American Thoracic Society (ATS) International Conference
May 14-19, 2021

Session: Generic Drug Development for Respiratory Products, US Food and Drug Administration Update

Denise S. Conti, PhD

EMERGING CONCEPTS AND NEW TECHNOLOGIES FOR BIOEQUIVALENCE OF ORALLY INHALED AND NASAL DRUG PRODUCTS

Disclosure to Learners

- **Financial relationships with relevant companies within the past 24 months:**
  - None

Disclaimers

- *The materials presented are available in the public domain.*

Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products

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Outline

- Generic Drug User Fee Amendments (GDUFA) Regulatory Science Program
- Research activities for locally acting orally inhaled and nasal drug products (OINDPs)
  - A new technology for particle size measurement in nasal suspension spray products and formulation/microstructure characterization in dry powder inhalers (DPIs)
  - In vitro dissolution for DPIs
  - The emerging concept of using pharmacokinetic (PK) studies to provide information on pulmonary performance characteristics
- Conclusions

GDUFA Regulatory Science Program

- Funding from GDUFA is used by FDA to help strategically stimulate innovation and growth of generic drugs in all therapeutic areas and product categories
  - Identify, study, and implement new methodologies and tools
  - Development and evaluation of quality and equivalence of new generic drug products
- Competitive research grants and contracts are awarded yearly
- FDA annual public workshop seeks stakeholder input on research priorities for generic drug development
  - Industry, Academia
  - Patient advocates, Professional societies

https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-regulatory-science
https://www.fda.gov/drugs/generic-drugs/science-research

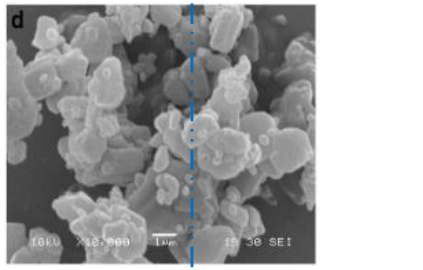
Research Initiatives for OINDPs

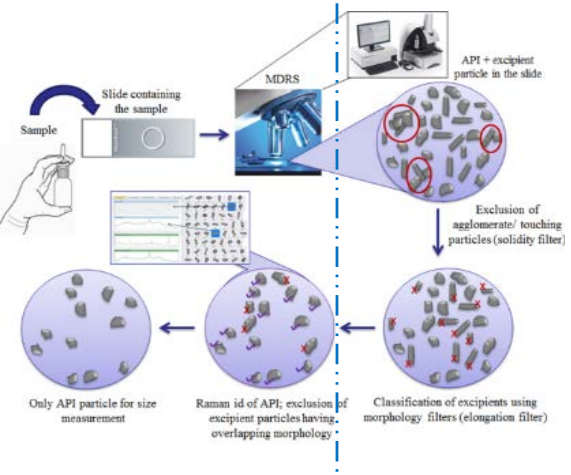
- Identification of formulation and device variables
- Development of clinically relevant in vitro methods for prediction of in vivo drug deposition and dissolution
- Identification, validation, and standardization of novel techniques that may have the potential to reduce the burden of current BE requirements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

https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2016-regulatory-science-report-locally-acting-orally-inhaled-and-nasal-drug-products

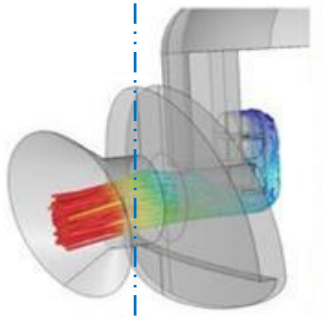
Research Activities for OINDPs

Formulation



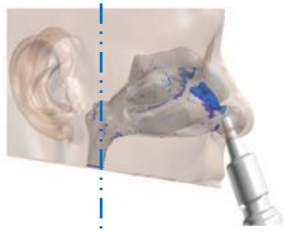


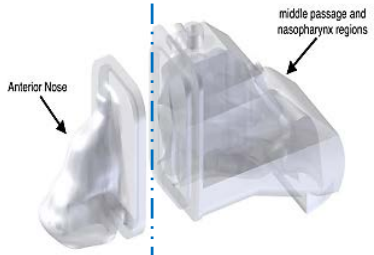
Device



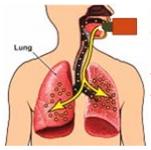
HF CONSIDERATIONS

User Interface



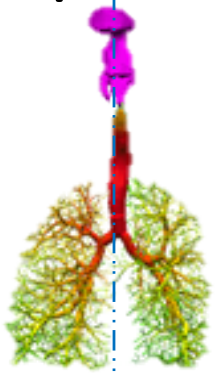


OUTCOME

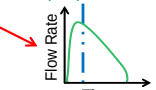


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Regional Deposition

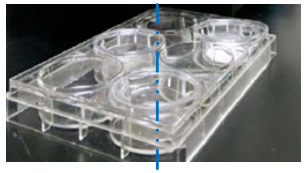


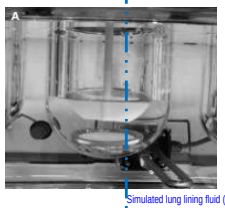
Physical mouth-throat (MT) models

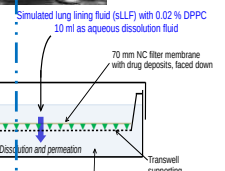


Representative inhalation profiles (IP)

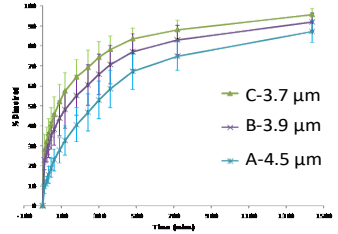
Dissolution



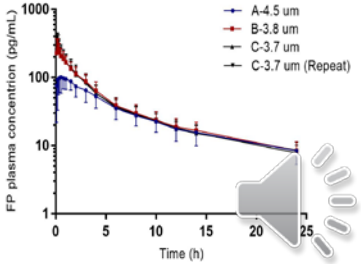




In vitro APSD test more predictive of in vivo deposition

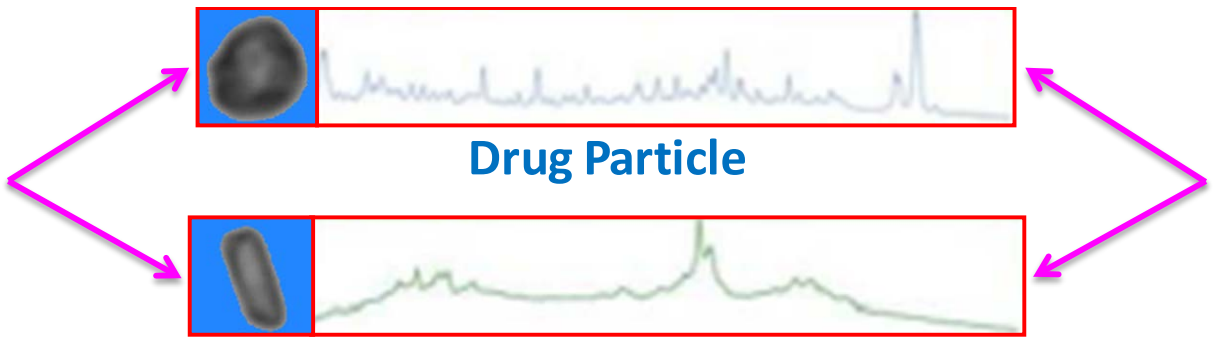


Absorption



MDRS for Nasal Suspension Sprays

- Drug particle size distribution (PSD) in nasal suspension formulations has the potential to influence **the rate and extent of drug availability** to nasal sites of action and systemic circulation
- 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



