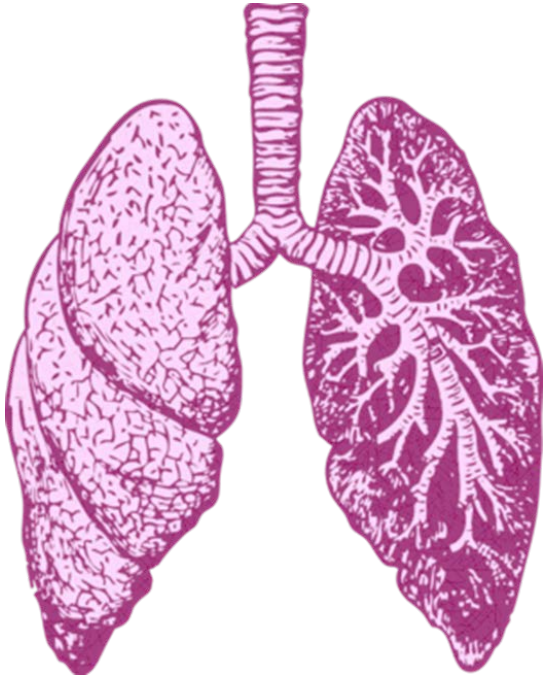


ATS 2019

Session L3

May 19, 2019

GENERIC DRUG DEVELOPMENT FOR RESPIRATORY PRODUCTS, US FOOD AND DRUG ADMINISTRATION UPDATE

Disclaimers

- *The materials presented are available in the public domain.*
- *This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.*

Session Objectives

- To recognize key aspects of generic drug regulatory approval process and how the Office of Generic Drugs (OGD) evaluates bioequivalence for complex inhaled generic drug products, using a weight-of-evidence approach
- To describe recent abbreviated new drug application (ANDA) approvals and product-specific guidances (PSGs) for generic drug products recently posted by the FDA, with a focus on how these can inform complex orally-inhaled and nasal generic drug development
- To articulate how emerging technologies and innovative approaches are being utilized for FDA-funded research, FDA guidance development, and regulatory decision-making

Session Outline

- Overview of FDA Generic Inhaled Drug Approval Process- Markham Luke, MD, PhD
- Update for Generic Orally Inhaled and Nasal Drug Products- Kimberly Witzmann, MD
- Emerging Concepts and New Technologies for Bioequivalence of OINDPs- Denise Conti, PhD
- Questions

Markham Luke, MD, PhD

OVERVIEW OF FDA GENERIC INHALED DRUG APPROVAL PROCESS

placeholder

Kimberly Witzmann, MD

UPDATE FOR GENERIC ORALLY INHALED AND NASAL DRUG PRODUCTS

Outline

- Recent Product Specific Guidance Postings
- Recent Abbreviated New Drug Application (ANDA) approvals
  - Epinephrine Auto-Injector
  - Fluticasone Propionate/Salmeterol Xinafoate Dry Powder Inhaler (DPI)
- Conclusions

Generic Products in the US Marketplace

- Generic drugs offer considerable savings to consumers
- $1.67 trillion saved over last decade
- FDA-approved generics account for 90% of prescriptions dispensed in the U.S. in 2018
- More than 1,000 generic products were approved or tentatively approved in 2018
- 10% were first generics, 14% were complex generics
- Development of product-specific guidances (PSGs) is vital to this process

https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm632128.htm
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm631710.htm#2018

Product-Specific Guidances Facilitate Generic Drug Development

- In 2018, we developed a total of 245 new and revised PSGs
- Identify the Agency's current thinking on methodology for developing drugs
- Generate evidence needed to support generic approvals
- Can be found at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
- Home page lists most recent additions to the listings, in addition to alphabetical listing arranged by active ingredient

PSGs for Generic Products

- Roles
  - To facilitate generic drug product availability
  - To assist generic pharmaceutical industry
  - To identify the most appropriate methodology to support ANDA
- Guiding Principles
  - 21 CFR 320.24
  - Different types of evidence may be used to establish bioequivalence (BE) for pharmaceutically equivalent drug products
  - Selection for BE method depends upon
    - Purpose of study
    - Analytical methods available
    - Nature of the drug product
  - Use the most accurate, sensitive, and reproducible approach available

PSGs for OINDP Generics

- Total: 57% of Orally Inhaled and Nasal Drug Products (OINDPs) eligible for PSGs have been posted (4/2019)
- Nasal Products
  - 63% of total nasal products, including solutions, suspensions, powders
  - For local and systemic action
- Orally Inhaled products
  - 50% of inhaled products
  - 54% of dry powder inhalers (DPIs)
  - 65% of pressurized metered dose inhalers (pMDIs)
  - 0% soft mist inhalers, but research is ongoing
  - Device constituent complexity influences rate of delivery to site of action

