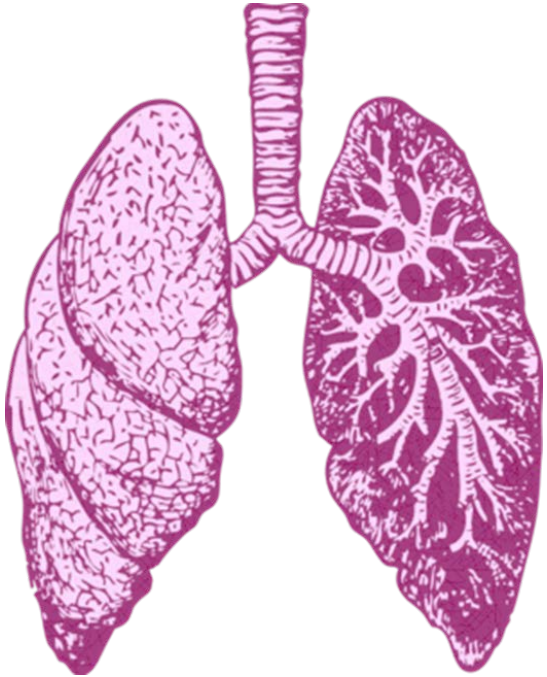


ATS 2019

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

Evaluating Therapeutic Performance of Complex Generic Drugs for Pulmonary Delivery: The FDA Generic Drug Approval Process

Markham C. Luke, MD PhD
Director, Division of Therapeutic Performance, ORS
Office of Generic Drugs, CDER

May 19th, 2019
American Thoracic Society Annual Meeting

Disclaimer

- The opinions and conclusions expressed in this breakout session are the viewpoints of the speaker(s) and do not necessarily reflect the official position of the U.S. Food and Drug Administration.

Generic Drugs are “Copies” of Brand Name Drugs

- Each ANDA (Abbreviated New Drug Application) relies on a reference listed drug (RLD)
- Generic drugs mostly cost less to develop because applicants do not repeat the safety and efficacy studies required to approve the RLD
- Instead applicants provide evidence of “sameness” and equivalence

Drug Competition Action Plan (DCAP)- To Improve Drug Access

- Announced by FDA's Commissioner in June 2017
- Goal is to bring more competition to drug market as a way to improve drug access
- This plan has three main components:
  - **Reducing gaming by branded companies** that can delay generic drug entry;
  - **Resolving scientific and regulatory obstacles** that can make it difficult to win approval of generic versions of certain complex drugs;
  - **Improving efficiency and predictability of FDA's generic review process** to reduce the time it takes to get a new generic drug approved and lessen the number of review cycles undergone by generic applications before they can be approved

https://blogs.fda.gov/fdavoice/index.php/2017/06/fda-working-to-lift-barriers-to-generic-drug-competition/

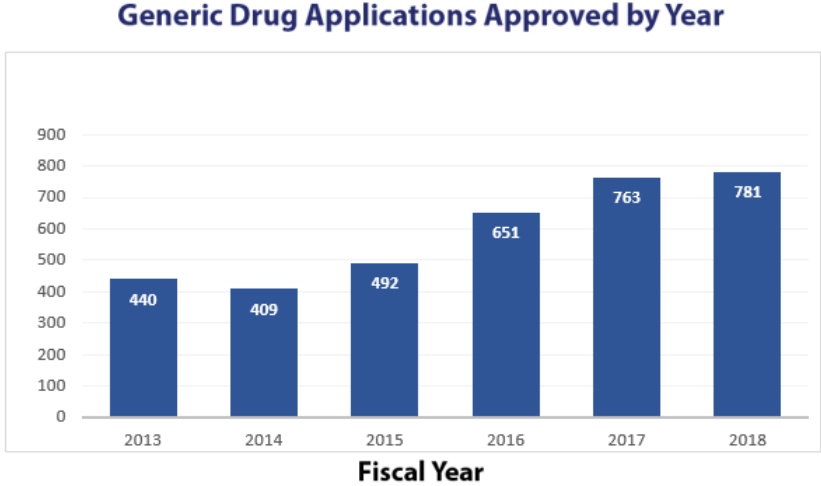
FDA Drug Competition Action Plan

- List of off-patent, off-exclusivity branded drugs without approved generics is published
- New policy to expedite review of generic drug applications where competition is limited
- Use of good review management practices
- Reduce application cycles – improved pre-ANDA interaction

GDUFA Regulatory Science

- GDUFA provides resources to allow FDA to perform and fund research to advance generic drug science
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Recent focus on complex drug products
- This provides new tools for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access

Generic Drug Science & Research Website:
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm



Product-Specific Guidances (PSGs)

- Assist generic pharmaceutical industry by describing the Agency's current thinking and expectations:
  - how to develop generic drug products that are therapeutically equivalent to specific reference drugs
  - the most appropriate methods for generating evidence needed to support ANDA approval
  - Published in an incremental manner – 1,682 PSGs as of February, 2019
  - Under GDUFA 2 – PSGs are to be published at least 2 years prior to the earliest lawful ANDA filing date for non-complex drugs that are:
    - New chemical entities and
    - Approved on or after October 1, 2017,

Generic Drug Product Substitutability

In relation to the Reference Listed Drug, generic products are expected to be:

