The Role of Comparative Analyses for Evaluation of Generic Drug-Device Combinations in an ANDA

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April 2018

Disclaimer

The opinions expressed in this presentation are those of the speaker and may not reflect the position of the U.S. Food and Drug Administration.

Outline

- Equivalence for OINDPs
- ANDA Considerations for OINDPs
- Comparative Analyses for ANDAs
- Paths for Communications with FDA
- Product Development Considerations for OINDPs

Generic OIDPs 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

General Framework for ANDAs

- Approval of generic drug starts with a listed drug – generally an innovator drug 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

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**

  Can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling

Determination of Generic Drug Product's Equivalence to its Reference Listed Drug

- Regulations require that applicants conduct testing using the most accurate, sensitive, and reproducible approach [21CFR320.24]
- The choice of methodology used for establishing and ensuring **Therapeutic Equivalence** throughout product's lifecycle will involve considerations for:
    - Formulation design
    - Product composition
    - Site of action
    - Mechanism of drug delivery and release
    - Ability to measure drug's availability at the site of action
    - Expected and measured therapeutic effects and their relationship to drug concentration
    - Other factors related to patient-product interaction

Generic Drug-Device Combination Products

- **Therapeutically equivalent**: can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling
- **Same** expectation for generic drug-device combination products
- Generic and RLD do not need to be identical, as long as differences do not preclude approval under an ANDA
- FDA expects that end-users 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