PSGs for OINDP Generics

- Nasal Products
  - Azelastine HCl solution metered spray (x2)
  - Beclomethasone dipropionate solution metered aerosol
  - Calcitonin-salmon solution metered spray
  - Ciclesonide solution metered aerosol
  - Cyanocobalmin solution metered spray
  - Dihydroergotamine solution metered spray
  - Fentanyl solution metered spray
  - Ketorolac tromethamine solution metered spray
  - Naloxone hydrochloride solution metered spray
  - Nicotine solution metered spray
  - Olopatadine HCl solution metered spray
  - Oxymetazoline HCl/Tetracaine HCl solution metered spray
  - Sumatriptan solution metered spray
  - Zolmitriptan solution metered spray
  - Azelastine HCl/Fluticasone propionate suspension metered spray
  - Fluticasone propionate suspension metered spray (x2)
  - Mometasone furoate suspension metered spray
  - Triamcinolone acetonide suspension metered spray
  - Mupirocin topical ointment
- Other Products
  - Epinephrine autoinjector (x2)
  - Epinephrine solution
  - Sterile talc intrapleural aerosol
- Orally Inhaled products
  - Aclidinium bromide DPI
  - Albuterol sulfate DPI
  - Budesonide DPI
  - Fluticasone furoate DPI
  - Fluticasone furoate/vilanterol DPI
  - Fluticasone propionate DPI
  - Fluticasone propionate/salmeterol xinafoate DPI
  - Formoterol fumarate DPI
  - Glycopyrrolate DPI
  - Indecaterol maleate DPI
  - Mometasone furoate DPI
  - Salmeterol xinafoate DPI
  - Tiotropium bromide DPI
  - Umeclidinium bromide DPI
  - Albuterol MDI (x3)
  - Beclomethasone dipropionate MDI
  - Budesonide/formoterol fumarate MDI
  - Ciclesonide MDI
  - Fluticasone propionate MDI
  - Formoterol fumarate/mometasone furoate MDI
  - Ipratropium bromide MDI
  - Levalbuterol MDI
  - Mometasone furoate MDI
  - Budesonide suspension inhalation aerosol

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

2019
>50% of all OIDPs have PSGs;
OIDP ANDA applications reviewed; One new OIDP ANDA approval to date!

Complex 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 reference listed drug (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

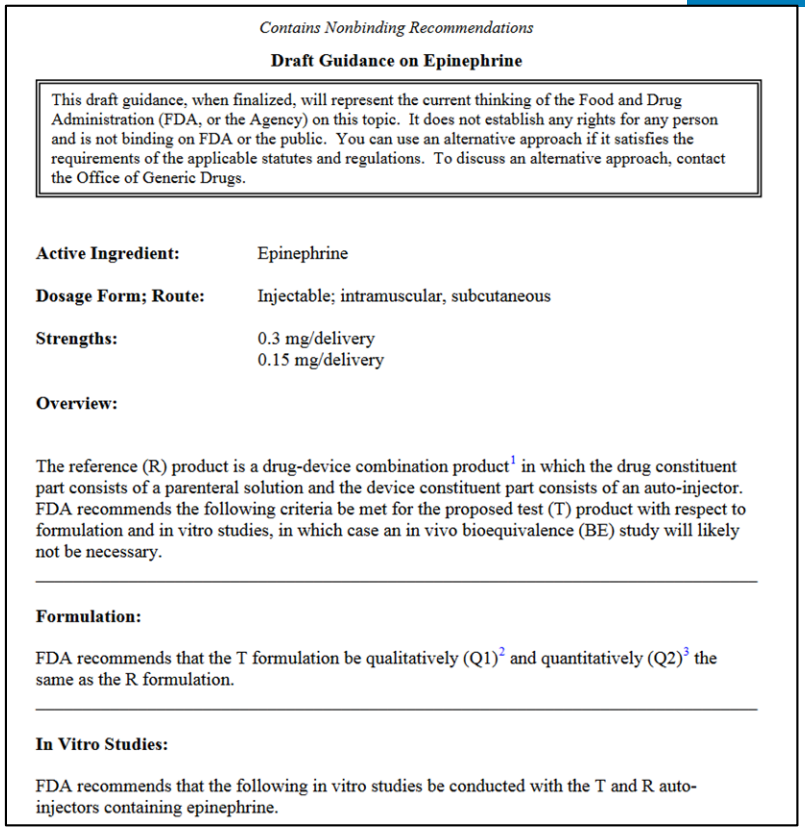
Draft PSG for Epinephrine Autoinjector (AI)