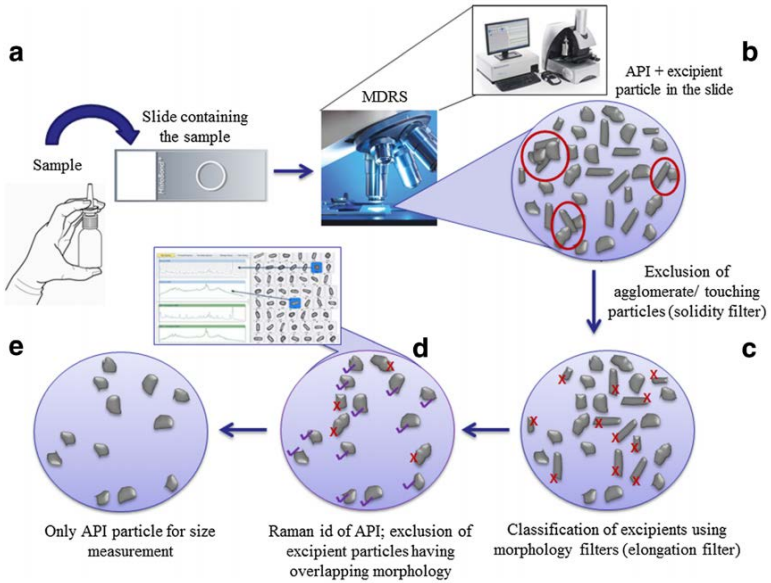
GDUFA Research Outcomes
Publications on MDRS

The AAPS Journal (2019) 21: 14
DOI: 10.1208/s12248-018-0283-9

Regulatory Note

Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective

Qing Liu,[1] Mohammad Absar,[1,2] Bhawana Saluja,[1,2] Changning Guo,[3] Badrul Chowdhury,[4,5] Robert Lionberger,[1] Dale P. Conner,[1] and Bing V. Li[1,6]



Basic operating steps of MDRS. **a** Sample preparation; **b** morphological measurement of particles in the sample, exclusion of aggregates, and touching particles; **c** selection of particle of interest using morphology filters; **d** identification of particles using Raman spectra; **e** size measurement of the particle of interest

Journal of Pharmaceutical Sciences 000 (2021) 1–11

Contents lists available at ScienceDirect

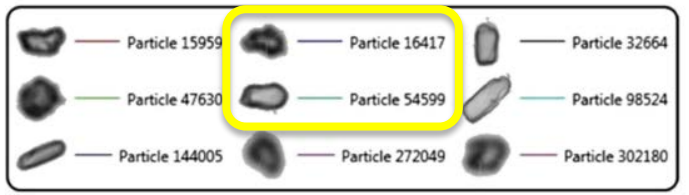
Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Analytical method development for characterizing ingredient-specific particle size distributions of nasal spray suspension products

Brandon J. Thomas[a,1], Mohammad Absar[b,2], Renishkumar Delvadia[b,3], Denise S. Conti[b], Kimberly Witzmann[b,4], Changning Guo[a,*]



Correlations

	Particle ID	15959	16417	32664	47630	54599	98524	144005	272049	302180
API		0.975	0.980	0.086	0.983	0.052	0.000	0.001	0.976	0.981
excipient		0.000	0.000	0.709	0.000	0.697	0.689	0.707	0.000	0.000

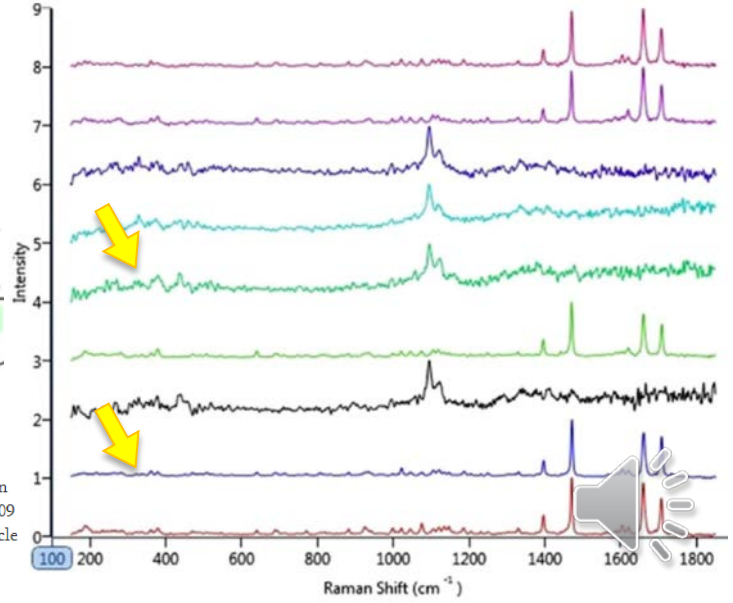
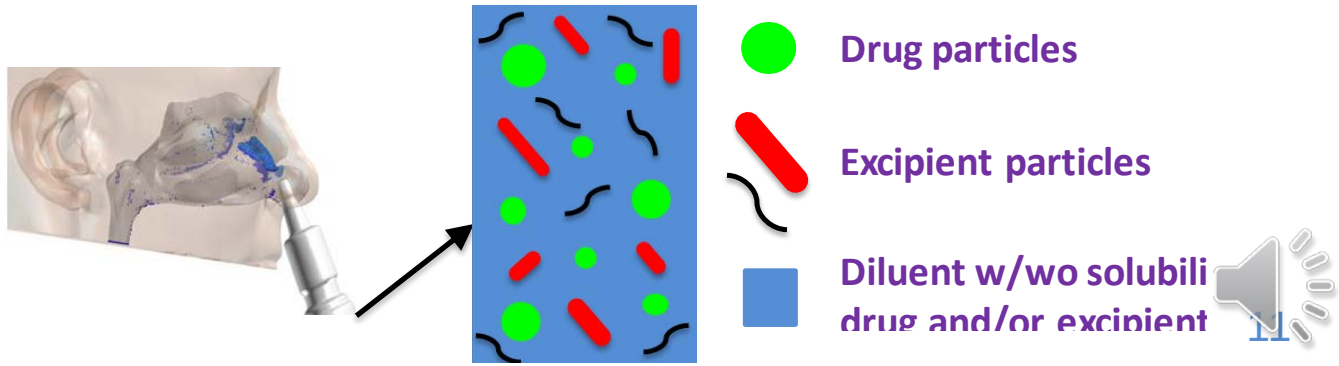


Fig. 3. Representative Raman spectra of API and excipient particles suspended in a mometasone furoate nasal spray formulation. In order of increasing particle ID, their Raman spectra are shown from bottom to top, and their respective particle sizes (in diameter) are 6.09 μm, 4.68 μm, 7.70 μm, 5.23 μm, 7.42 μm, 13.87 μm, 7.12 μm, 3.50 μm, and 4.65 μm. Each particle spectrum was compared to API and excipient reference spectra and assigned a correlation score.

GDUFA Research Has Informed ANDA Review Process and PSG Development

- We have been able to use MDRS
  - to support **BE assessment** for complex nasal suspension spray products, which precluded an applicant from repeating a comparative clinical endpoint BE study, and led to ANDA approval for the first generic Mometasone Furoate Nasal Suspension [RLD: Nasonex® NDA 20762]
  - in **PSGs as alternative approach** to the comparative clinical endpoint BE study for other nasal suspension spray products
    - Fluticasone Propionate and Azelastine Hydrochloride
    - Fluticasone Propionate
    - Fluticasone Furoate
    - Triamcinolone Acetonide
    - Mometasone Furoate
    - Budesonide



Microstructure of DPIs Using Orthogonal Analytical Approaches

- FY-17 Contract # HHSF223201710116C awarded to University of Bath (UK)
- 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 dry powder inhaler (DPI) formulations
  - Product selection: DPIs manufactured by the same pharmaceutical company
  - Sample: Impactor-sized mass (ISM) using aerosol dose collection (ADC) system*
  - In vitro dissolution: modified USP Apparatus V, Paddle Over Disk (POD), ISM collected from 500 µg fluticasone propionate (FP)*
  - MDRS: filter substrate with ISM from one actuation using Morphology G3-ID®

https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582981.pdf

* Price, R., Shur, J., Ganley, W. et al. Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products. AAPS J 22, 47 (2020). https://doi.org/10.1208/s12248-020-0422-y

