EMERGING TECHNOLOGIES FOR BIOEQUIVALENCE OF GENERIC COMPLEX DRUG-DEVICE COMBINATION PRODUCTS

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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

- Generic Drug User Fee Amendments (GDUFA) of 2012
- GDUFA Regulatory Science Program
- Research initiatives for locally-acting orally-inhaled and nasal drug products (OINDPs)
  - Development of a **clinically relevant in vitro test** for prediction of in vivo drug deposition in the lungs
  - A **novel technique** for particle size measurement in nasal suspension products that may have the potential to reduce the burden of current bioequivalence (BE) requirements
- Conclusions

Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 to speed access to safe and effective generic drugs to the public
- Requires user fees to supplement costs of reviewing generic drug applications and provides additional resources, including support for **regulatory science research**
- Agreement that user fees can directly support regulatory science research activities

GDUFA Regulatory Science Program

- Supports access to **generic drugs in all product categories**
  - Inhalation, nasal
  - Topical dermatological, transdermal
  - Ophthalmic, liposomal
  - Sustained release parenteral
- Development of **new tools** to evaluate drug equivalence and support generic drug development
  - Simulation tools to predict drug absorption
  - Advanced analytical methods for product characterization
  - In vitro methods to predict in vivo performance

Goals of GDUFA Research

- Enhance access to generic versions of **complex products**
  - Expand the use of **in vitro BE approaches**
- Research identifying issues that need to be addressed in pharmaceutical development
- Provide characterization methods and performance tests that are needed for in vitro BE approaches

GDUFA Regulatory Science Program

- Over **100** extramural grants/contracts awarded since 2013 by the **Office of Research and Standards** in the Office of Generic Drugs
  - External collaborations: academia, industry
  - Internal collaborations: FDA labs, other government agencies

Regulatory Science Priorities

- Post-market evaluation of generic drugs (16 extramural projects awarded)
- Equivalence of complex drug products (32)
- Equivalence of locally acting products (23)
- Therapeutic equivalence evaluation and standards (20)
- Computational and analytical tools (19)

Locally-Acting Orally-Inhaled and Nasal Drug Products (OINDPs)

- Performance is governed by **complex** interactions between **formulation**, **device**, and **patient factors**
- Current regulatory pathway for BE demonstration utilizes the **weight-of-evidence** approach
  - Qualitative and quantitative sameness of formulation
  - In vitro comparative studies
  - In vivo pharmacokinetic (PK) studies
  - Pharmacodynamic (PD) or comparative clinical endpoint study
  - Device substitutability
- The Office of Generic Drugs continues to explore **new methods** to make development and BE demonstration more cost- and time-effective

Research Coordination for OINDPs

Formulation

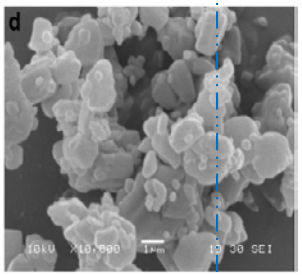
Device

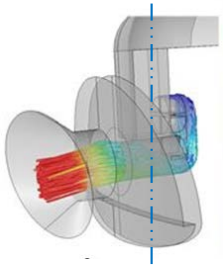
Human Factors

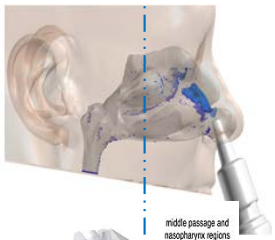
Regional Deposition

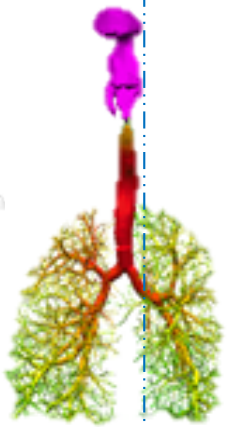
Dissolution

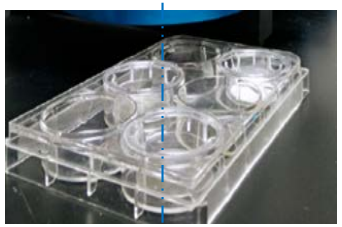
Absorption

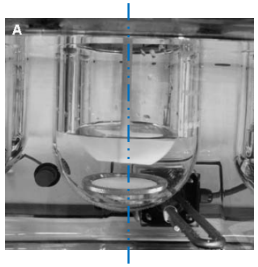


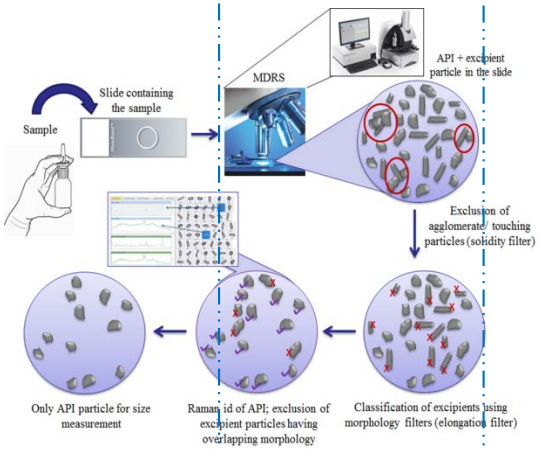


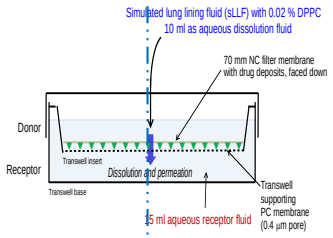












www.fda.gov

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
- 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

Clinically Relevant In Vitro Performance Test

- Research grant # U01FD005231 awarded to Virginia Commonwealth University (VCU) in 2014

- To determine whether **realistic physical mouth-throat models** provide better in vivo predictability to characterize aerodynamic particle size distribution (APSD) of orally-inhaled drug products (OIDPs)

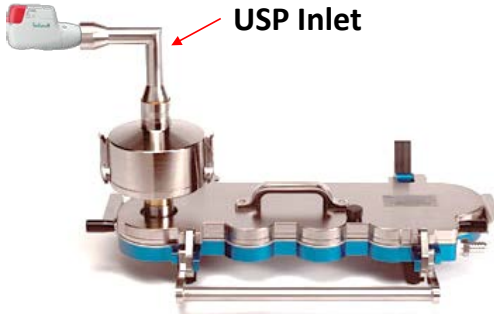
Why should we perform more realistic APSD in vitro tests for OIDPs?

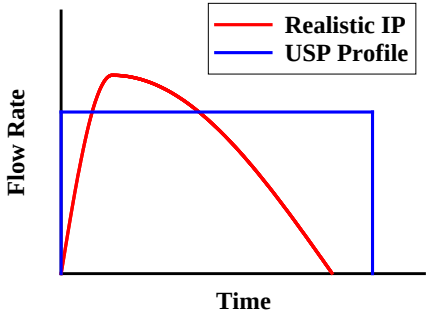
- APSD defines where the particles are likely to be deposited following inhalation
  - 1 - 5 μm: Lungs
  - > 5 μm: Oropharynx and swallowed
  - < 1 μm: Exhaled
- Current in vitro methods for APSD determination are designed for **quality control** and may not be predictive of deposition in vivo
- USP inlet and inhalation profile are **less predictive** and do not account for variability

Andersen Cascade Impactor (ACI)

Next Generation Impactor (NGI)

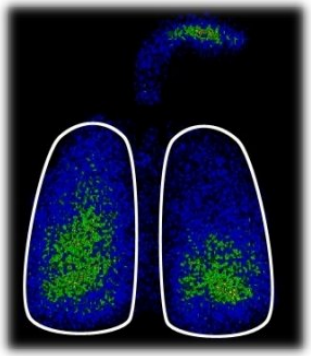
http://www.copleyscientific.com/downloads/brochures





