations

***Timing is Everything***

- Device design impacts critical parameters for drug delivery
- In vivo BE should be conducted with to-be-marketed device
- User interface should be considered early on and throughout development
- If device is re-designed late in product development to address substitutability, it may affect in vitro characterizations
- Bridging data may be needed between device versions

# Conclusions

- OINDPs have a number of complex regulatory and scientific challenges
- Device design can impact in vitro and in vivo performance and delivery of drug to the site of action
- User interface design should be considered throughout generic complex product development
- Comparative analyses are used to evaluate potential differences in the user interface of Test vs. RLD
- Assessment of TE includes multiple considerations
- Opportunities for frequent communications with FDA throughout a product's Pre-ANDA life


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