Fluticasone Propionate (FP) Fractions Across DPI Products

MDRS

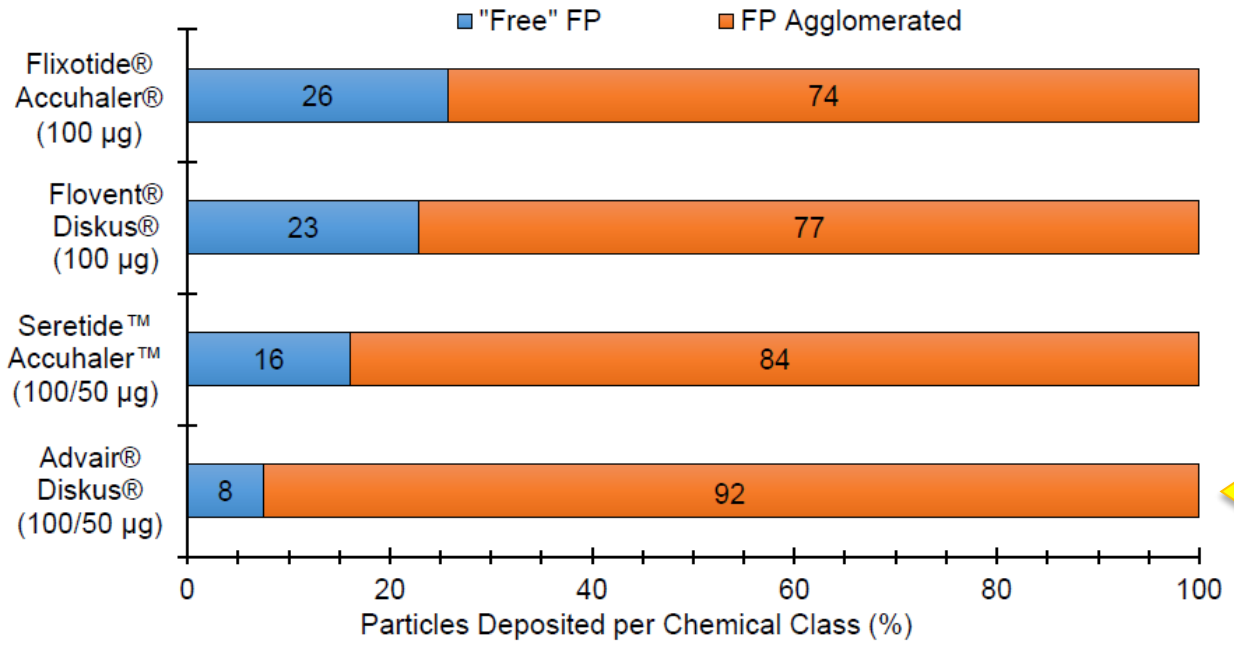


Figure 3: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg). These are presented as mean ± standard deviation (n=5).

In Vitro Dissolution

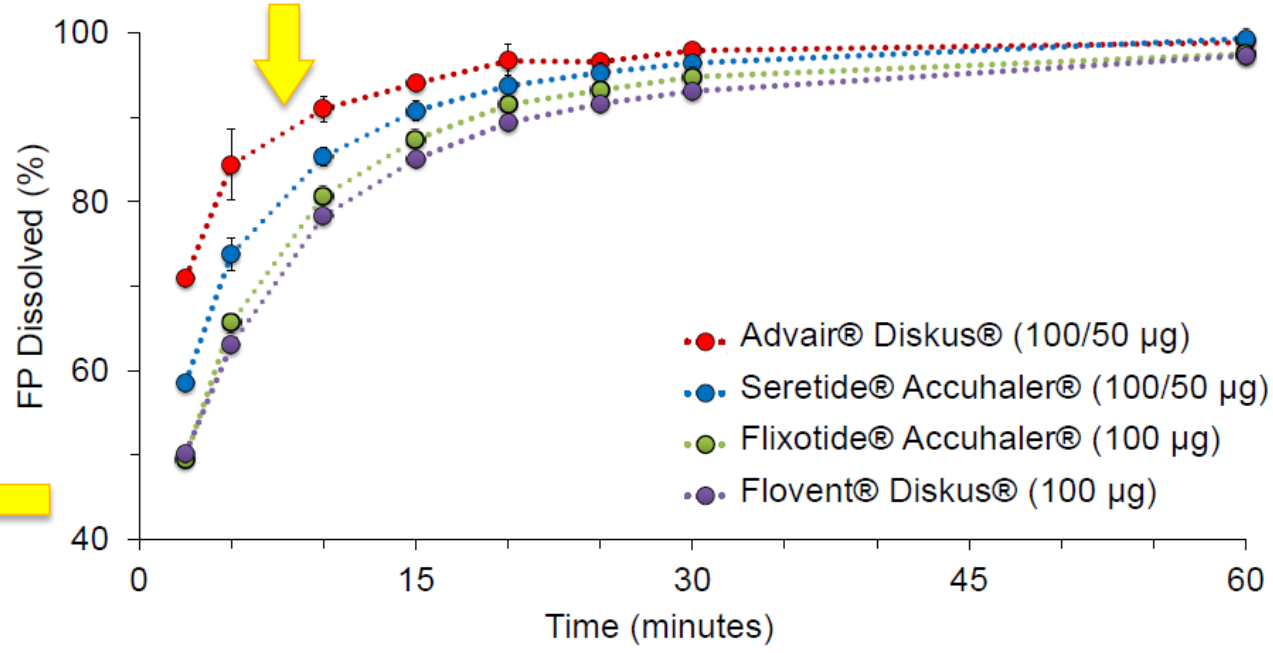


Figure 4: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide® Accuhaler® (100 µg), Flovent® Diskus® (100 µg), and Seretide® Accuhaler® (100/50 µg). These are presented as mean ± standard deviation (n=2).

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.