- **Pharmaceutically Equivalent (PE)**

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

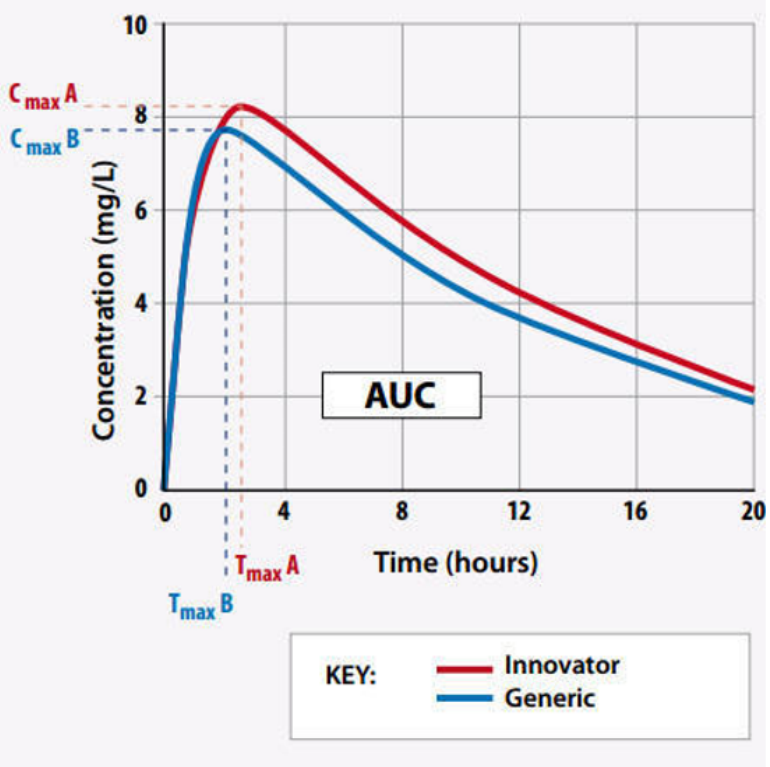
- **Bioequivalent (BE)**

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

- **Therapeutically Equivalent (TE)**

  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

Bioequivalence Determinations



- For products with systemic site of action, BE via systemic PK endpoints (e.g., C_{max} and AUC) helps infer comparable safety and efficacy
- For products that are locally acting, it is more difficult to assess local exposure
- The site of action may not be directly correlated with systemic PK

OINDPs: Weight-of-Evidence Approach

- Includes the following:
  - Qualitative and quantitative sameness of formulation
  - In vitro comparative studies
  - In vivo PK studies
  - Pharmacodynamic (PD) or comparative clinical endpoint study
  - Device substitutability

Formulation Considerations

- Qualitative (Q1) sameness
  - Same inactive ingredient(s)
    - Critical to establishing equivalence between the test and reference DPI products
    - Limited choices of inactive ingredients for DPIs
- Quantitative (Q2) sameness
  - Same inactive ingredient(s) but may differ in concentration
    - Cannot exceed the levels used in other FDA approved products administered by the same route of administration
    - Effect of Q2 difference on bioequivalence assessed by in vitro and/or in vivo BE studies
    - Submit pharmaceutical development data to support the selected test formulation

In Vitro Considerations

- Single Actuation Content (SAC) and aerodynamic particle size distribution (APSD)
  - Critical attributes that are believed to affect the total and regional deposition of drugs in the lung
- SAC and APSD depend on, and sensitive to, product- and process-related factors
  - Physicochemical properties of API(s) and carrier
  - Device component properties
  - Process conditions

In Vivo Pharmacokinetic study Considerations

- This test is considered to be a reliable, sensitive, and objective method to determine differences in drug products
- Single dose studies are done in healthy subjects for all product strengths
- Dose is based on minimizing the number of inhalations balanced with assay sensitivity
- PK dose proportionality across doses and how product characteristics affect levels of target analyte in blood are ongoing research topics
- The blood level of drug drawn is after the site of deposition and action of the drug

In Vivo Pharmacodynamic study Considerations

- Pharmacodynamic (PD) testing is usually performed when there is an adequate dose response relationship (e.g., short-acting Beta-agonists)
- These PD BE studies are preferred over a comparative clinical endpoint BE study (next slide) when comparing test vs. reference drug products
- It is difficult to do PD BE studies for drugs with longer time of onset of effect (e.g., inhaled corticosteroids) or for products which do not demonstrate an adequate dose-response relationship

Comparative Clinical Endpoint Study Considerations

- Not necessarily the same endpoint as the NDA study
- Usual arms: Test (T), Reference (R), Placebo control
  - Lowest labeled dose
  - One indicated population for study reduces variability
  - BE is met if 90% confidence interval for T:R ratio falls within 80 to 125 percent.
- Comparative clinical endpoint bioequivalence studies are relatively blunt instruments (limited sensitivity)
- These studies can require large numbers of patients (usually hundreds), last for several weeks, and can be expensive to do

Acknowledgements

- **The Orally and Nasally Inhaled Generic Drug Product Team**
  - Kim Witzmann, MD – Lead for Orally and Nasally Inhaled Drug Products, Division of Therapeutic Performance, and Chair, Generic Drug Device Combination Product Working Group
  - Denise Conti, PhD, Bryan Newman, PhD, Sneha Dhapare, PhD, Han Liangfeng, MD, and ORISE Fellows: Elizabeth Bielski, PhD Susan Boc, PhD
- **Robert Lionberger, PhD**, Director, Office of Research and Standards

Questions? – Markham.Luke@fda.hhs.gov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U.S. FOOD & DRUG
ADMINISTRATION

