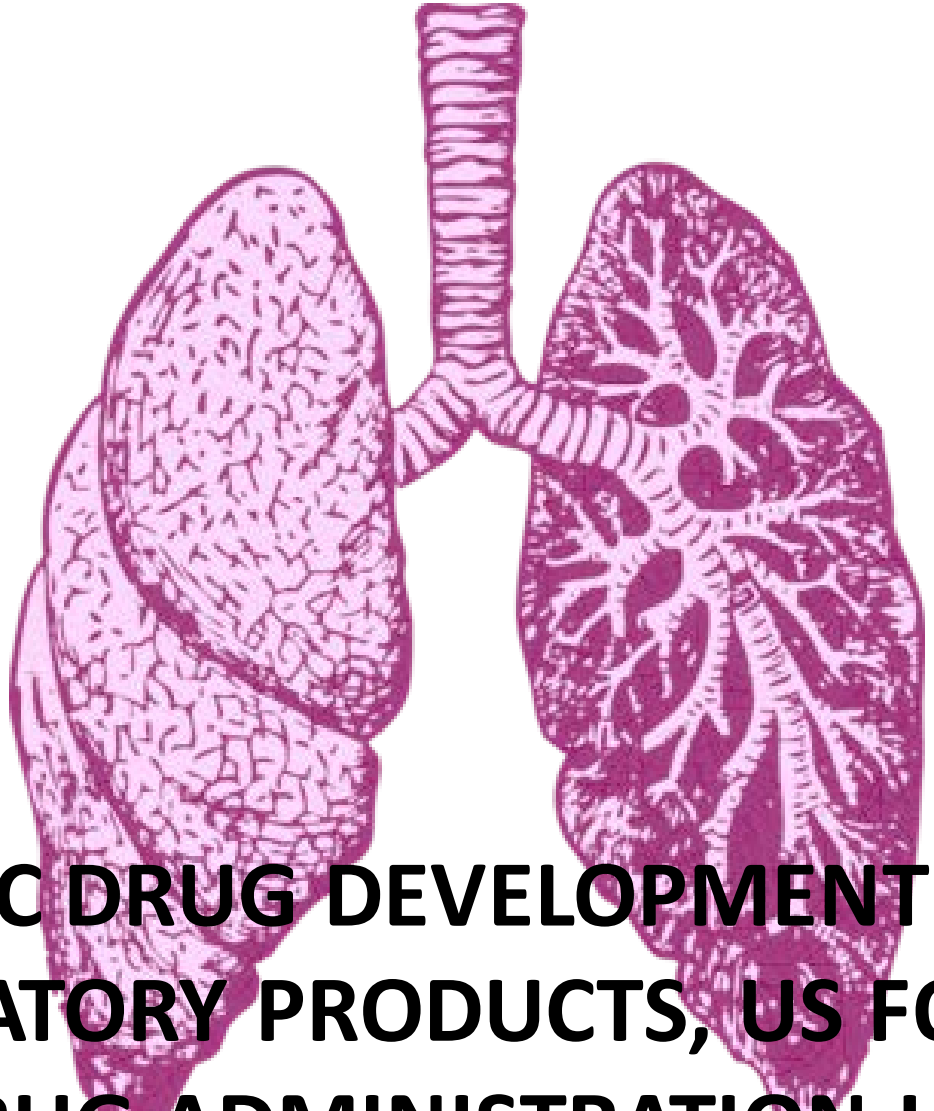


ATS 2017

Session L14

May 22, 2017

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

Faculty Disclosures

Markham Luke, Kimberly Witzmann, Denise Conti

1. **Relevant financial relationships with a commercial interest:**

No relevant commercial interests.

Disclaimer

- In this presentation we are relaying personal views and opinion. This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred.

- The materials presented are available in the public domain.

Purpose

This session will describe development of orally inhaled and nasal drug products (OINDPs) within the US, focusing on paths forward to make safe, efficacious, and cost-effective generic respiratory and nasal products available to the American public.

Session Outline

- Regulatory perspective for generic drug product development
- Generic Drug User Fee Amendments (GDUFA)
- Approach to determine bioequivalence for OIDPs
- Special considerations for OIDPs
- Product-specific recommendations
- Generic drug-device combination products
- Case studies and GDUFA research
- Conclusions
- Questions

Markham Luke, MD, PhD

OVERVIEW OF FDA GENERIC DRUG REGULATORY SCIENCE

Generic Drugs – what are they?