Dissolution and Microstructure of DPIs

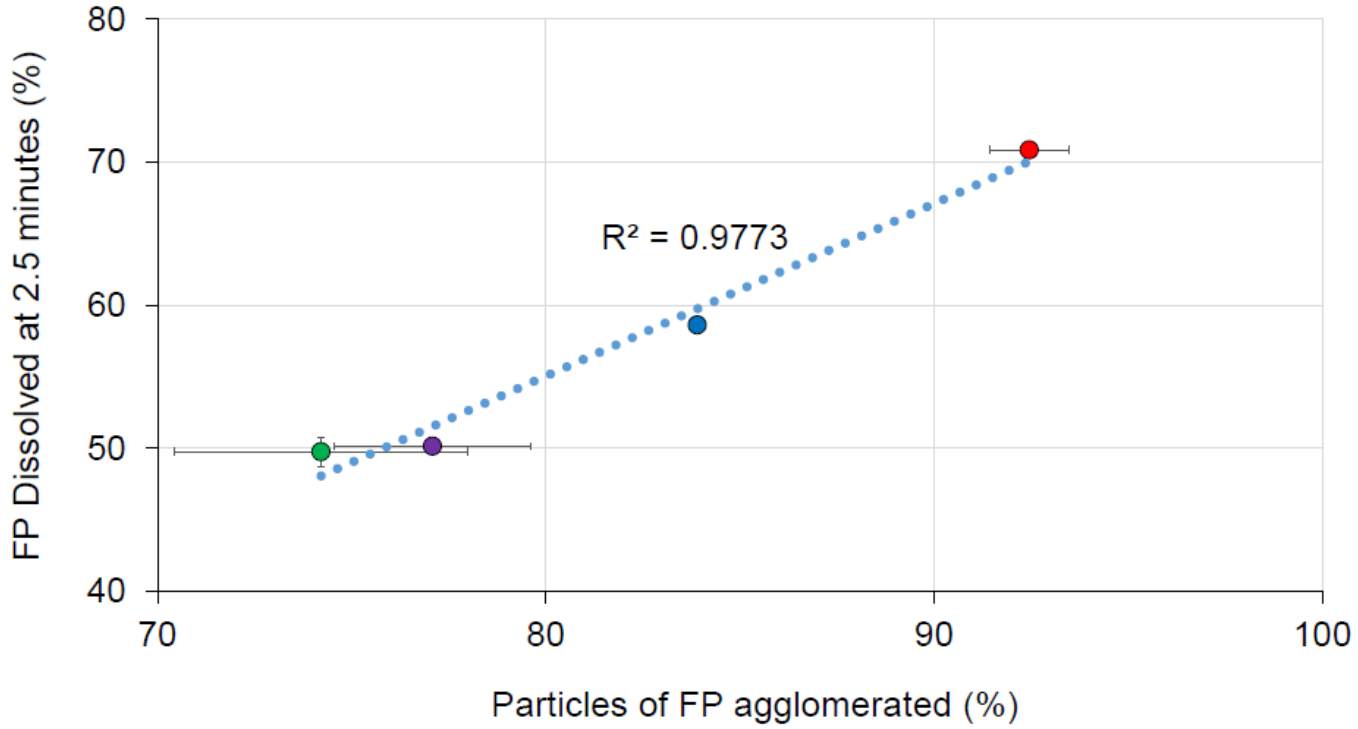


Figure 5: FP dissolved at 2.5 minutes (%) as a function of FP-lactose agglomerates (%) for Advair® Diskus® (100/50 µg, red circle); Flixotide® Accuhaler® (100 µg, green circle); Flovent® Diskus® (100 µg, purple circle); and Seretide® Accuhaler® (100/50 µg, blue circle).

- FP dissolved vs. FP agglomerated – good correlation
- In vitro dissolution is able to capture differences in DPI formulations

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.

PK Comparison of Locally Acting DPIs

- Contracts awarded to University of Florida (US)
  - FY-13 Contract # HHSF223201110117A
  - FY-16 Contract # HHSF223201610099C
- To evaluate whether PK profiles are sensitive to DPI formulations that differ in the central to peripheral (C/P) lung deposition ratio, a clinical study was conducted to evaluate the PK profiles of healthy adult subjects after a single-dose of different orally inhaled FP formulations administered using a DPI
  - Formulation development
  - In vitro characterization
  - PK clinical study
  - PK data analysis

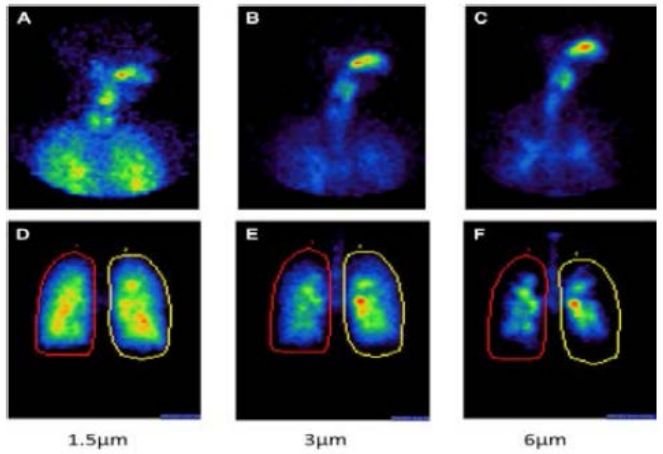
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM526210.pdf

GDUFA Research Outcomes
Publication on DPI-PK Study

- Hypothesis – for slowly dissolving drugs, such as FP, a formulation that deposits drug particles more centrally yields to smaller AUC and Cmax, even though comparing two formulations that provide the same dose to the lung

	Central deposit	Peripheral deposit
Absorption	Slow	Fast
Mucociliary clearance	Yes	No
Mass median aerodynamic diameter (MMAD)	↑	↓
Cmax	↓	↑
AUC	↓	↑

Cmax: peak plasma concentration
AUC: area under the plasma concentration time curve



The AAPS Journal (2021) 23:48
DOI: 10.1208/s12248-021-00569-x

Research Article

Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate?

Günther Hochhaus,[1,14] Mong-Jen Chen,[1,2] Abhinav Kurumaddali,[1] Uta Schilling,[1] Yuanyuan Jiao,[3] Stefanie K. Drescher,[1] Elham Amini,[1] Bhargava Kandala,[1] Christine Tabulov,[1] Jie Shao,[1] Brandon Seay,[4] Mutasim N. Abu-Hasan,[4] Sandra M. Baumstein,[3] Lawrence Winner,[5] Jagdeep Shur,[6] Robert Price,[6] Michael Hindle,[7] Xiangyin Wei,[7] Cynthia Carrasco,[8] Dennis Sandell,[9] Oluwamurewa Oguntimein,[10] Minori Kinjo,[10] Renishkumar Delvadia,[10,11] Bhawana Saluja,[10,12] Sau L. Lee,[13] Denise S. Conti,[10] and Jürgen B. Bulitta[3,14]

Received 3 October 2020; accepted 6 February 2021

Formulation Development

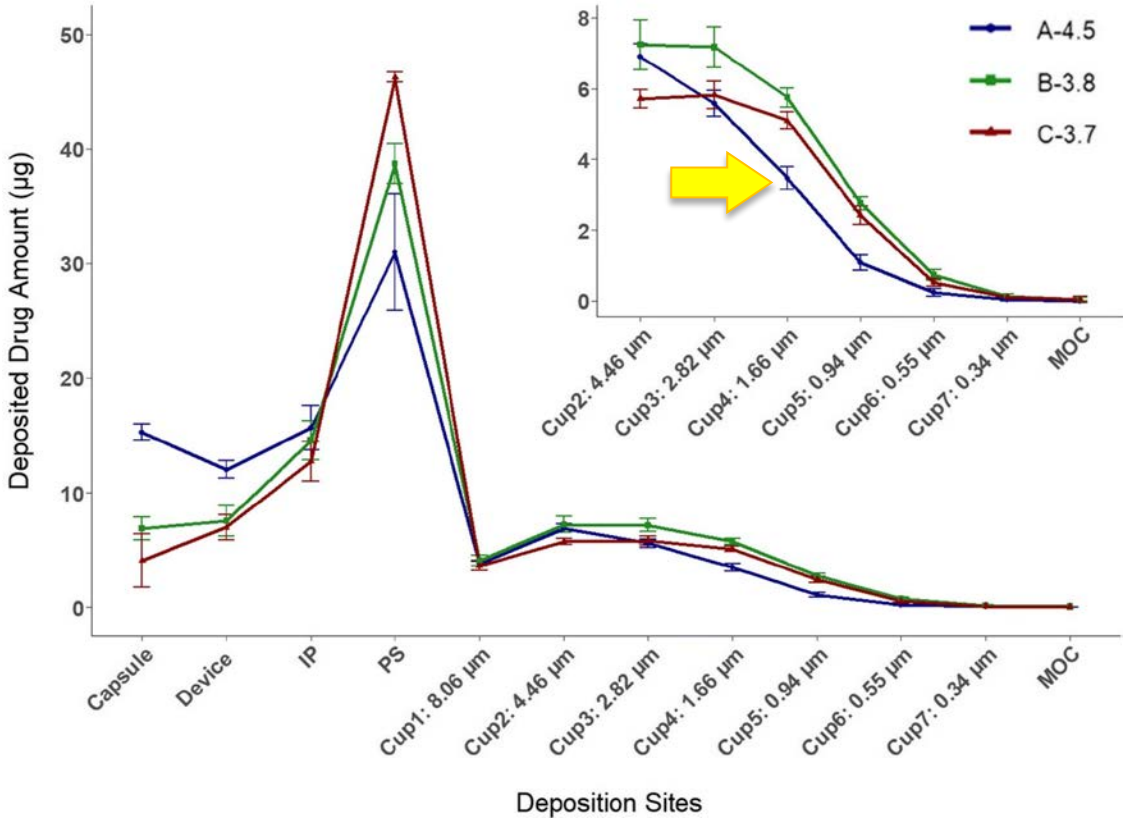
- In collaboration with University of Bath (UK)
- Three DPI formulations only differing in lactose fines

Product Name	Formulation (% w/w)	MMAD
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 96.72 Lactohale LH300: 2.48	C-3.7µm
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 79.36 Lactohale LH201: 19.84	A-4.5µm
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 89.28 Lactohale LH230: 9.92	B-3.8µm

Günther Hochhaus and Jürgen Bullita. Pharmacokinetic Comparison of Locally Acting Dry Powder Inhalers. In: DIA Meeting on Complex Drug-Device Generic Combination Products, Oct 9-10, 2018, Silver Spring, MD, USA. Podium Presentation.