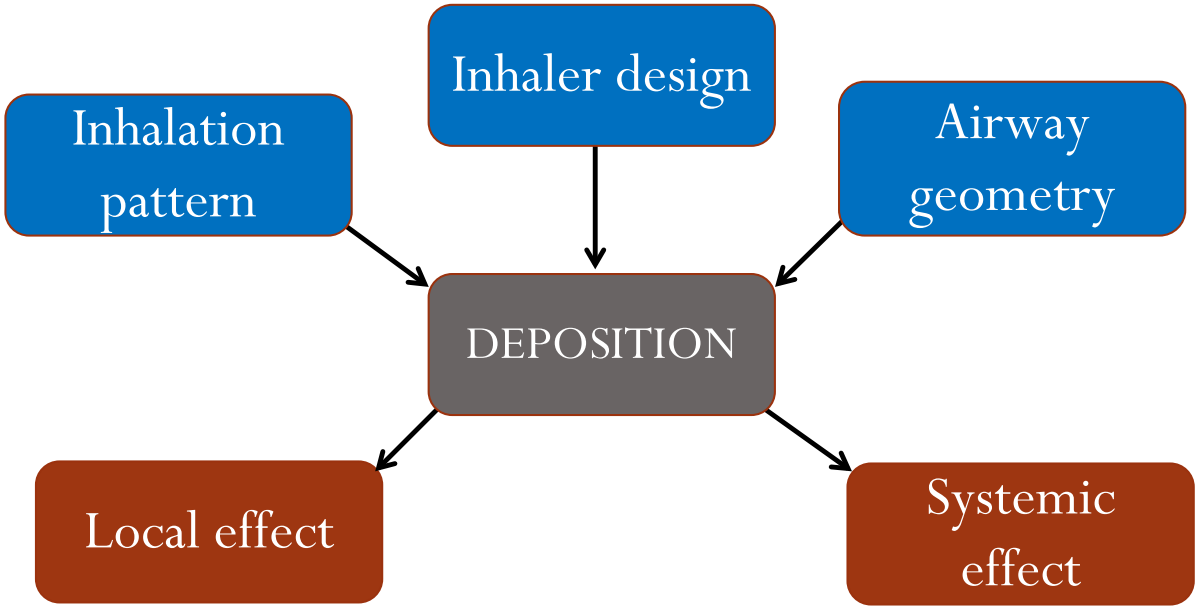
Why should we perform more realistic APSD in vitro tests for OIDPs?

- In vivo imaging methods (e.g., Gamma scintigraphy) are expensive and expose patients to radiation



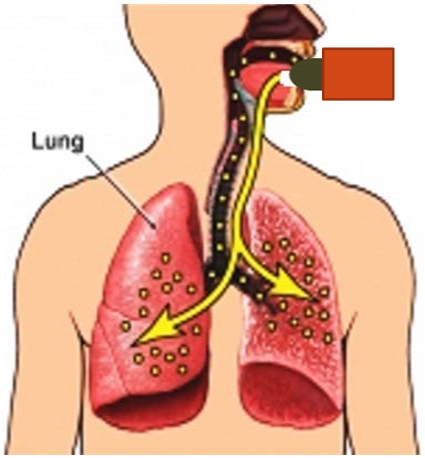
http://www.flowcaps.com/trial.htm

- Several factors influence the fate of inhaled medication



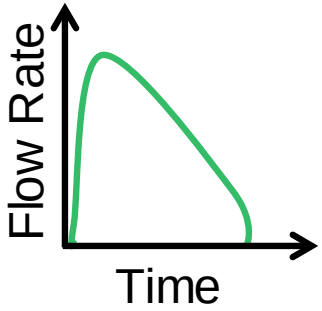
Clinically Relevant APSD In Vitro Test

A **more realistic in vitro APSD method** is important for pharmaceutical development and quality control of OIDPs

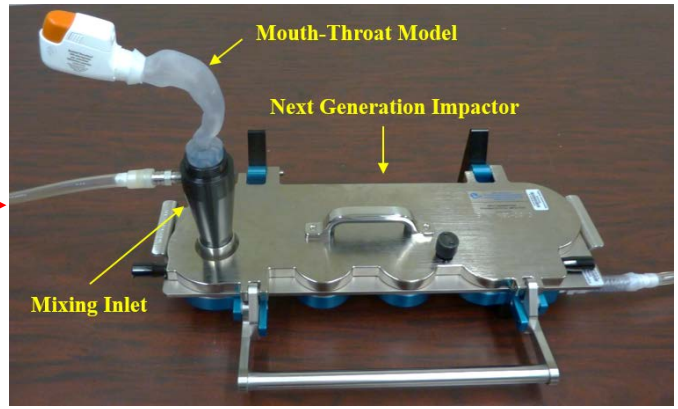


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Physical mouth-throat (MT) models



Representative inhalation profiles (IP)

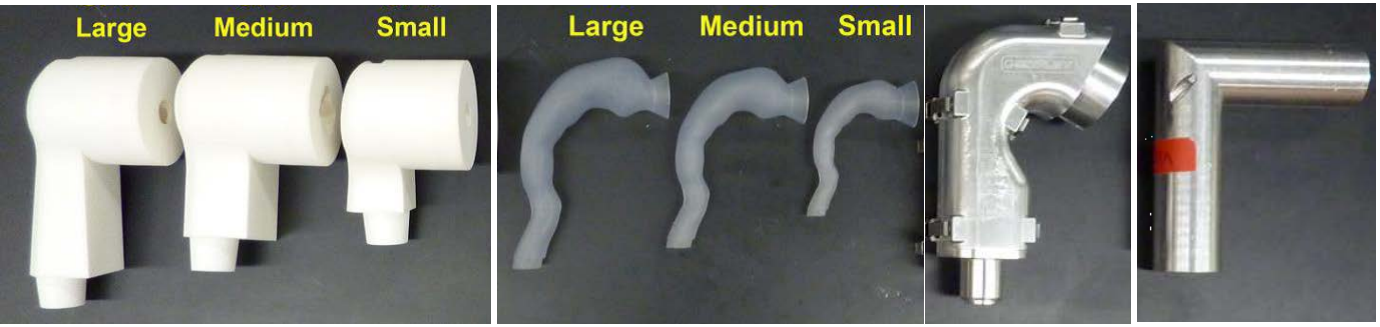


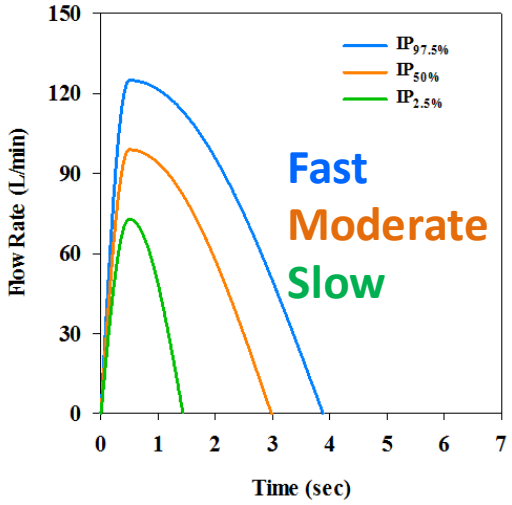
In vitro APSD test more predictive of in vivo deposition

Study Variables

Various **realistic MT models** coupled with **representative IPs**

OPC **VCU** **AIT** **USP**





https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503040.htm

Different inhalers based on availability of flow rate information and in vivo scintigraphy deposition data

* Budesonide Dry Powder Inhaler (DPI)

Albuterol Metered Dose Inhaler (MDI)

* Fenoterol Inhalation Spray

* Products not approved in the US.