Posted December 2016

In Vitro Studies for BE:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle Integrity Post-Injection

Device Considerations



Contains Nonbinding Recommendations

Draft Guidance on Epinephrine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Epinephrine

Dosage Form; Route: Injectable; intramuscular, subcutaneous

Strengths: 0.3 mg/delivery
0.15 mg/delivery

Overview:

The reference (R) product is a drug-device combination product[1] in which the drug constituent part consists of a parenteral solution and the device constituent part consists of an auto-injector. FDA recommends the following criteria be met for the proposed test (T) product with respect to formulation and in vitro studies, in which case an in vivo bioequivalence (BE) study will likely not be necessary.

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the R formulation.

In Vitro Studies:

FDA recommends that the following in vitro studies be conducted with the T and R auto-injectors containing epinephrine.

Generic Epinephrine Autoinjector

- First generic epinephrine AI was approved in August 2018

"Today's approval of the first generic version of the most-widely prescribed epinephrine auto-injector in the U.S. is part of our longstanding commitment to advance access to lower cost, safe and effective generic alternatives once patents and other exclusivities no longer prevent approval," said FDA Commissioner Scott Gottlieb, M.D.

U.S. Department of Health and Human Services

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FDA News Release

FDA approves first generic version of EpiPen

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For Immediate Release: August 16, 2018

Release

Español

The U.S. Food and Drug Administration today approved the first generic version of EpiPen and EpiPen Jr (epinephrine) auto-injector for the emergency treatment of allergic reactions, including those that are life-threatening (anaphylaxis), in adults and pediatric patients who weigh more than 33 pounds. Teva Pharmaceuticals USA gained approval to market its generic epinephrine auto-injector in 0.3 mg and 0.15 mg strengths.

Inquiries

Media

Angela Stark
301-796-0397

Consumers

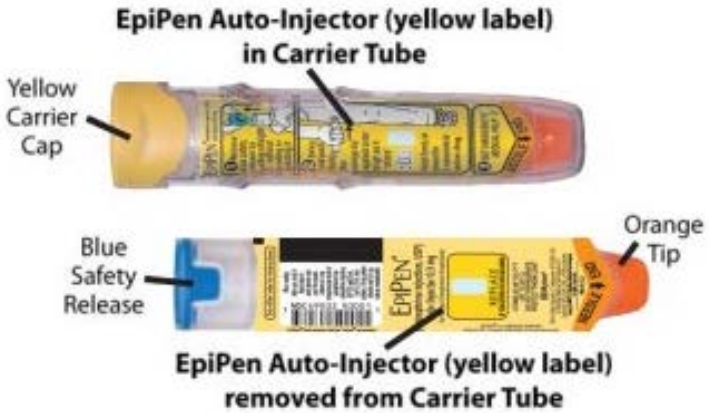
888-INFO-FDA

Related Information

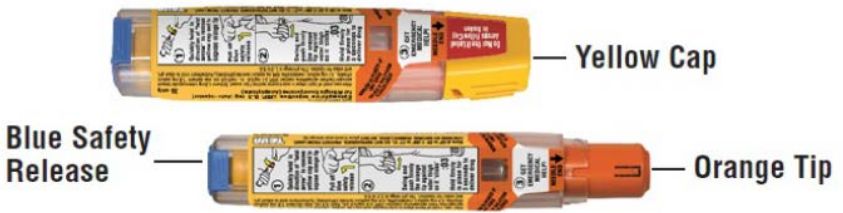
- Generic Drugs
- First Generic Drug Approvals
- Drug Competition Action Plan
- Authorized Generics
- NIH: Anaphylaxis

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm617173.htm

RLD and Generic Epinephrine AI



- A CARRYING TUBE IS NOT PROVIDED AS SEEN WITH OTHER PRODUCTS.
- **Epinephrine Injection, 0.3 mg Auto-Injector (yellow label) with Yellow Cap**



- **Epinephrine Injection, 0.3 mg Auto-Injector (yellow label) with Yellow Cap Removed**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019430s074lbl.pdf