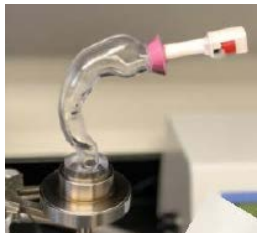
In Vitro Characterization

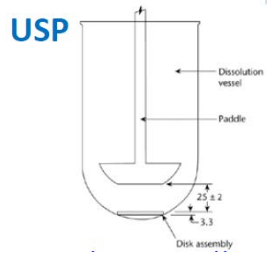
- Aerodynamic Particle Size Distribution (APSD)

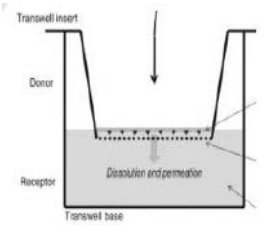


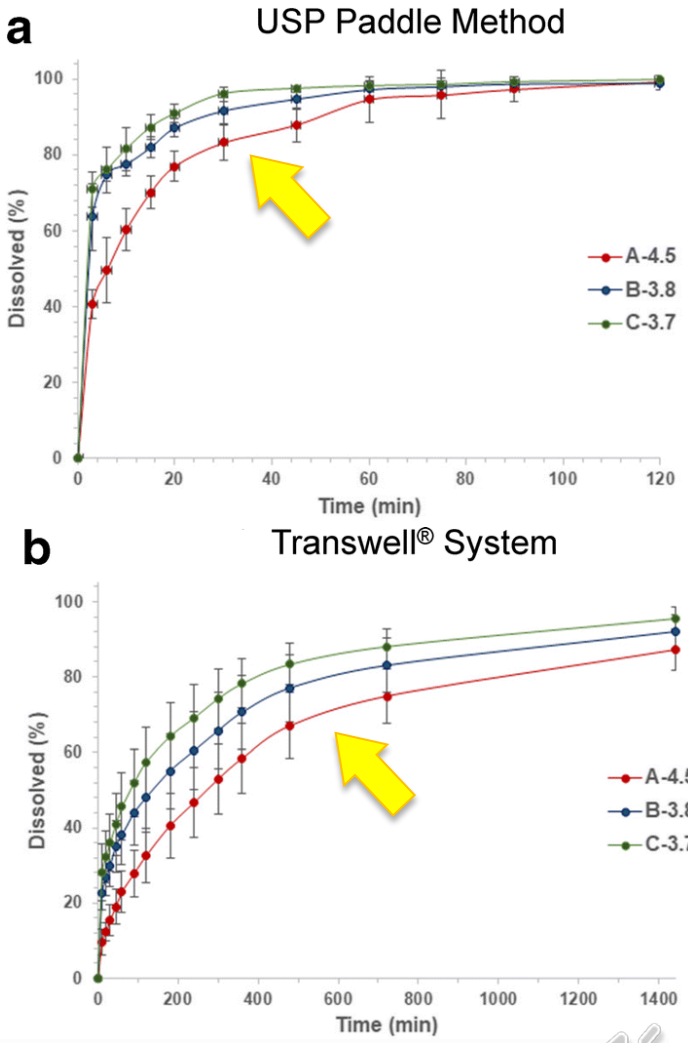
APSD deposition profiles from compendial NGI *in vitro* testing (mean ± standard deviation of at least 5 replicates; data combined from samples stored from 12 to 20 months at ambient conditions (25°C; 60% RH) which is a good representation of the FP DPI formulations administered in the PK study). IP, induction port; PS, pre-separator; MOC, micro-orifice collector **NGI: Next Generator Impactor**

- Dissolution





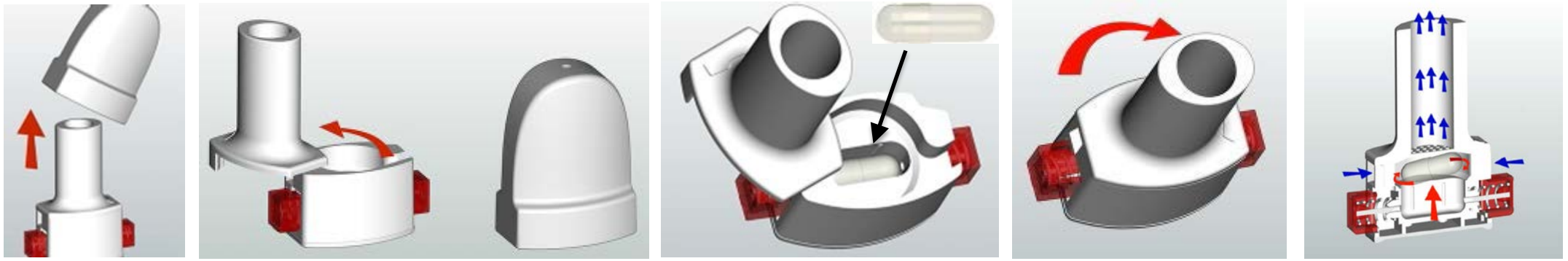




Dissolution of FP DPI formulations. Percent dissolved (mean ± standard deviation) of FP DPI formulations A-4.5, B-3.8, and C-3.7 using either the USP paddle apparatus (**a**) or the Transwell® system (**b**)

PK Study Design

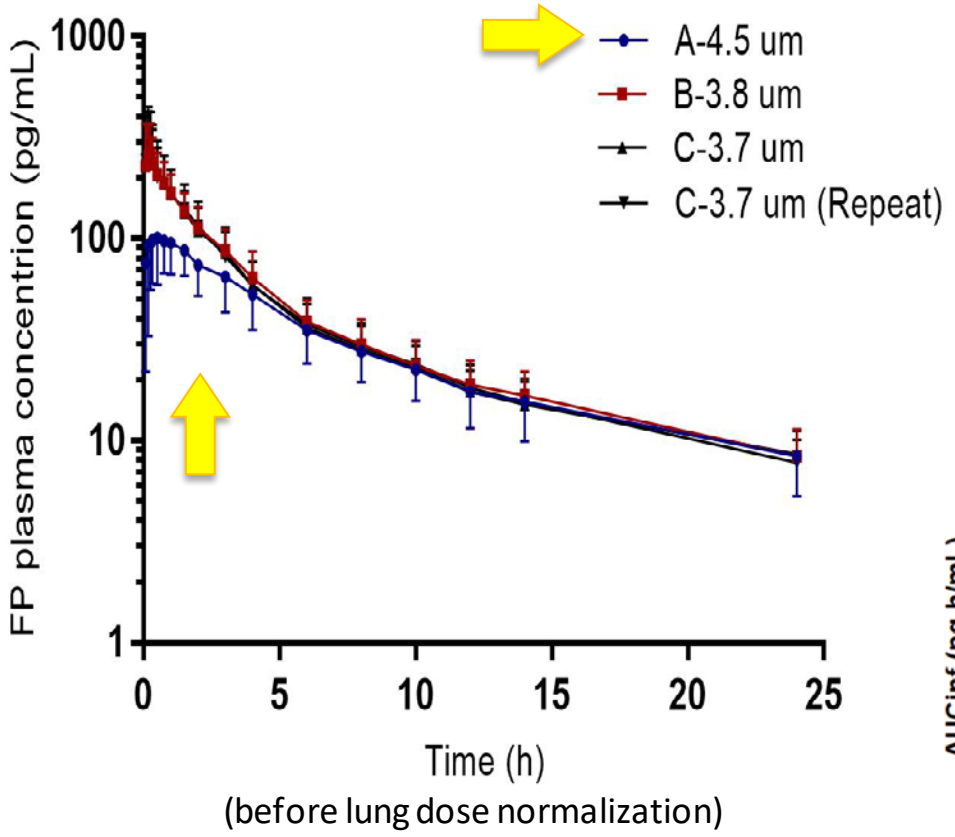
- Randomized, double-blind, four-way crossover study in 24 healthy adult subjects (informs intra-subject variability)
- FP DPI formulations delivered with Plastiape device