Experimental Set Up

Mouth-Throat Model

Inhaler

50 L/min

90 L/min

50 L/min

ASL 5000-XL Breath Simulator

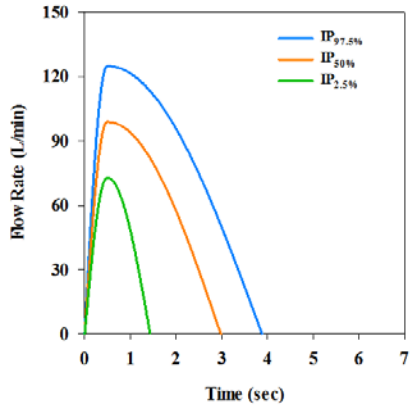
Compressed Air 140 L/min

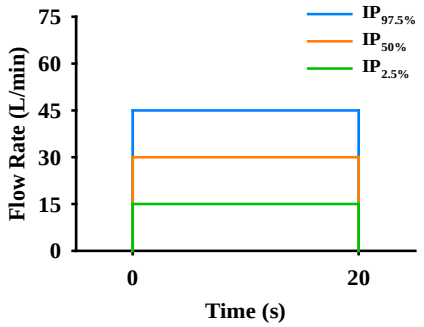
Nephele III Mixing Inlet

140 L/min

Modified NGI with W7 Impactor

Vacuum Pump





Fast

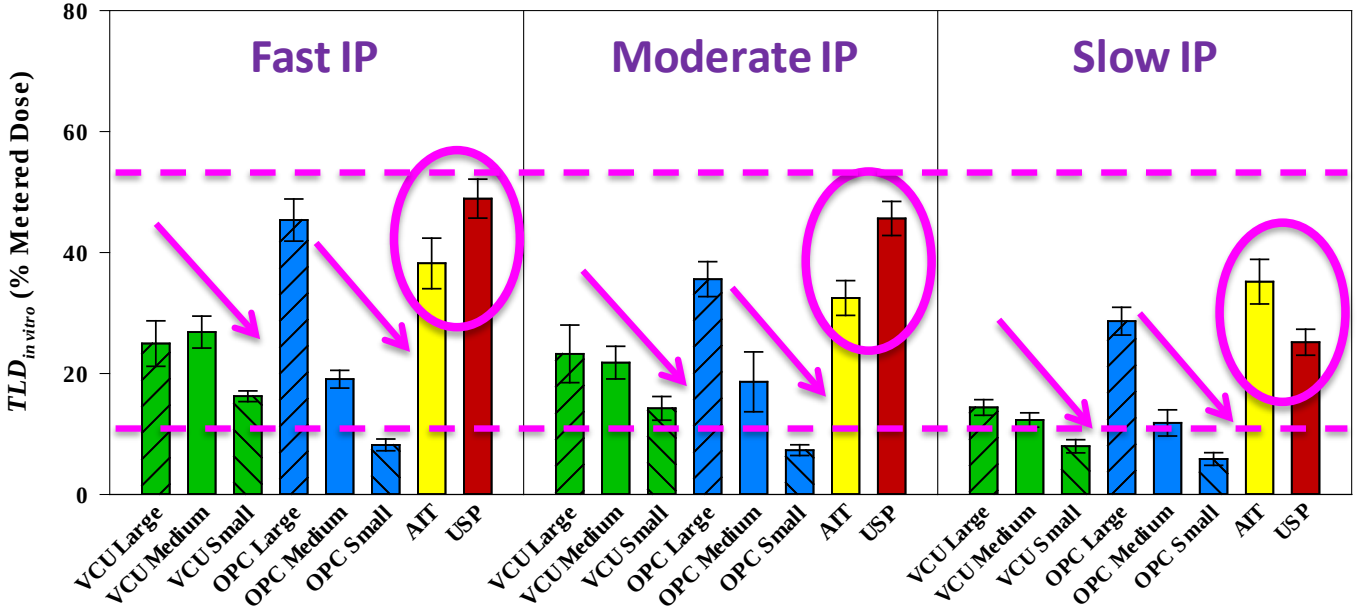
Moderate

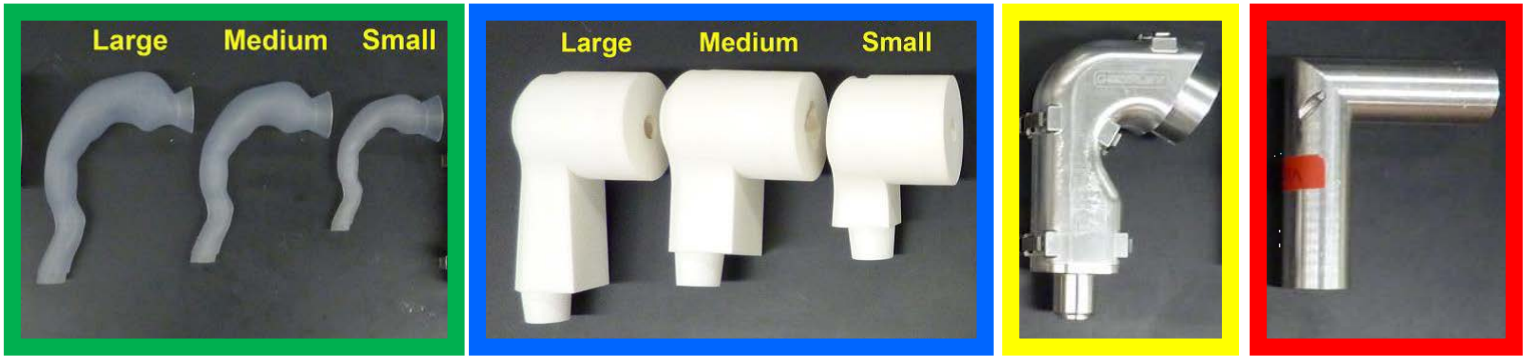
Slow

Courtesy of Dr. Renish Delvadia, Ph.D. (FDA/OGD/ORS)

MDI Results

The in vitro performance of the MDI depends on both the realistic MT model and representative Inhalation Profile

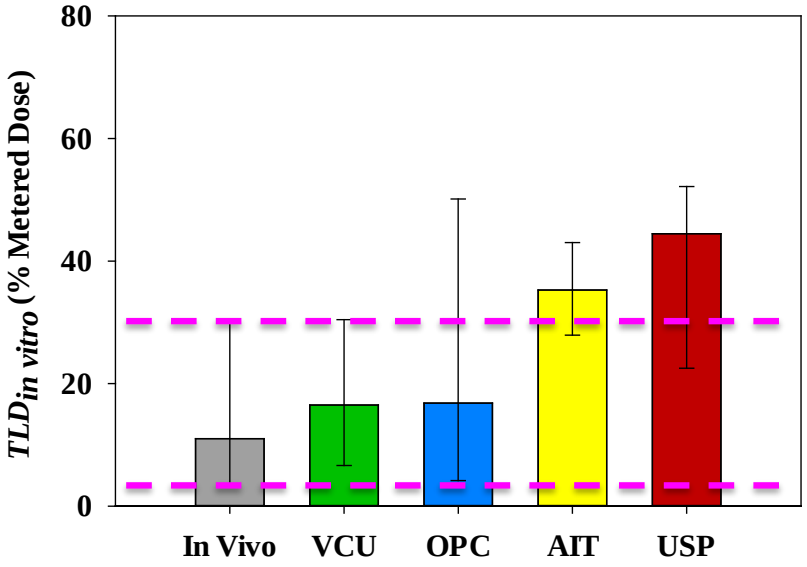


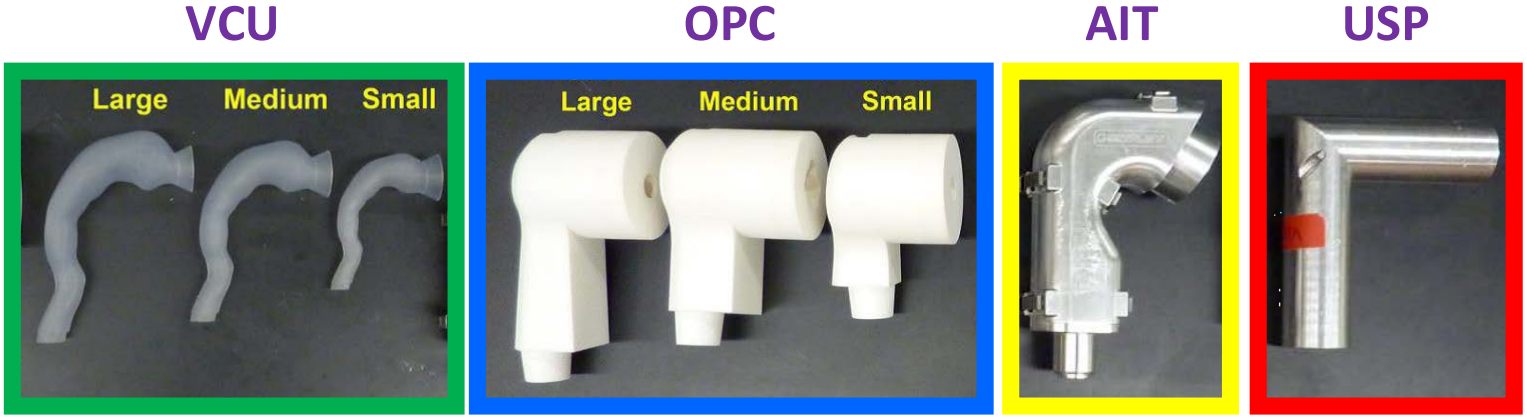


MDI Results

In vitro - in vivo total lung deposition (TLD) comparison

- VCU and OPC: good prediction
- AIT and USP: over-prediction





Conclusions

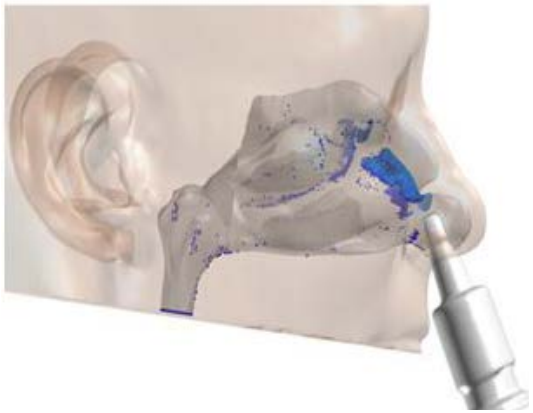
- A more realistic APSD in vitro test for OIDPs provides a **better prediction** of where inhaled particles may be deposited in the lungs compared to the current APSD in vitro test which uses the USP inlet
- Importance for **generic** OIDPs
  - Product development
  - Quality control
  - Faster, less expensive and more sensitive method compared to clinical endpoint bioequivalence studies