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

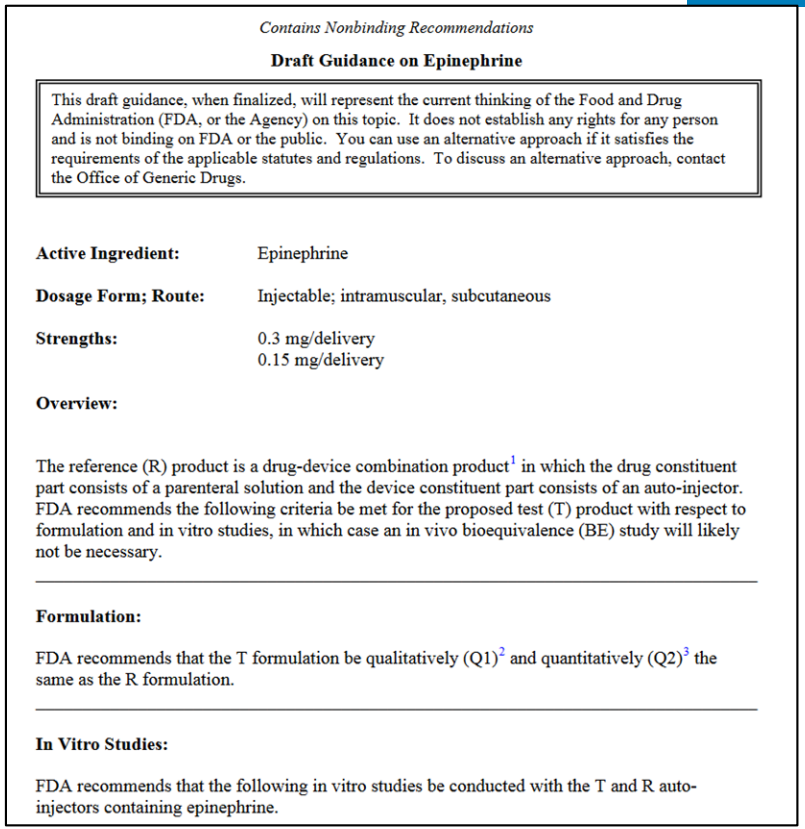
Draft PSG for Epinephrine Autoinjector (AI)

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

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

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

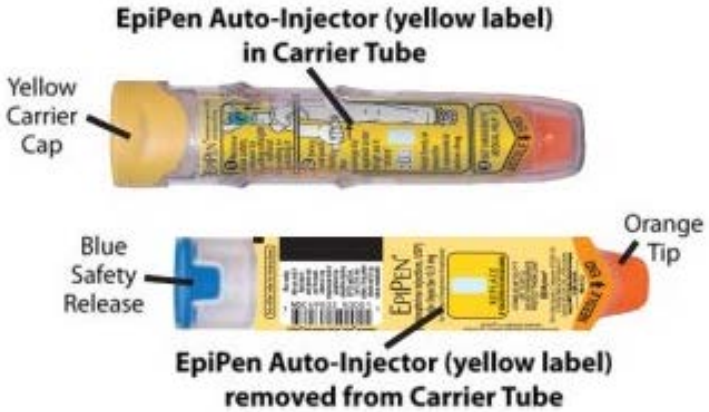
888-INFO-FDA

Related Information

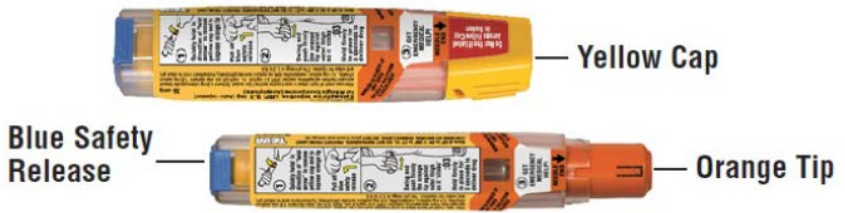
- Generic Drugs
- First Generic Drug Approvals
- Drug Competition Action Plan
- Authorized Generics
- NIH: Anaphylaxis

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

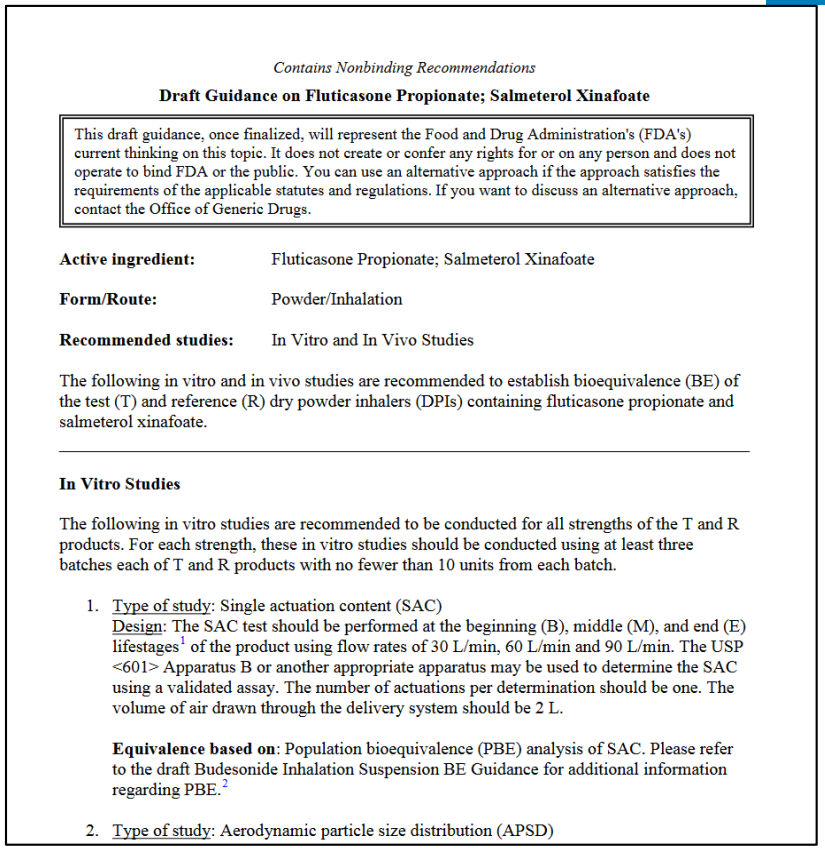
Posted September 2013

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]