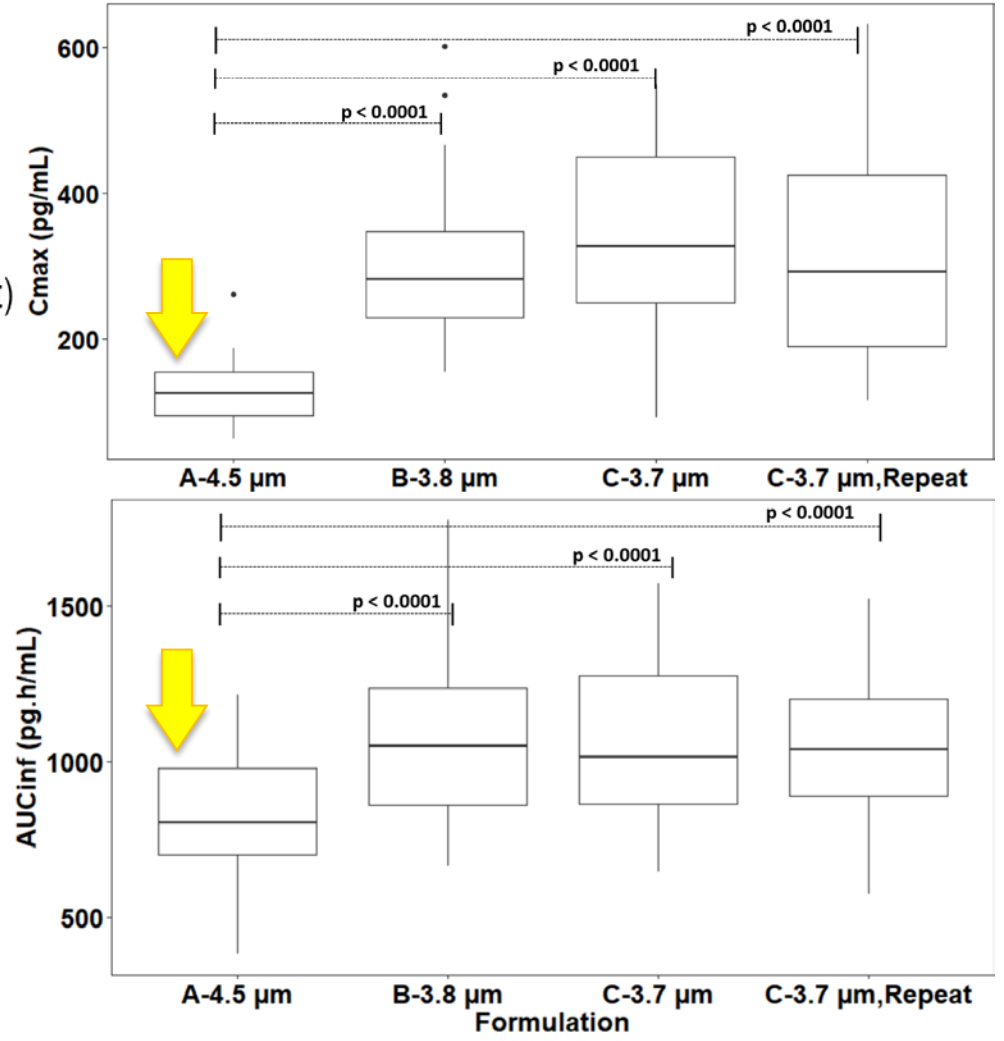
https://www.worldpharmaceuticals.net/contractors/drug-delivery-systems/plastiape/

- Dose: 5 x 100 µg FP
- Individual inhalation profiles recorded
- LC-MS/MS assay sensitivity: 1 pg/mL
- Non-compartmental Analysis + Compartmental Analysis (population-PK)

PK Study Results



(before lung dose normalization)



- This work supports the use of PK studies to provide relevant information on pulmonary performance characteristics (e.g., available dose, residence time, and regional lung deposition)

Günther Hochhaus and Jürgen Bullita. Pharmacokinetic Comparison of Locally Acting Dry Powder Inhalers. In: DIA Meeting on Complex Drug-Device Generic Combination Products, Oct 9-10, 2018, Silver Spring, MD, USA. Podium Presentation.

Additional New Technologies for Alternative BE Approaches for OINDPs

- In general, if a generic OINDP shows formulation sameness (qualitative and quantitative) and device similarity to the reference OINDP, additional supportive studies **may** provide a foundation to help ensure **equivalence at the local site of action potentially without conducting comparative clinical endpoint BE studies**

More Predictive APSD Testing (representative mouth-throat models and breathing profiles)
- Understand impact of patient variability

Characterization of Emitted Sprays (velocity profiles and evaporation rates)
- Understand droplet size and evaporation process of formulation emitted from the device

Morphology Imaging Comparisons (characterization of full range of residual drug particle sizes)
- Understand residual particle morphology and size distribution of formulation emitted from the device

Dissolution
- Understanding how API dissolved at site of action for absorption once deposited

Quantitative Methods and Modeling (e.g., **physiologically-based PK; computational fluid dynamic studies)**
- In vitro-in vivo correlations (IVIVCs; bridge gap between in vitro product performance and regional drug deposition)

Alternative PK BE Studies
- Understanding how PK studies may correlate to in local deposition

Conclusions

- GDUFA Science and Research supports guidance development, ANDA assessment, and approval
- Research initiatives for locally acting OINDPs **explore new technologies and new concepts** to make generic product development and BE demonstration feasible, faster, efficient and more cost-effective potentially without comparative clinical endpoint BE studies
  - Advanced analytical techniques, such as **MDRS**, enabled comparison of drug PSD in generic and reference nasal suspension spray products and improved understanding of formulation/microstructure of DPIs that may help to explain **dissolution** performance
  - Alternative **PK studies** for OIDPs may provide relevant information on pulmonary performance characteristics (e.g., available dose, residence time, and regional lung deposition)

Acknowledgements

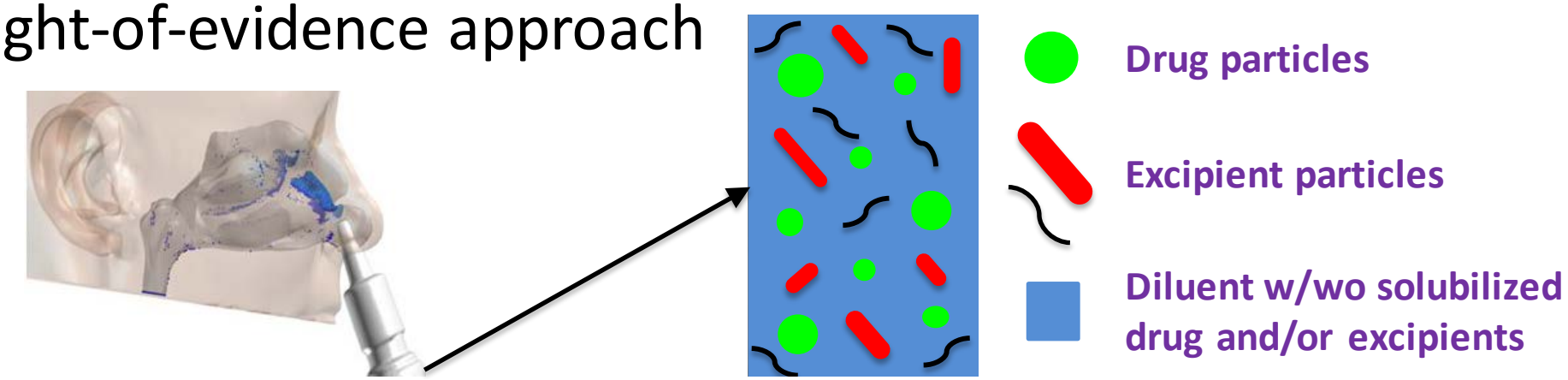
• Elizabeth Bielski, PhD	FDA
• Liangfeng Han, MD, PhD	FDA
• Bryan Newman, PhD	FDA
• Murewa Oguntimein, PhD	FDA
• Kimberly Witzmann, MD	FDA
• Markham Luke, MD, PhD	FDA
• Robert Lionberger, PhD	FDA
• Lei Zhang, PhD	FDA
• Changning Guo, PhD	FDA
• Renish Delvadia, PhD	FDA
• Jag Shur, PhD	University of Bath
• Robert Price, PhD	University of Bath
• Jürgen Bulitta, PhD	University of Florida
• Güenther Hochhaus, PhD	University of Florida