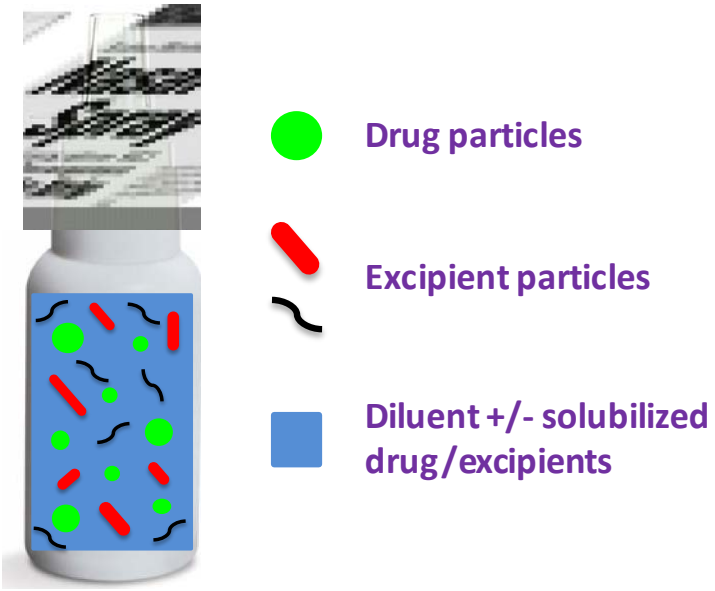
Research Initiatives for OINDPs

- Identification of formulation and device variables
- Development of **clinically relevant in vitro methods** for prediction of in vivo drug deposition and dissolution
- 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

Locally-Acting Nasal Spray Suspensions

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



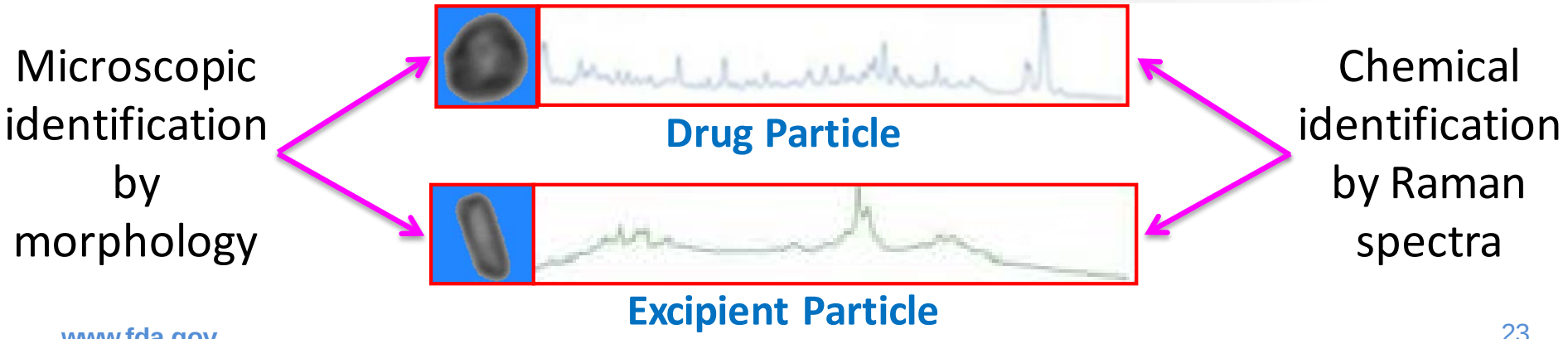


- Drug particle size distribution (PSD) in suspension formulations has the potential to influence **the rate and extent of drug availability** to nasal sites of action and systemic circulation
- Inability to adequately characterize drug PSD in aerosols and sprays using **common analytical methods**

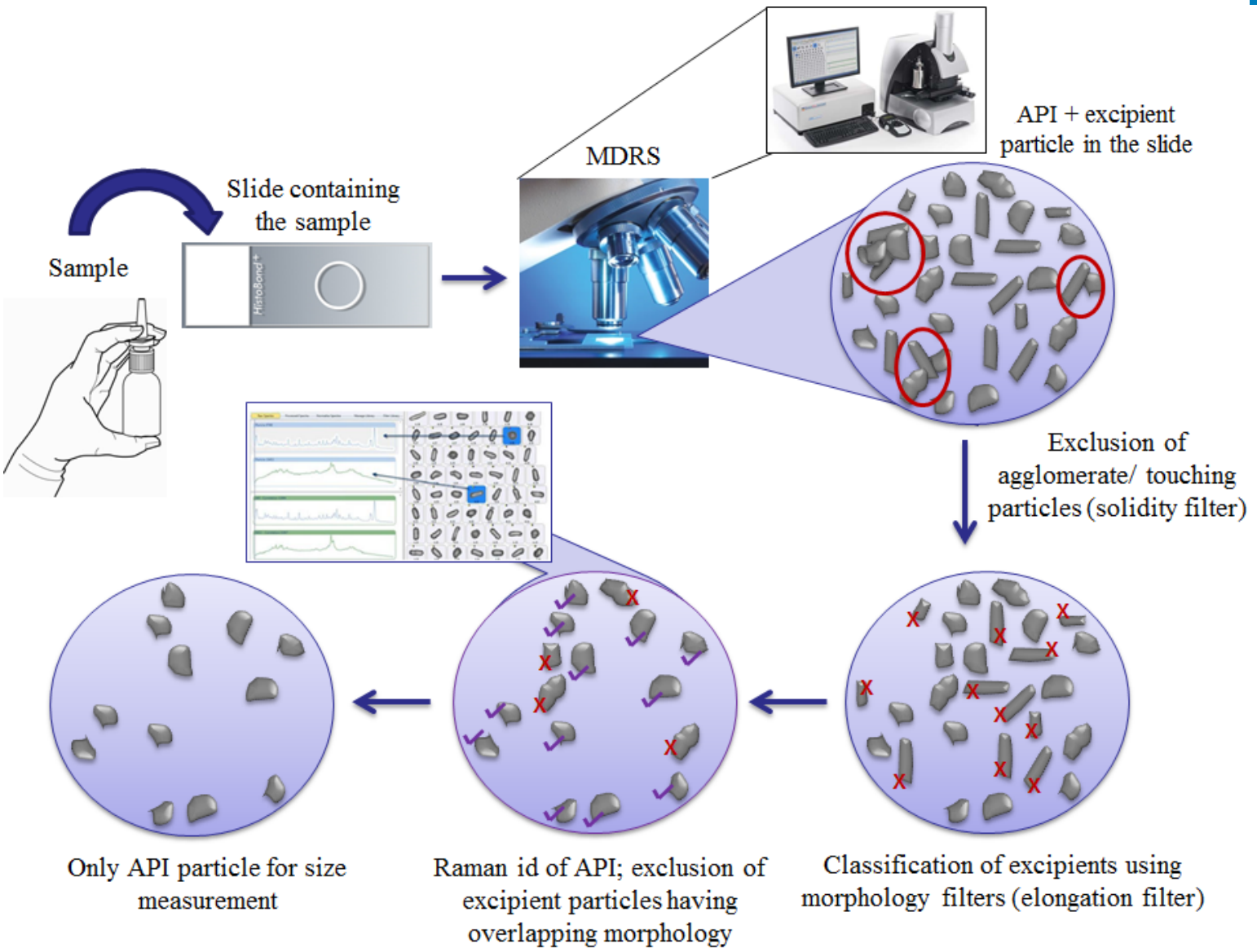
MDRS for Nasal Spray Suspensions

- If drug PSD in test and reference products can be accurately measured using a validated **advanced analytical method**, generic sponsors 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?