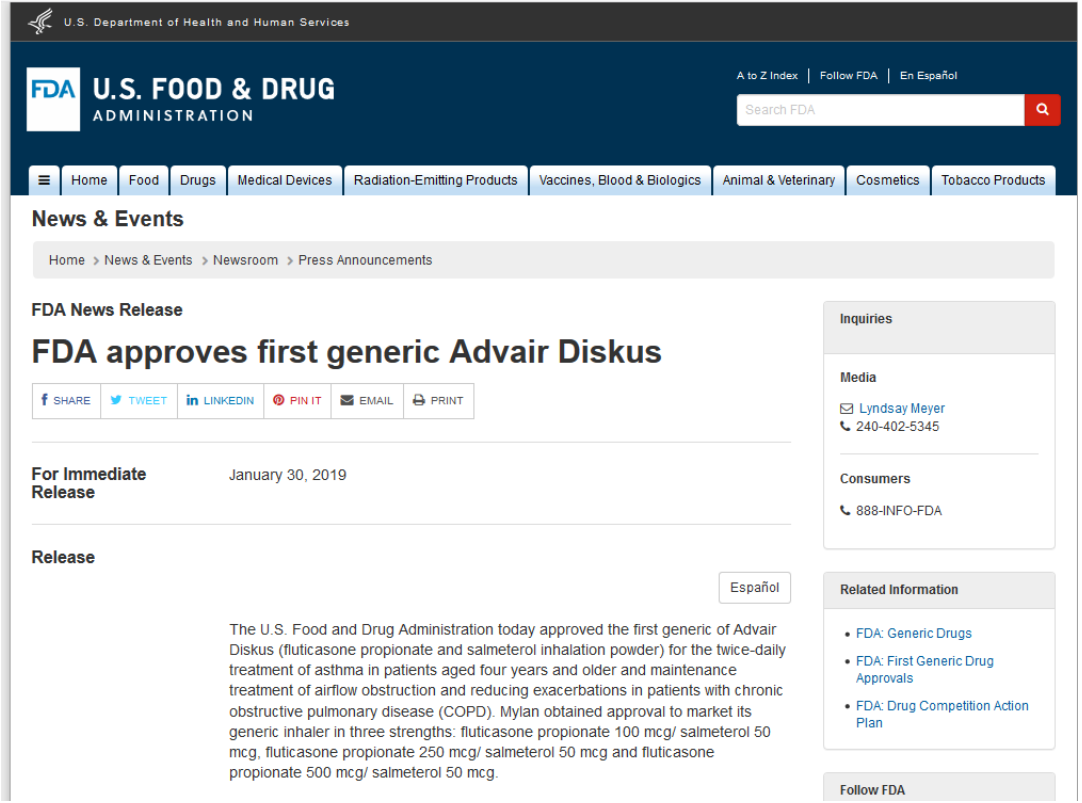
2. Type of study: Aerodynamic particle size distribution (APSD)

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.



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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

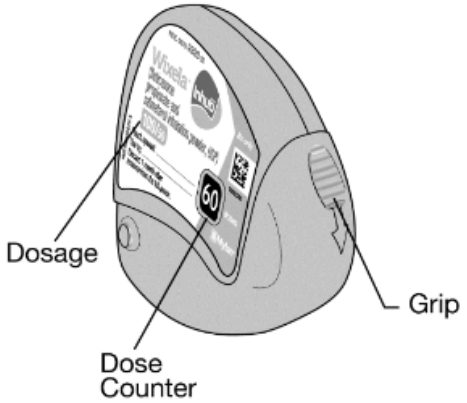
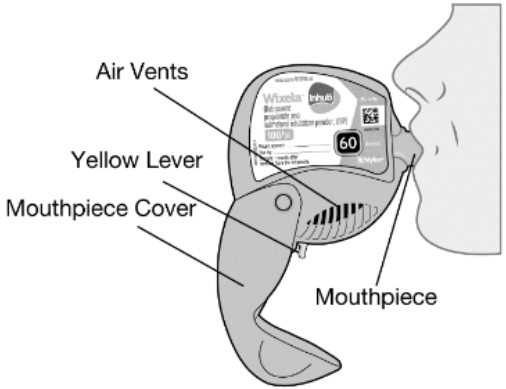


Figure A

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

Outline

- GDUFA Regulatory Science Program
- Research initiatives for locally acting orally inhaled and nasal drug products (OINDPs)
  - A **novel technique** for particle size measurment in nasal suspension products and formulation/microstructure characterization in dry powder inhalers
- Conclusions

GDUFA Regulatory Science Program

- Competitive research grants and contracts are awarded yearly
- GDUFA funds are specifically allocated to stimulate innovation and growth in the generic drug field
  - Identify, study, and implement new methodologies and tools
  - Development and evaluation of quality and equivalence of new generic drug products
  - All therapeutic areas and product categories
- FDA annual public meeting provides stakeholder input on research priorities for generic drug development and regulation
  - Industry, Academia
  - Patient advocates, Professional societies