FDA
U.S. FOOD & DRUG
ADMINISTRATION

BACKUP SLIDES

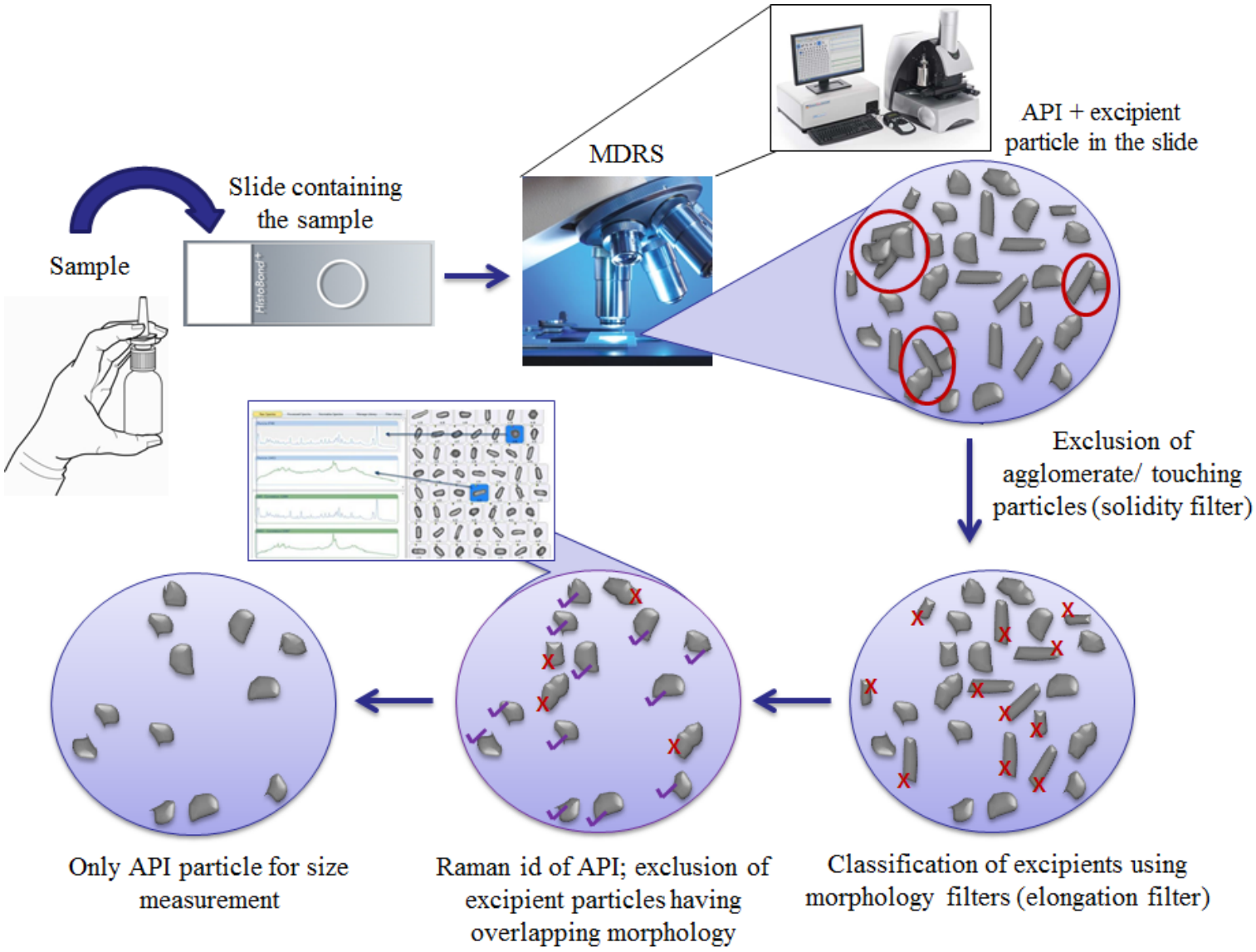
Locally Acting Nasal Suspension Sprays

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



- Drug particle size distribution (PSD) in nasal 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: How does it work?

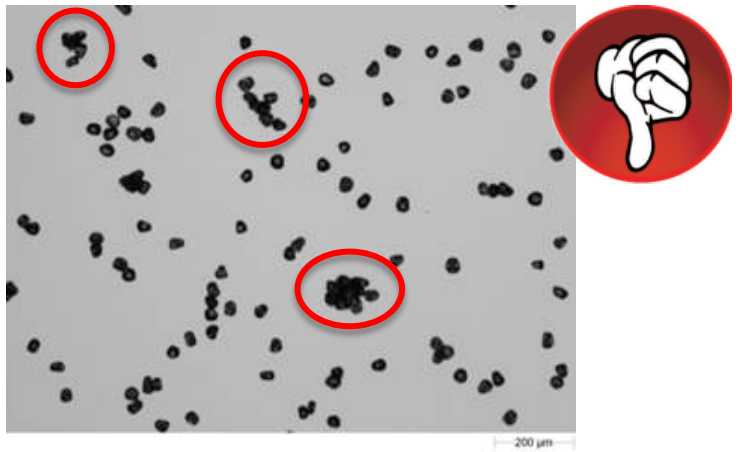


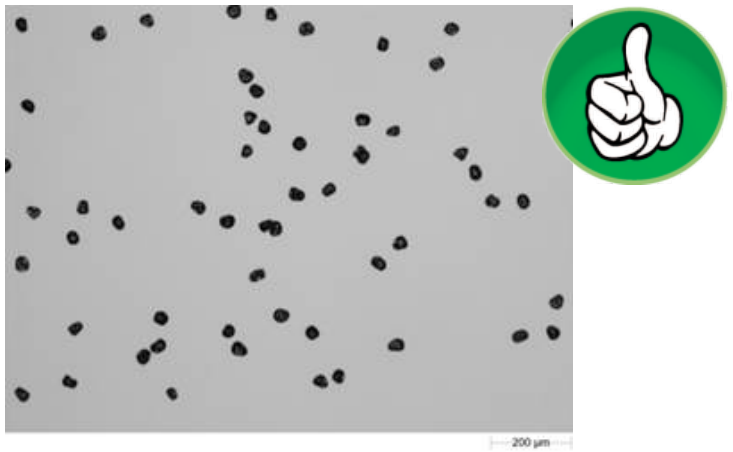
Courtesy of Dr. Abir Absar, Ph.D. (FDA/OCP)