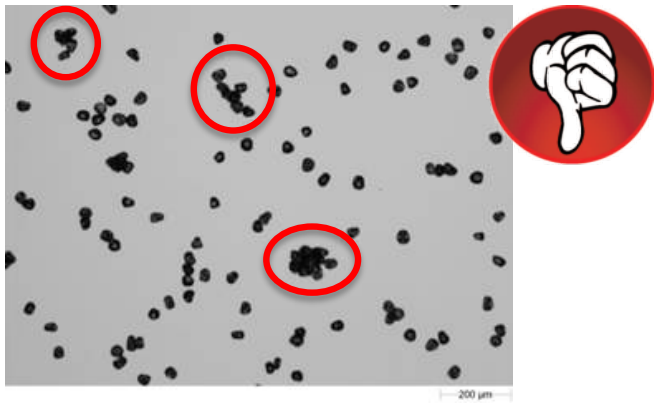


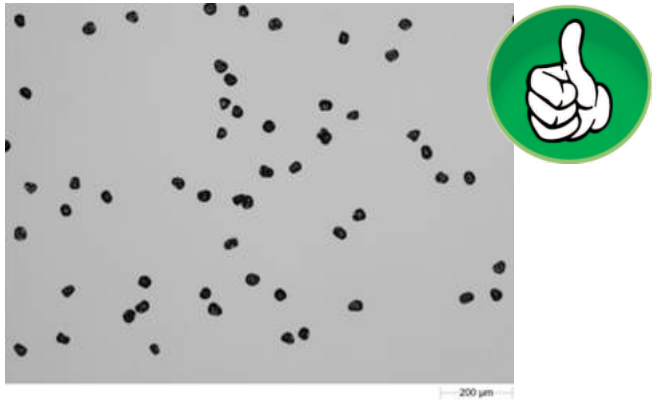
Courtesy of Dr. Abir Absar, Ph.D. (FDA/OCP)

Removal of Agglomerates and Touching Particles

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

- Can give misleading data





Particle Classification Using Morphology Filters

- Should exclude as many excipient particles as possible
- Should not exclude drug particles
- Morphology filters
  - Circularity
  - Elongation
  - Convexity

Circularity = 1
Convexity = 1
Elongation = 0

Circularity = 0.47
Convexity = 1
Elongation = 0.82

Circularity = 0.89
Convexity = 1
Elongation = 0

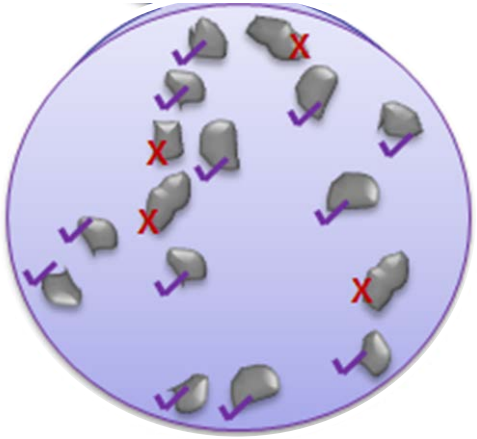
Circularity = 0.47
Convexity = 0.7
Elongation = 0.24

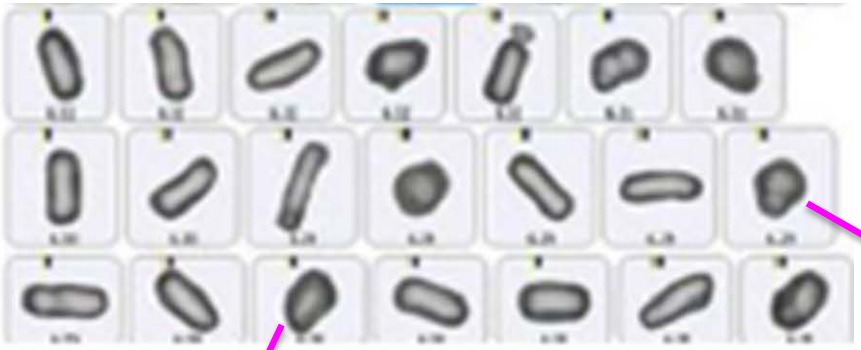
Circularity = 0.21
Convexity = 0.73
Elongation = 0.83

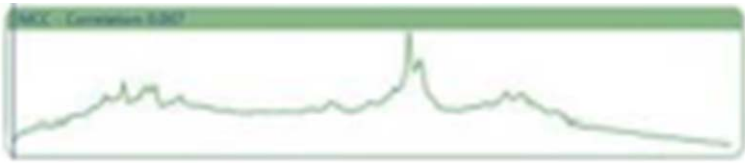
Circularity = 0.52
Convexity = 1
Elongation = 0.79

Chemical Identification by Raman Spectra

- Identifies particles with overlapping morphological features







Conclusions

- An **advanced analytical method** for measuring drug PSD in nasal spray suspension products, **such as MDRS**
  - Enables a comparison of drug PSD in the generic and reference products
  - Similar drug PSD provides indication of equivalent effect in the sites of action
  - Faster, cleaner, less expensive and more sensitive method compared to clinical endpoint bioequivalence studies
- Potential **limitations**
  - Lower limit of quantitation of instrument (e.g., for particles < 1 μm, an orthogonal method may be needed)
  - If drug and excipient have similar morphology
  - If sample has multiple drug and excipient suspended particles

Final Remarks

- GDUFA funding provides support for **regulatory science research**
- GDUFA Regulatory Science Program
  - Supports access to **generic drugs in all product categories**
  - Development of **new tools** to evaluate drug equivalence and support generic drug development
- Research initiatives for locally-acting OINDPs explore **new methods** to make development and BE demonstration faster and more cost-effective. Examples:
  - A **more realistic APSD in vitro test** provides a better prediction of where inhaled particles may be deposited in the lung compared to the current APSD in vitro test which uses the USP inlet and square-shape inhalation profile
  - An **advanced analytical method** for measuring drug PSD in nasal spray suspension products, **such as MDRS**, enables a comparison of drug PSD in the generic and reference products

Thank you!

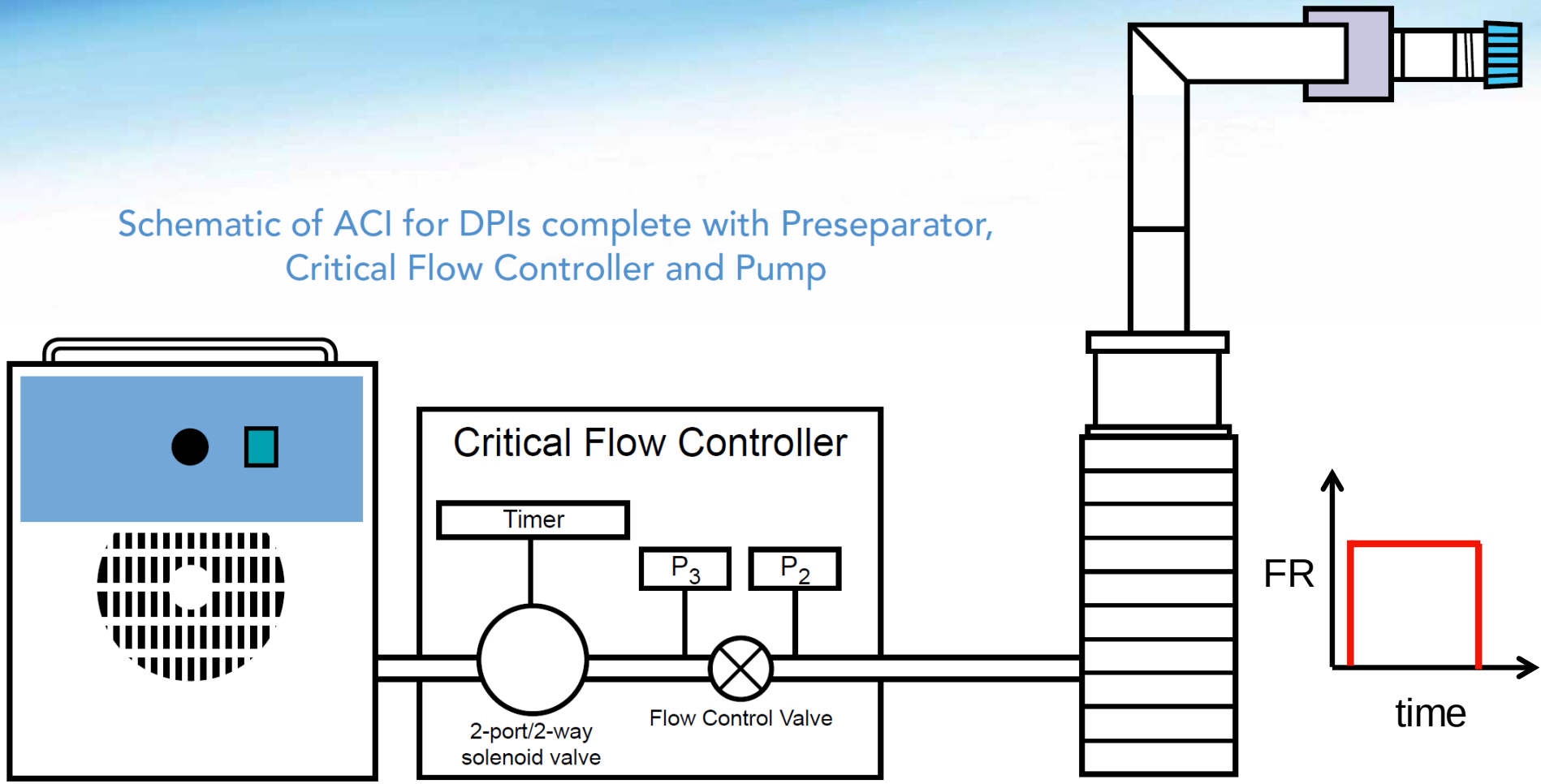
- Acknowledgement
  - Kimberly Witzmann, M.D.
  - Renish Delvadia, Ph.D.
  - Abir Absar, Ph.D.
  - Markham Luke, M.D., Ph.D.
  - Robert Lionberger, Ph.D.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Backup Slides