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=090589

RLD and Generic Epinephrine AI

Prepare Injection

Pull off blue safety release

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019430s074lbl.pdf

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=090589

Draft PSG for FP/SX Dry Powder Inhaler

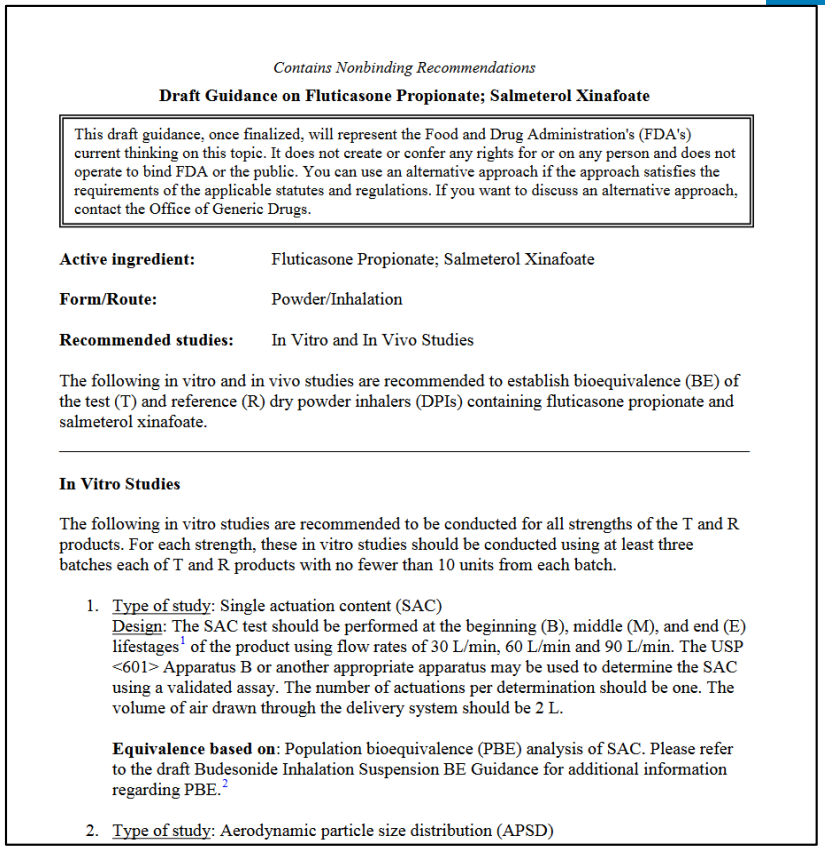
Posted September 2013

Studies for BE:

- In vitro BE (SAC, APSD)
- PK BE
- Comparative Clinical Endpoint
- Formulation sameness

Device Considerations

FP: Fluticasone Propionate
SX: Salmeterol Xinafoate



Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Fluticasone Propionate; Salmeterol Xinafoate

Form/Route: Powder/Inhalation

Recommended studies: In Vitro and In Vivo Studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing fluticasone propionate and salmeterol xinafoate.

In Vitro Studies

The following in vitro studies are recommended to be conducted for all strengths of the T and R products. For each strength, these in vitro studies should be conducted using at least three batches each of T and R products with no fewer than 10 units from each batch.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[1] of the product using flow rates of 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one. The volume of air drawn through the delivery system should be 2 L.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE.[2]

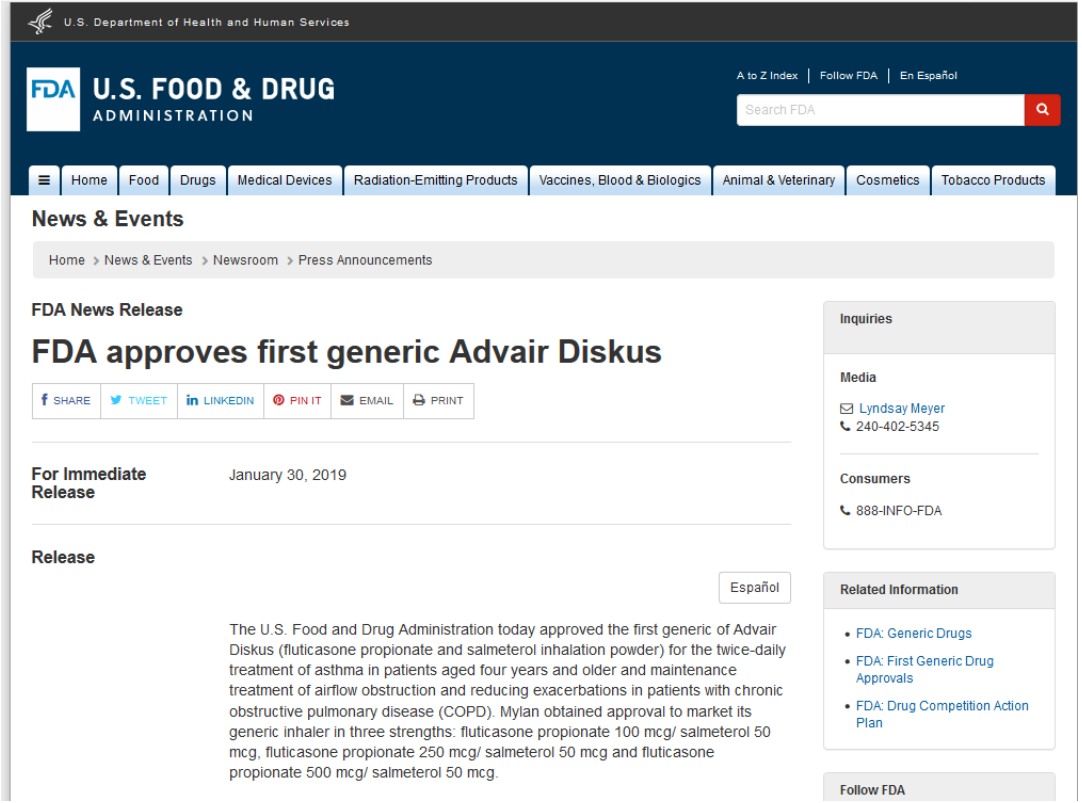
2. Type of study: Aerodynamic particle size distribution (APSD)