Removal of Agglomerates and Touching Particles

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

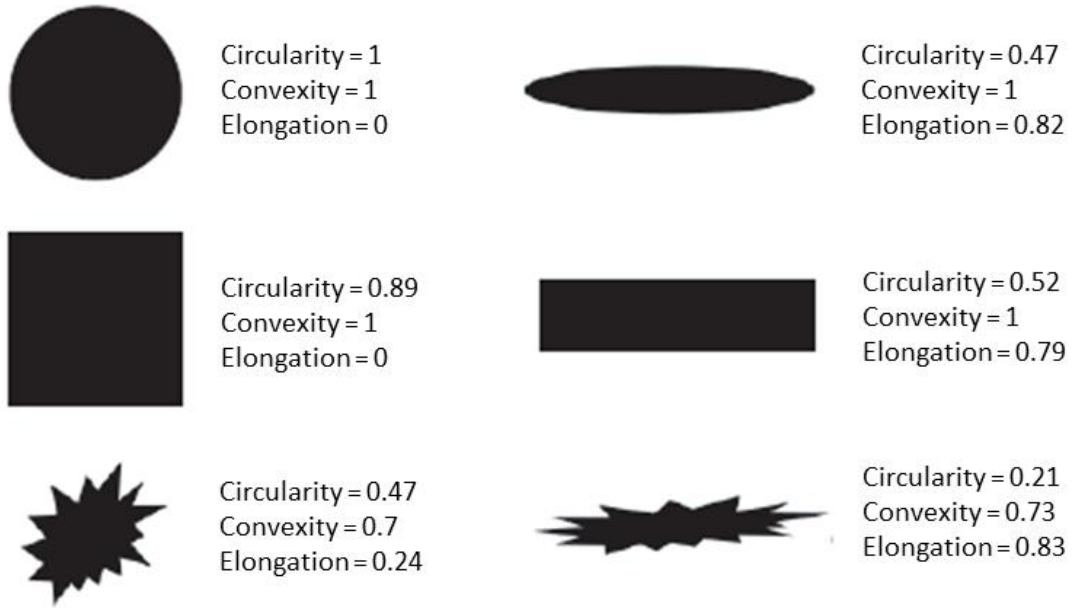
- Sample preparation – Can give misleading data





Particle Classification Using Morphology Filters

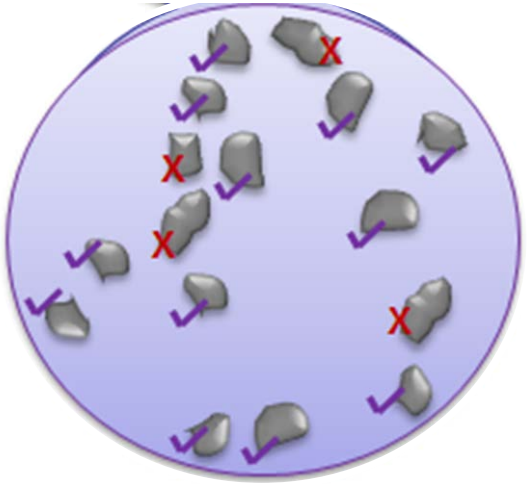
- Should exclude as many excipient particles as possible
- Should not exclude drug particles
- Morphology filters
  - Size
    - Circular equivalent (CE) diameter
  - Shape
    - Aspect ratio
    - Elongation
    - Circularity
    - Convexity
    - Solicity



<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.

MDRS for DPIs – 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

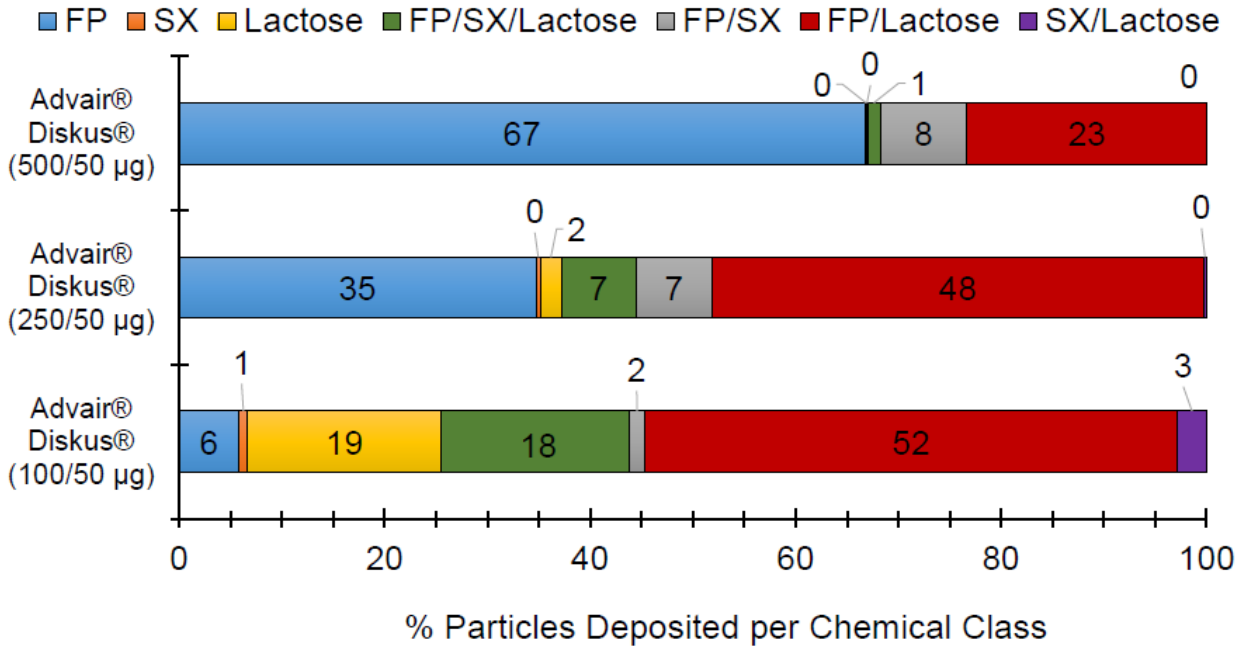


Figure 1: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Advair® Diskus® (FP/SX; 250/50 µg), and Advair® Diskus® (FP/SX; 500/50 µg). These are presented as mean ± standard deviation (n=5).

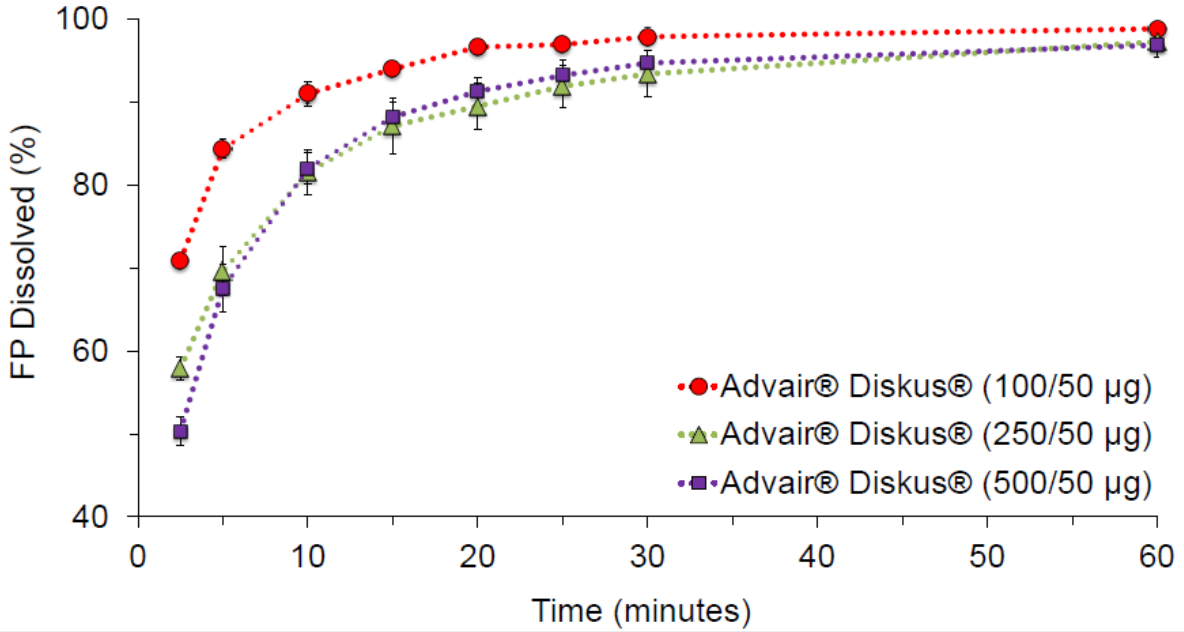


Figure 2: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg) as Red Circle, Advair® Diskus® (250/50 µg) as Green Triangle, and Advair® Diskus® (500/50 µg) as Purple Square. These are presented as mean ± standard deviation (n=2).

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.