Operating Principle of Cascade Impactors

Schematic of ACI for DPIs complete with Preseparator, Critical Flow Controller and Pump

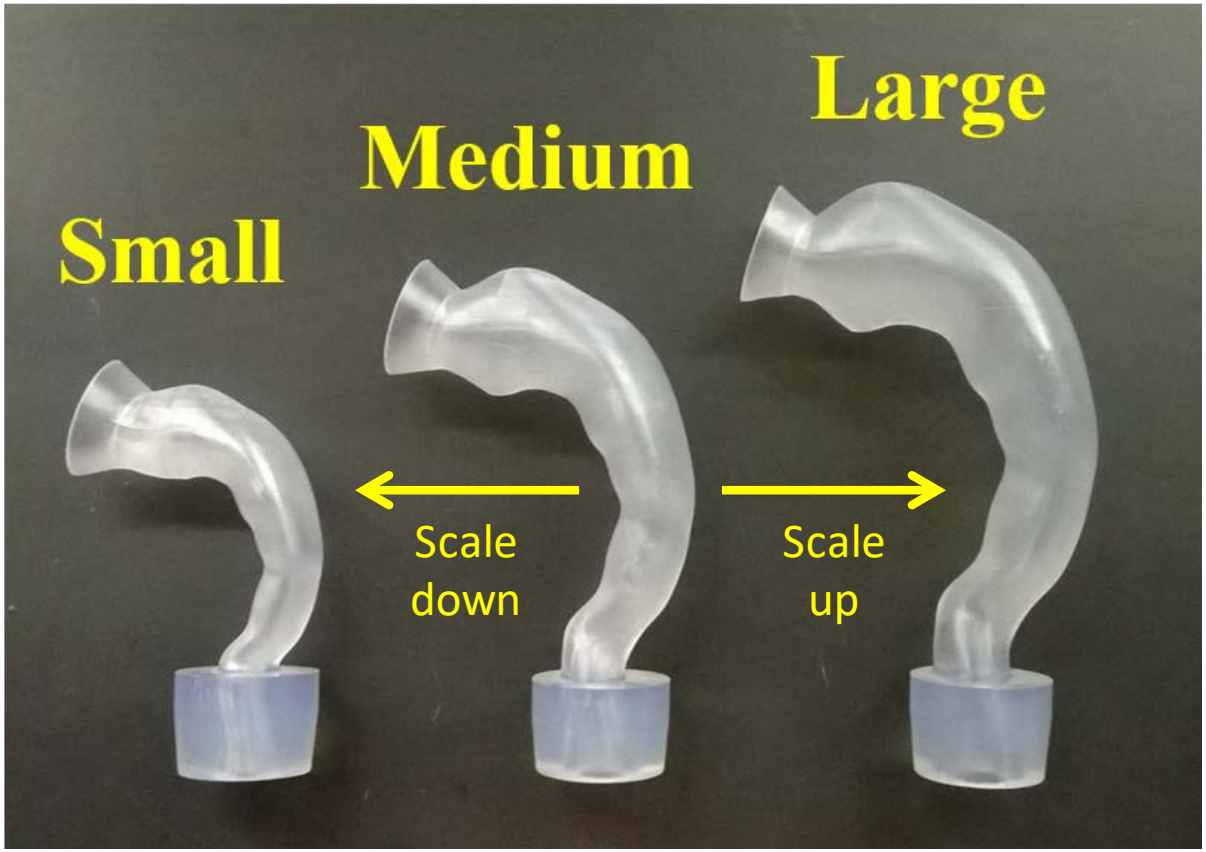


NGI Cutoff Diameters

Cut-off diameters at	15	30	60	100	L/min
• Stage 1	14.10	11.76	8.06	6.12	microns
• Stage 2	8.61	6.40	4.46	3.42	microns
• Stage 3	5.39	3.99	2.82	2.18	microns
• Stage 4	3.30	2.30	1.66	1.31	microns
• Stage 5	2.08	1.36	0.94	0.72	microns
• Stage 6	1.36	0.83	0.55	0.40	microns
• Stage 7	0.98	0.54	0.34	0.24	microns
• MOC	0.70	0.36	0.14	0.07	microns

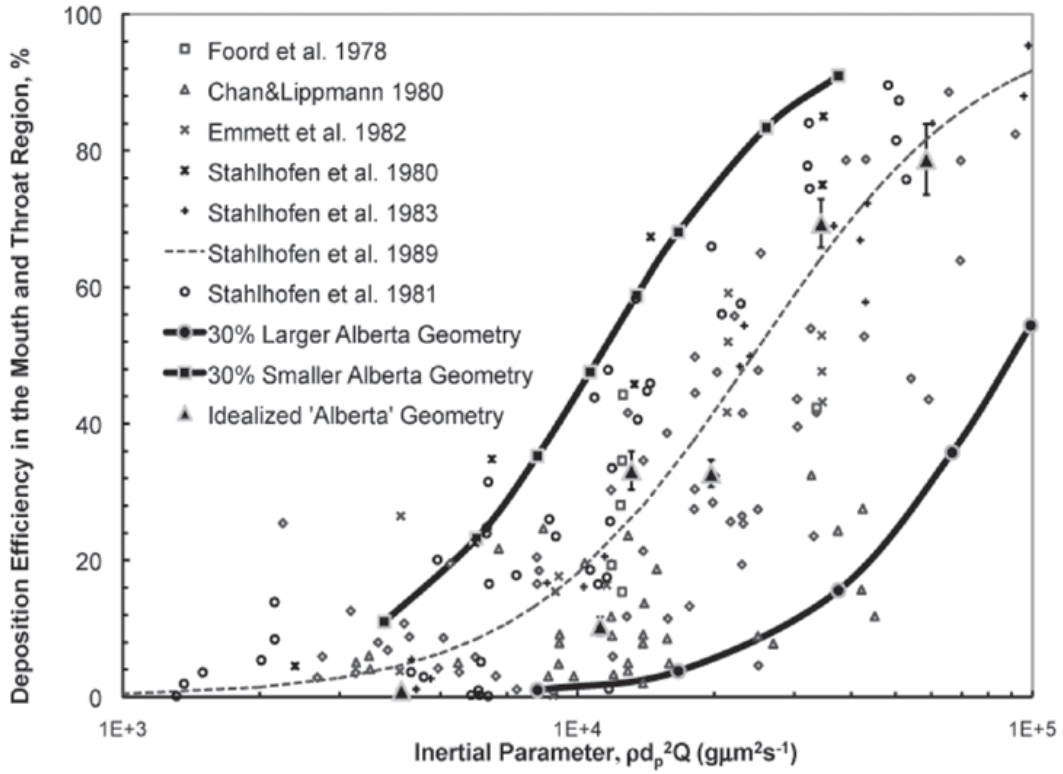
VCU Models

Scaling average model to capture anatomical variability



Alberta Idealized Throat (AIT) Model

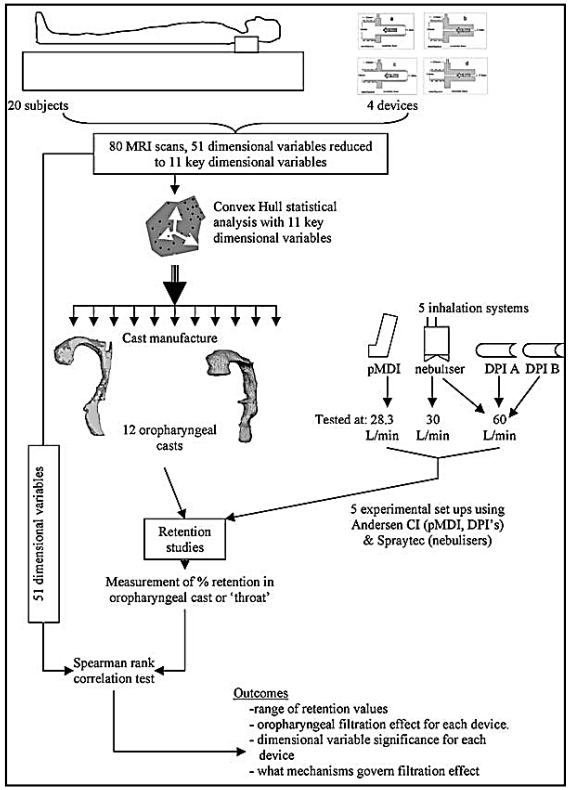
Scaling average model that span the aerosol deposition behavior