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf

Generic FP/SX Dry Powder Inhaler

- First generic Dry Powder Inhaler was approved in January 2019

"Today's approval of the first generic drug product for one of the most commonly prescribed asthma and COPD inhalers in the U.S. is part of our longstanding commitment to advance access to lower cost, high quality generic alternatives," said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.



U.S. Department of Health and Human Services

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FDA News Release

FDA approves first generic Advair Diskus

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release January 30, 2019

Release

Español

The U.S. Food and Drug Administration today approved the first generic of Advair Diskus (fluticasone propionate and salmeterol inhalation powder) for the twice-daily treatment of asthma in patients aged four years and older and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Mylan obtained approval to market its generic inhaler in three strengths: fluticasone propionate 100 mcg/ salmeterol 50 mcg, fluticasone propionate 250 mcg/ salmeterol 50 mcg and fluticasone propionate 500 mcg/ salmeterol 50 mcg.

Inquiries

Media

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Consumers

888-INFO-FDA

Related Information

- FDA: Generic Drugs
- FDA: First Generic Drug Approvals
- FDA: Drug Competition Action Plan

Follow FDA

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630151.htm

RLD and Generic FP/SX DPI

Figure A

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021077s061lbl.pdf

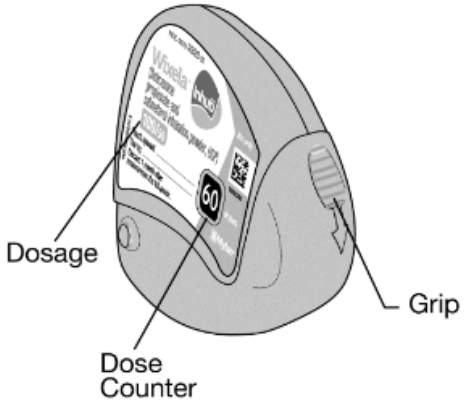
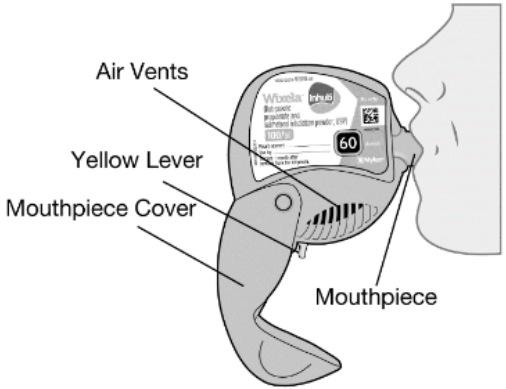


Figure A

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208891Orig1s000lbl.pdf

RLD and Generic FP/SX DPI

Inhale your medicine



Close the device

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021077s061lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208891Orig1s000lbl.pdf

Conclusions

- FDA-approved generics account for the majority of prescriptions dispensed in the U.S., and convey considerable cost savings
- Due to their complexity, OINDPs lag behind other product categories for approved generics
- OGD is actively facilitating complex generic OINDP development through our scientific research and communication programs
- Product-specific guidances identify the most appropriate methodology to support OINDP ANDAs, and assist the generic pharmaceutical industry to develop these products
- Ultimate goal of bringing safe, effective, and affordable generic drug products available to the American public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Denise Conti, PhD

EMERGING CONCEPTS AND NEW TECHNOLOGIES FOR BIOEQUIVALENCE OF OINDPS

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QUESTIONS?