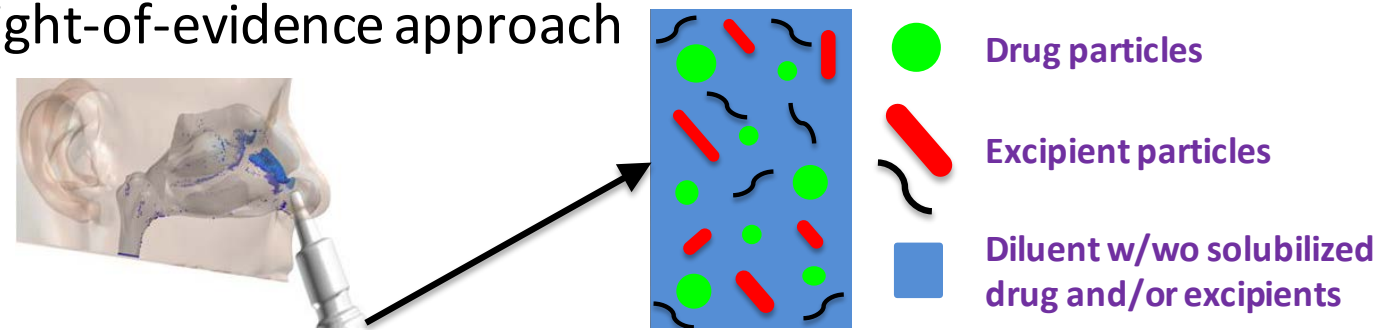
Research Initiatives for Locally Acting Orally Inhaled and Nasal Drug Products (OINDPs)

- Identification of **formulation** and device variables
- Development of clinically relevant in vitro methods for prediction of in vivo drug deposition and dissolution
- Development of computational fluid dynamic (CFD) and physiology-based pharmacokinetic (PBPK) models for prediction of the fate of drugs
- Identification, validation, and standardization of **novel techniques** that may have the potential to reduce the burden of current BE requirements

https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM626329.pdf

Locally Acting Nasal Suspension Sprays

- Current regulatory pathway for BE demonstration utilizes the aggregate weight-of-evidence approach

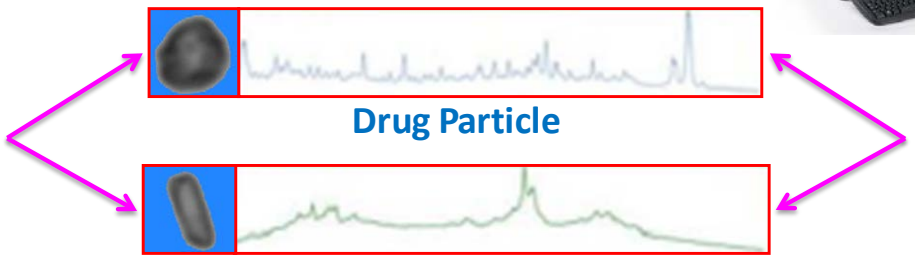


- Drug particle size distribution (PSD) in suspension formulations has the potential to influence **the rate and extent of drug availability** to nasal sites of action and systemic circulation
- Inability to adequately characterize drug PSD in aerosols and sprays using **common analytical methods**