Finlay et al., RDD 2010, Vol 1, 185-194

Oropharyngeal Pharmaceutical Consortium (OPC) Models

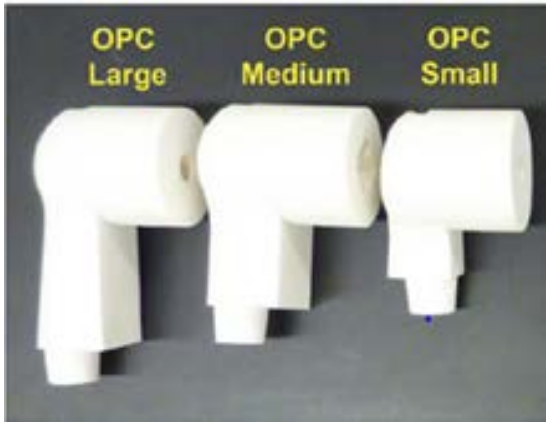
Scanning several airway geometries under different inhalation conditions



Burnell et al., J aerosol Med, 20(3), 2007, 269-281

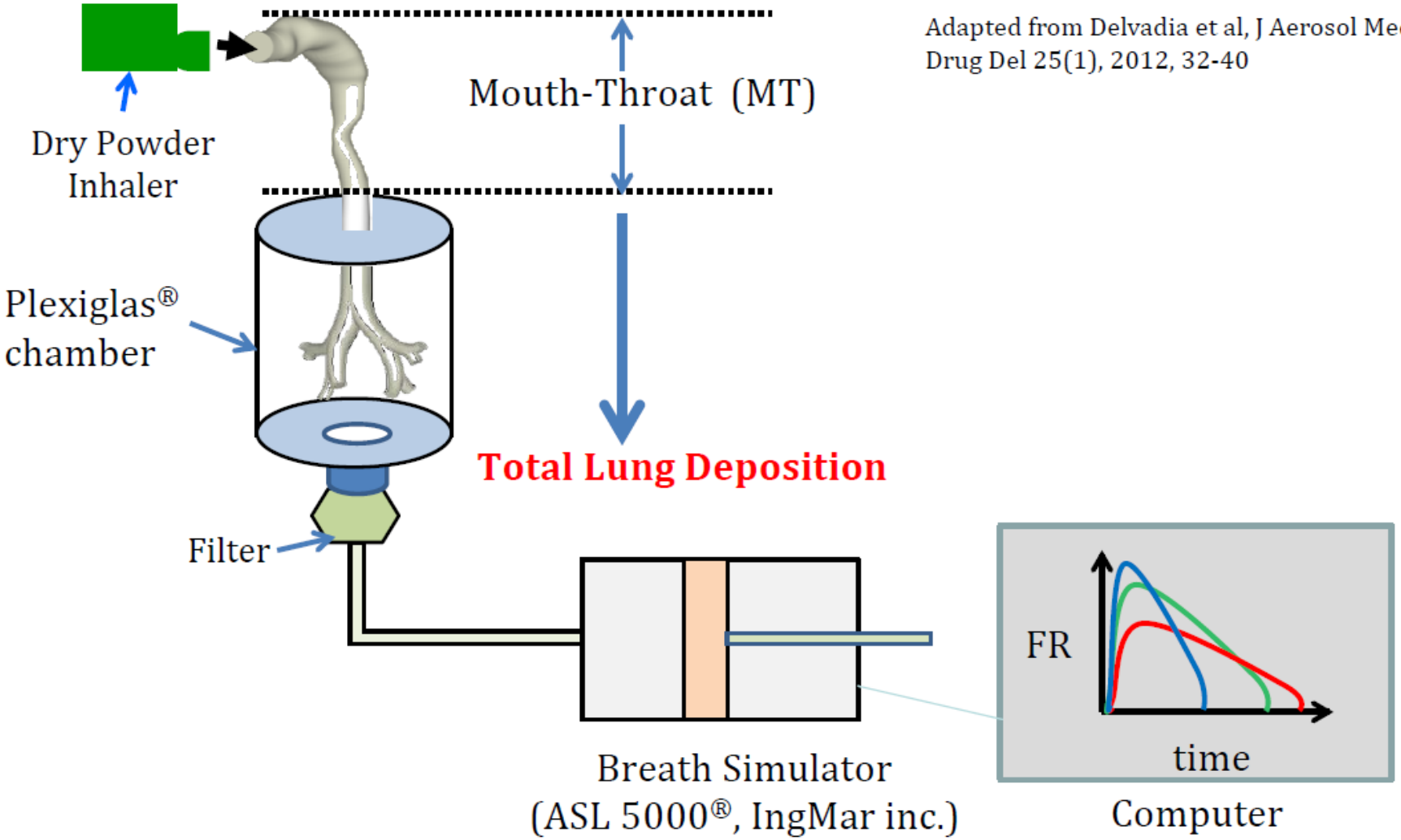
Pick representative models

Olsson Bo et al., J Aerosol Med Pul Drug Del 26(6), 2013 ,355-369



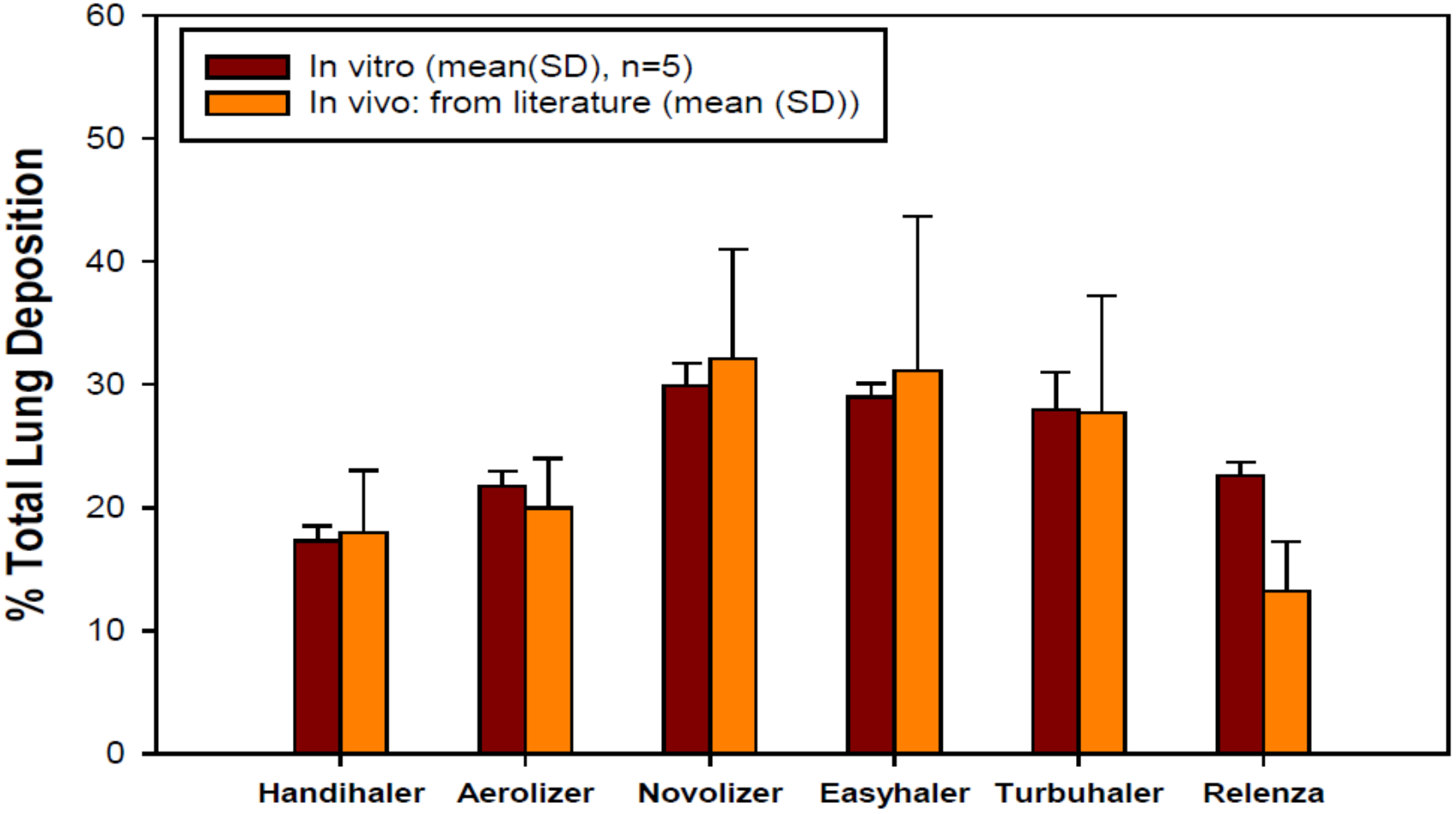
Adapted from Byron et al., RDD 2013, Vol 1, 85-92