Complex Orally Inhaled Drug Products: Weight-of-Evidence Approach

2013
No generic OIDP products;
1st product-specific guidance for OIDP published

Device and Formulation Design

Comparative In Vitro Studies

Comparative Pharmacokinetic Studies

Comparative Pharmacodynamics or Clinical Endpoint Studies

2017
>50% of all OIDPs have PSGs;
OIDP ANDA applications reviewed

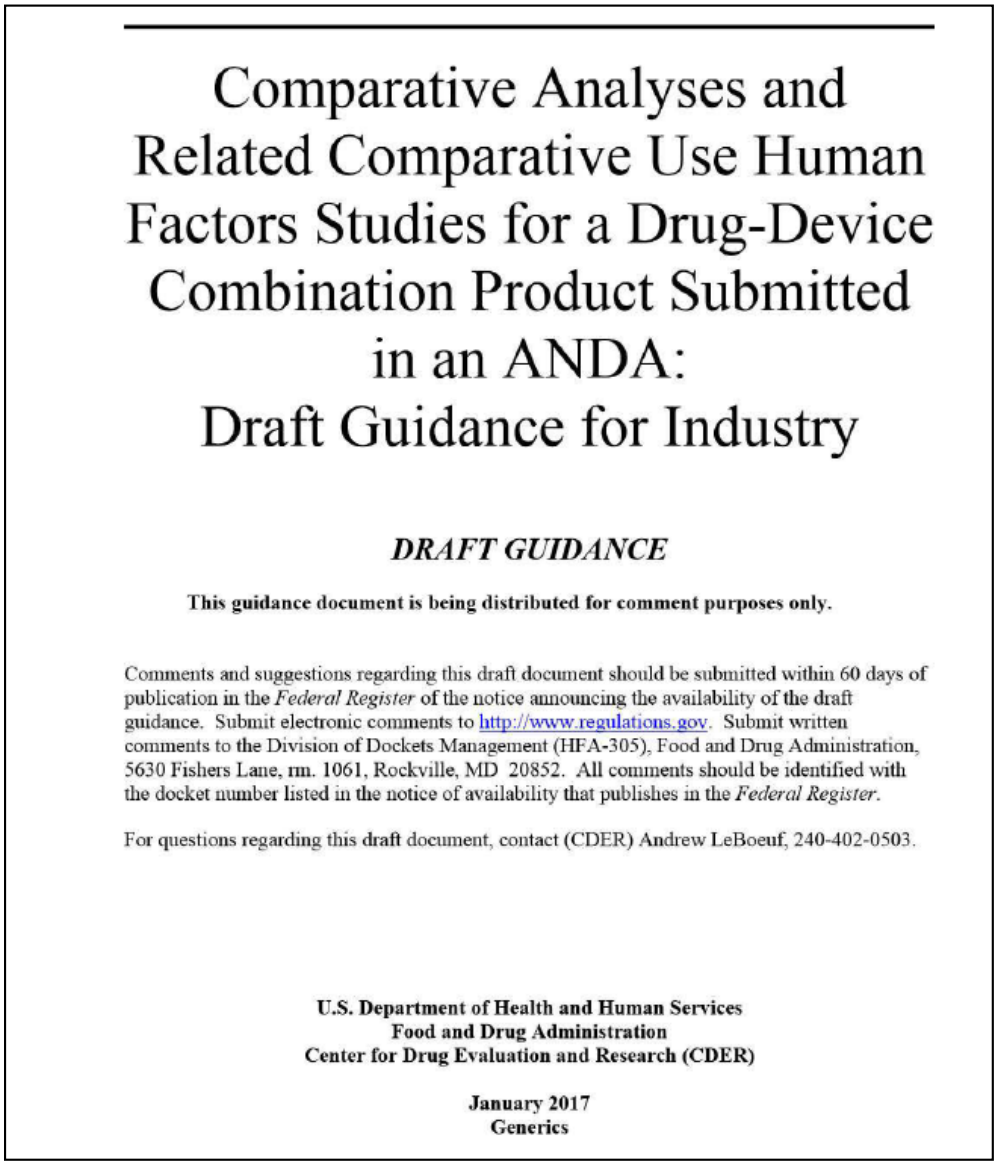
User Interface

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

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

Comparative Analyses

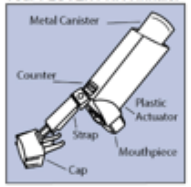
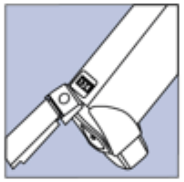
1. Labeling Comparison
2. Comparative Task Analysis
3. Physical Comparison of Delivery Device Constituent Part

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

- Labeling differences that stem from permissible differences in design between the user interface for the proposed generic combination product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA [21CFR 314.94(a)(8)(iv)]

Sample Labeling Comparison

IFU of Flovent® HFA	Proposed T product IFU
Your FLOVENT HFA inhaler  **Figure A**  **Figure B** • The metal canister holds the medicine. **See Figure A.** • 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.** • 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**. • **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. • 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. • **Do not** use the plastic actuator with a canister of medicine from any other inhaler. • **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 • The inhaler should be at room temperature before you use it. • 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  **Figure C**  **Figure D** • **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.** • 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.** • Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **120**. **See Figure D.** • 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

Pre-ANDA Program for Complex Products Under GDUFA II

- Clarify regulatory expectations for prospective applicants early in product development
- Help applicants develop more complete submissions
- Promote a more efficient and effective review process
- Reduce the number of review cycles necessary to obtain ANDA approval of complex products

Pre-ANDA Communications with FDA

- General Guidances
  - *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf
- Product Specific Guidances
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
- Pre-ANDA meetings
- Controlled Correspondences

Pre-ANDA Meetings

- **Product Development**
  - Annually throughout product development
  - Proposed Study design
  - Alternative approach
  - Additional study expectations
- **Pre-submission**
  - 6 months before proposed submission
  - Discuss content and format of package to be submitted
  - Data to support equivalence claims
  - Types of data to include
  - Identification of items to be clarified in submission of ANDA
- Guidance
  - *Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf

Controlled Correspondence

- Requests for information on a specific element of generic drug product development
- Specific types of requests within scope
  - Related to Inactive Ingredient Database
  - Q1/Q2 formulation assessment
  - Related to Product quality
  - Comparative analyses of proposed user interface
- Guidance
  - *Controlled Correspondence Related to Generic Drug Development* (Nov 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm583436.pdf

Drug-Device Combination Products

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
- Device should be substitutable
- 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, including a product's user interface
- Opportunities for frequent communications with FDA throughout a product's Pre-ANDA life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