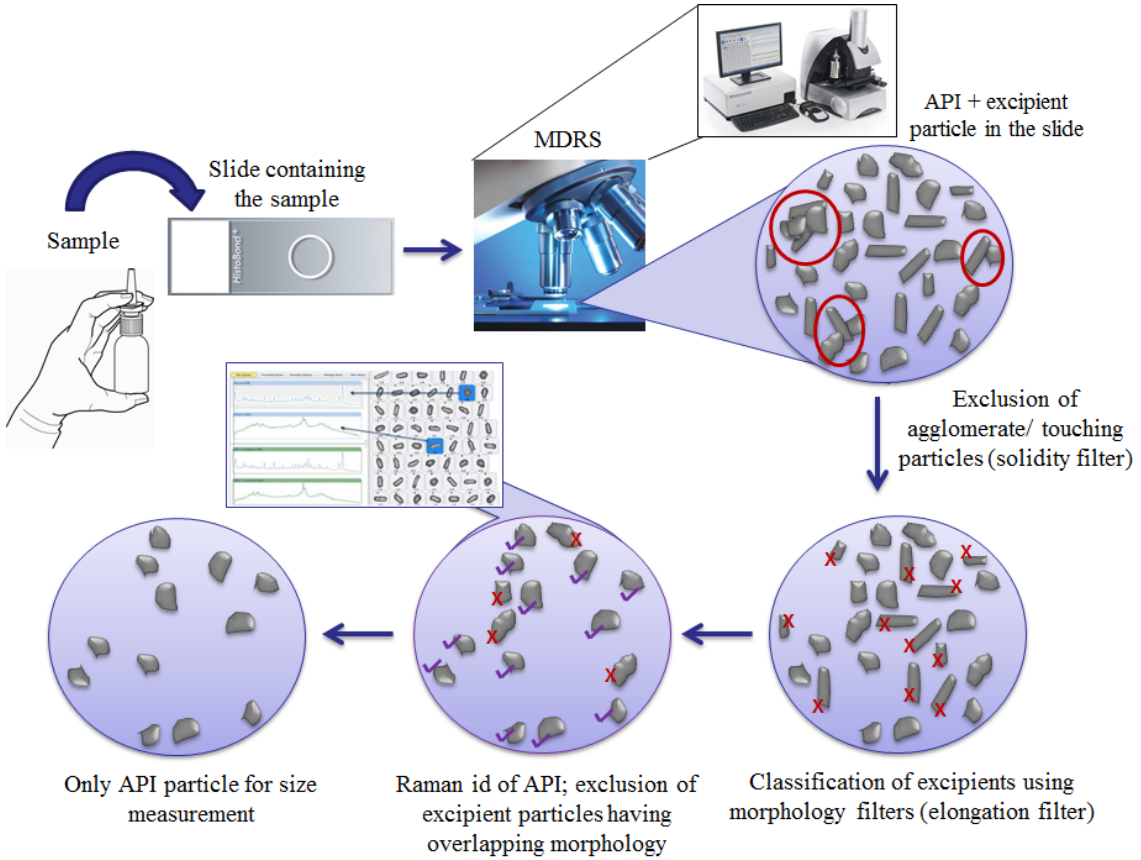
MDRS for Nasal Suspension Sprays

- If drug PSD in test and reference products can be accurately measured using a validated **advanced analytical method**, generic applicants may submit comparative drug PSD data
- The **Morphologically-Directed Raman Spectroscopy (MDRS)** opens this possibility
  - Novel in vitro technology
  - Enables drug PSD comparison

http://www.news-medical.net/news



MDRS: How does it work?

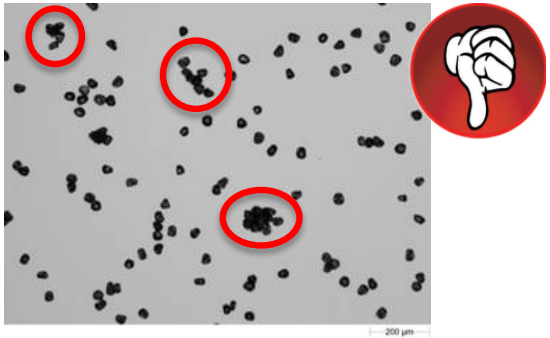


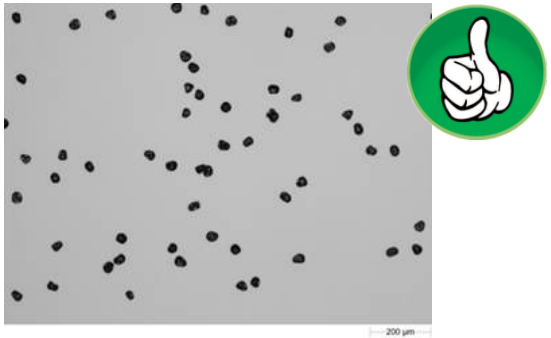
Courtesy of Dr. Abir Absar, Ph.D. (FDA/OCP)

Removal of Agglomerates and Touching Particles

- May consist of
  - Excipient-excipient particles
  - Drug-drug particles
  - Drug-excipient particles

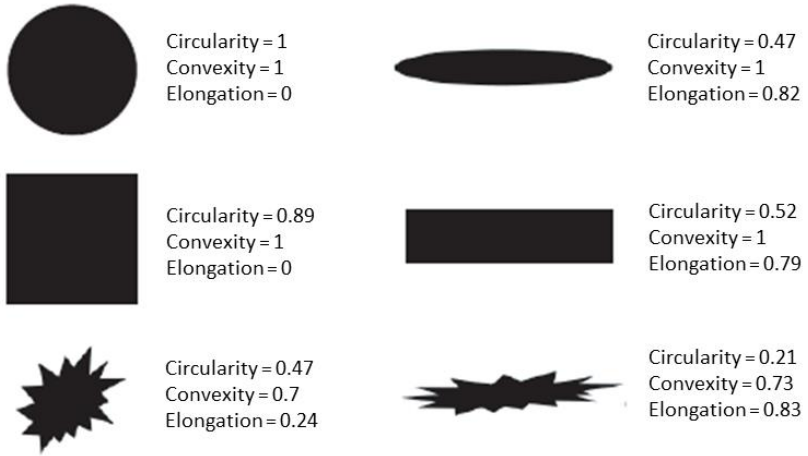
- Sample preparation – Can give misleading data





Particle Classification Using Morphology Filters

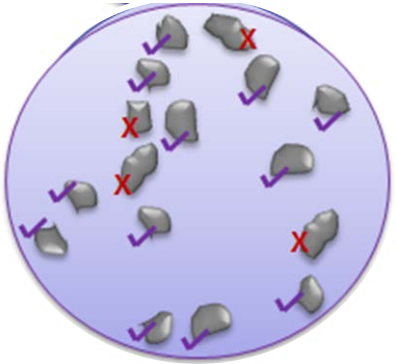
- Should exclude as many excipient particles as possible
- Should not exclude drug particles
- Morphology filters
  - Size
    - Circular equivalent (CE) diameter
  - Shape
    - Aspect ratio
    - Elongation
    - Circularity
    - Convexity
    - Solicity



<u>Disadvantage</u>: Cannot completely separate API and excipient particles due to particles with overlapping morphological features.

Chemical Identification by Raman Spectra

- Identifies particles with overlapping morphological features
- API/Excipient particles typically show different Raman profiles
  - Each molecule has a unique spectrum



Disadvantage:
Slow measurement, time-consuming.