Example of In Vitro Set Up for In Vivo TLD Prediction



Adapted from Delvadia et al, J Aerosol Med Pul Drug Del 25(1), 2012, 32-40

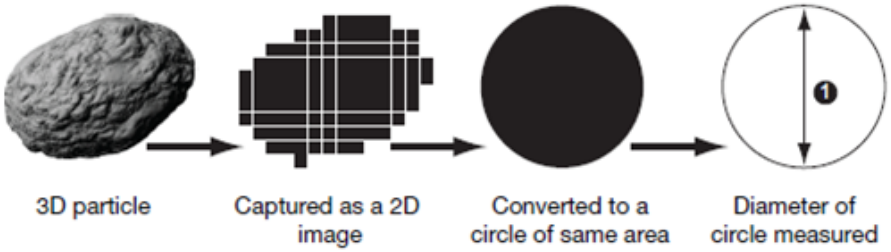
In Vitro – In Vivo TLD Comparison



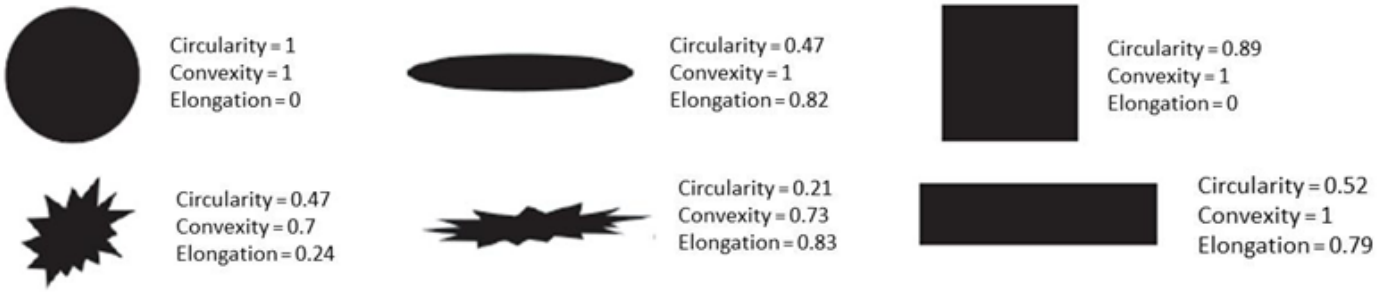
Based on results published in Delvadia et al, J Aerosol Med Pul Drug Del 25(1), 2012, 32-40 and Delvadia et al, J Aerosol Med Pul Drug Del 26(3), 2013 ,138-144

MDRS: Size and Shape Parameters

- Circular Equivalent (CE) diameter: Diameter of a circle with the same area as the 2D image of the particle



- Circularity: ratio of the perimeter of circle with the same area as the particle divided by the perimeter of the actual particle image
- Convexity: measurement of surface roughness; calculated by dividing the convex hull perimeter by the actual particle perimeter
- Elongation: defined as [1-aspect ratio] or [1-width/length]



MDRS: Removal of Touching Particles and Agglomerates

Fig: Identification of touching particles using solidity filters

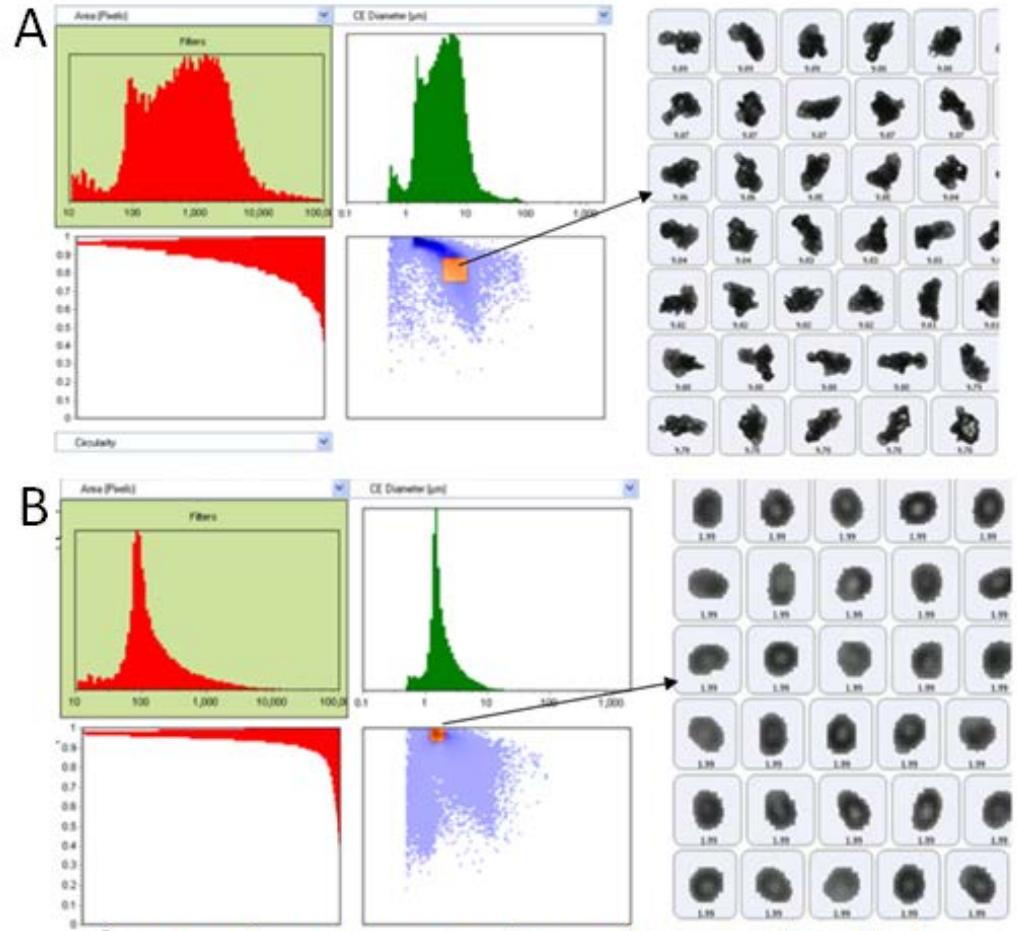


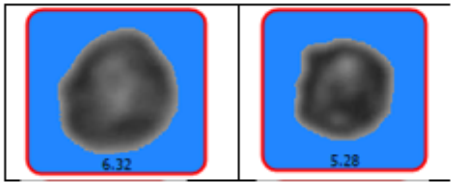
Fig: Agglomerates show lower circularity and higher CE diameter

MDRS: Classification of Particles

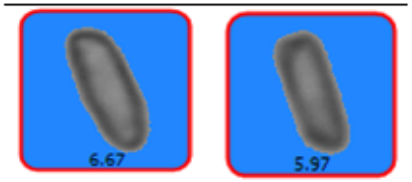
- Classify the particles based on morphological features
- Use of morphology filters – circularity, elongation, convexity/solidity

How to identify the filter parameters?

- Objective is not to exclude API particles, while excluding as many excipient particle as possible
- Depending on the difference in shape, the morphology properties of API and excipient particles should be investigated
- In this case, the API particles are round whereas MCC/CMC particles are needle shaped.



MF particles



Avicel particles

Nasal Suspension Spray Product