GDUFA Research Has Informed ANDA Review Process and PSG Development

- We have been able to use MDRS
  - to support **BE review** for complex nasal suspension products, which precluded an applicant from repeating a comparative clinical endpoint study, and led to ANDA approval for the first generic Mometasone Furoate Nasal Suspension [RLD: Nasonex® NDA 20-762]
  - in PSGs as **alternate approach** to the comparative clinical endpoint study for other nasal suspension products
    - Fluticasone Propionate
    - Fluticasone Propionate and Azelastine Hydrochloride
    - Triamcinolone Acetonide

Microstructure of DPIs Using Orthogonal Analytical Approaches

- FY-17 contract # HHSF223201710116C
  - Awarded to University of Bath
- The objective of this project is to evaluate a range of orthogonal analytical techniques and utilize a combination of them to support the development and validation of methods in characterizing microstructures of an array of reference listed drug (RLD) dry powder inhaler (DPI) formulations

Methods

- Product selection: all products were commercially manufactured by the same pharmaceutical company
- Aerosolized fraction collection (impactor-sized mass, ISM): Unidose® aerosol collection system via USP inlet port at a fixed flow rate of 60 L/min for 4 seconds
- MDRS: filter substrate with ISM from one actuation mounted on the sample stage of a Morphologi G3-ID®
- In vitro dissolution: modified USP Apparatus V, samples taken at 2.5, 5, 10, 15, 25, 30, 60, 120, 180, 240 min, ISM collected from equivalent 500mcg fluticasone

Mangal, S.; Conti, D. S.; Delvadia, R.; Oguntimein, O.; Shur, J.; Price, R. "Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization." In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.

Results: Same DPI product, but different FP fractions

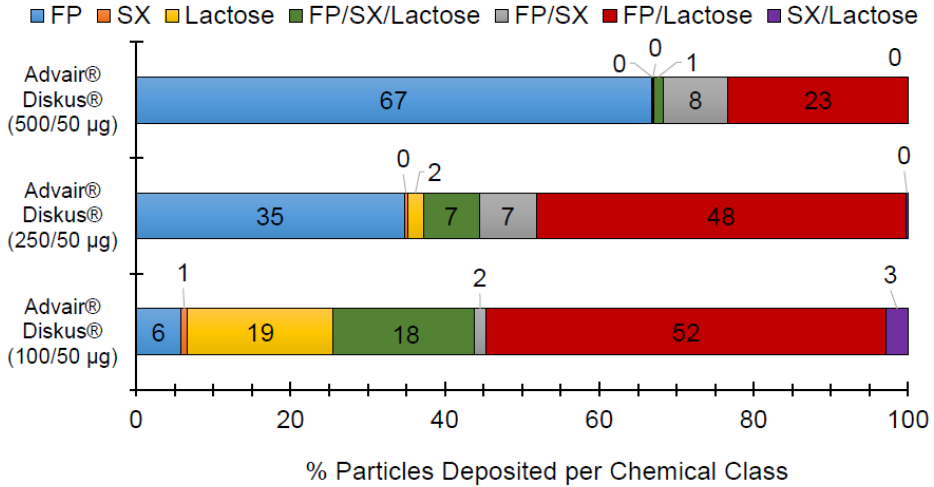


Figure 1: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Advair® Diskus® (FP/SX; 250/50 µg), and Advair® Diskus® (FP/SX; 500/50 µg). These are presented as mean ± standard deviation (n=5).

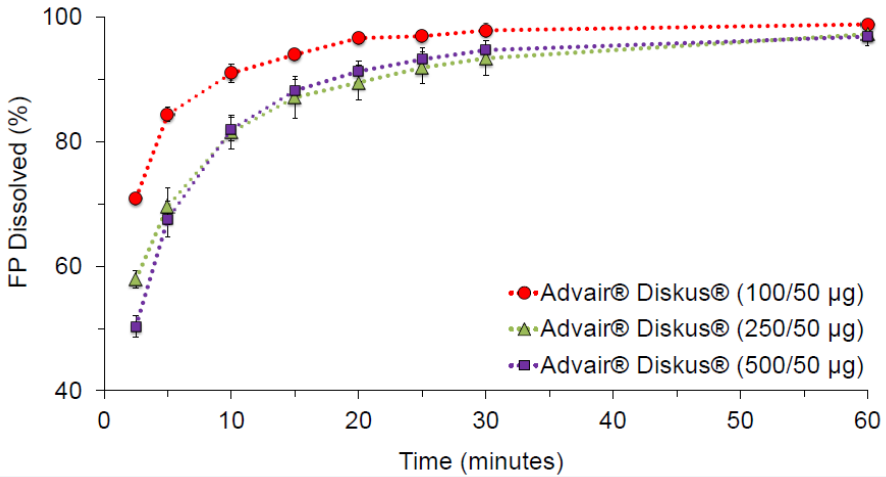


Figure 2: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg) as Red Circle, Advair® Diskus® (250/50 µg) as Green Triangle, and Advair® Diskus® (500/50 µg) as Purple Square. These are presented as mean ± standard deviation (n=2).

Mangal, S.; Conti, D. S.; Delvadia, R.; Oguntimein, O.; Shur, J.; Price, R. "Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization." In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.

Results: FP fractions across DPI products

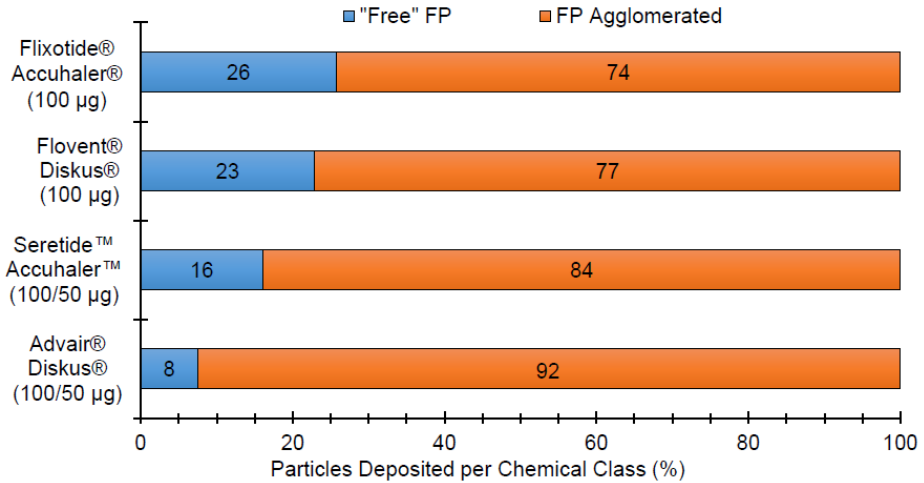


Figure 3: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg). These are presented as mean ± standard deviation (n=5).

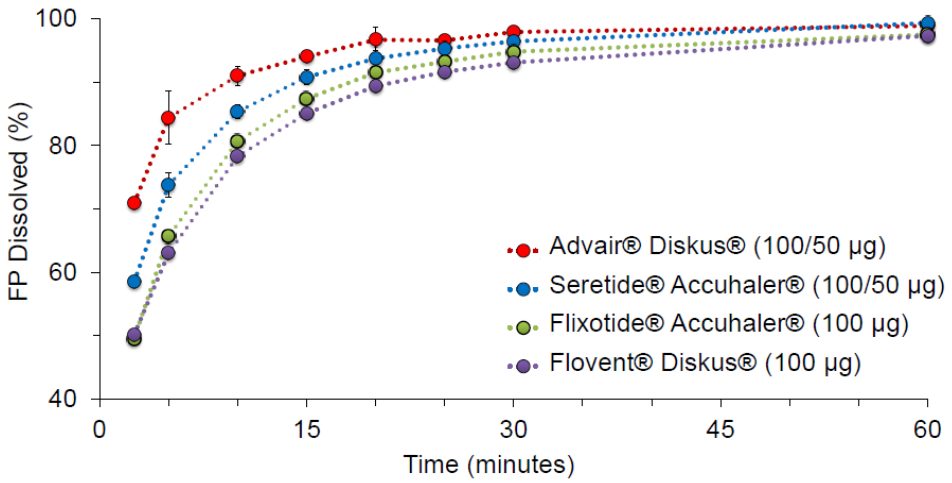


Figure 4: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide® Accuhaler® (100 µg), Flovent® Diskus® (100 µg), and Seretide® Accuhaler® (100/50 µg). These are presented as mean ± standard deviation (n=2).

Mangal, S.; Conti, D. S.; Delvadia, R.; Oguntimein, O.; Shur, J.; Price, R. "Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization." In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.

Results: FP in different DPI products

FP microstructure vs. FP dissolved – good correlation

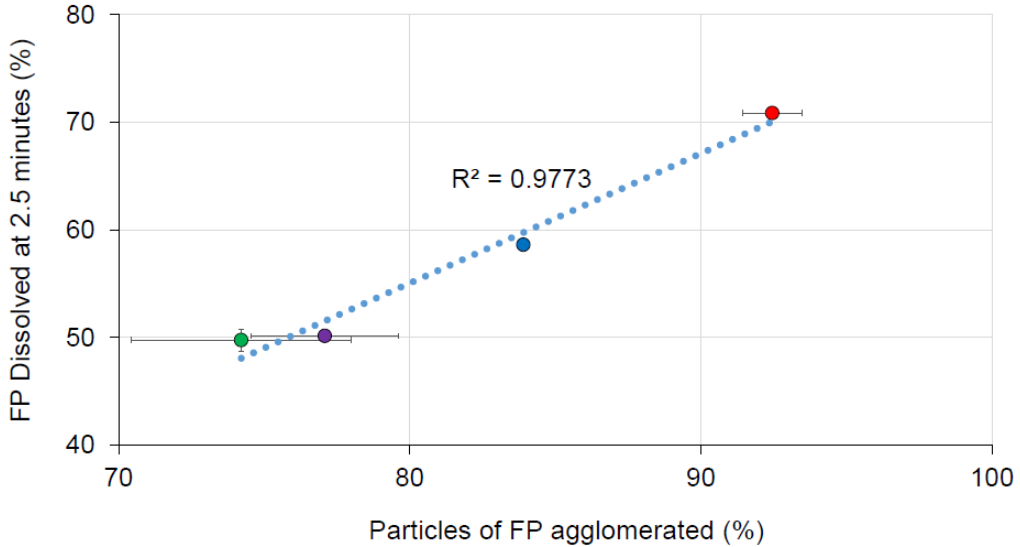


Figure 5: FP dissolved at 2.5 minutes (%) as a function of FP-lactose agglomerates (%) for Advair® Diskus® (100/50 µg, red circle); Flixotide® Accuhaler® (100 µg, green circle); Flovent® Diskus® (100 µg, purple circle); and Seretide® Accuhaler® (100/50 µg, blue circle).

Mangal, S.; Conti, D. S.; Delvadia, R.; Oguntimein, O.; Shur, J.; Price, R. "Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization." In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.

Conclusions

- GDUFA Regulatory Science Research supports ANDA review, approval and guidance development
- Research initiatives for locally-acting OINDPs explore new techniques to make generic product development and BE demonstration faster and more cost-effective
- An advanced analytical method, such as MDRS:
  - enables a comparison of drug PSD in generic and reference nasal spray suspension products
  - has the potential to provide information on formulation and/or microstructure differences between DPI products

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QUESTIONS?