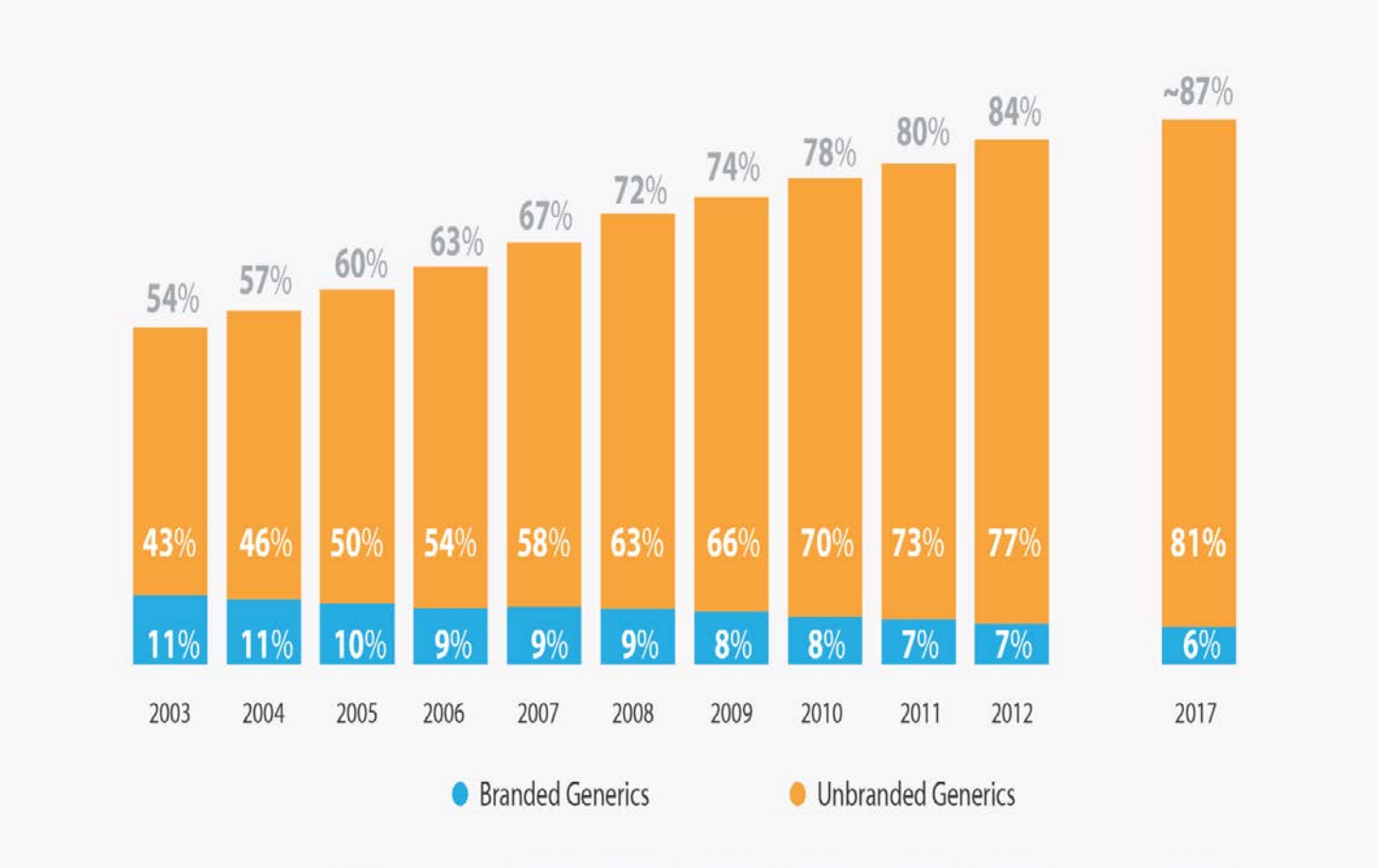
- Are copies of brand-name drugs
- Are the same as those brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

From FDA website – Understanding Generic Drugs
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

Office of Generic Drugs

- Located in the Center for Drug Evaluation and Research
- Offices of Bioequivalence, Regulatory Operations, Generic Drug Policy, Research and Standards
- Office of Research and Standards – leads the implementation of regulatory science commitments and translates research results into standards for safe, effective, and equivalent generic drugs.

Share of Prescriptions for Generic Drugs



IMS Report: Declining Medicine Use and Costs: For Better or Worse? May 2013

Introduction to Generic Drugs

- Each ANDA (Abbreviated New Drug Application) has a reference listed drug (RLD)
- Generic drugs cost less to develop because sponsors do not repeat the safety and efficacy studies used to approve the RLD. Instead they demonstrate **equivalence**
  - Generic and RLD should have equivalent product quality
  - Generic and RLD should be therapeutically equivalent

Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength
- **Bioequivalence (BE)**
  - No significant difference in rate and extent of drug at site of action
- **Therapeutic Equivalence (TE) of Generic Products**
  - Generics must demonstrate PE and BE to the reference product
  - Generics rely on the safety and efficacy of the reference product
  - Generics must have adequate labeling and cGMP manufacturing
  - TE products can be substituted freely

GDUFA Regulatory Science

- Yearly Regulatory Science Plan and Public Meeting
- ~$25 million per year on generic drug regulatory science
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Focus on complex products

GDUFA Regulatory Science Priorities

- Post-market Evaluation of Generic Drugs
- **Equivalence of Complex Products**
- **Equivalence of Locally Acting Products**
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

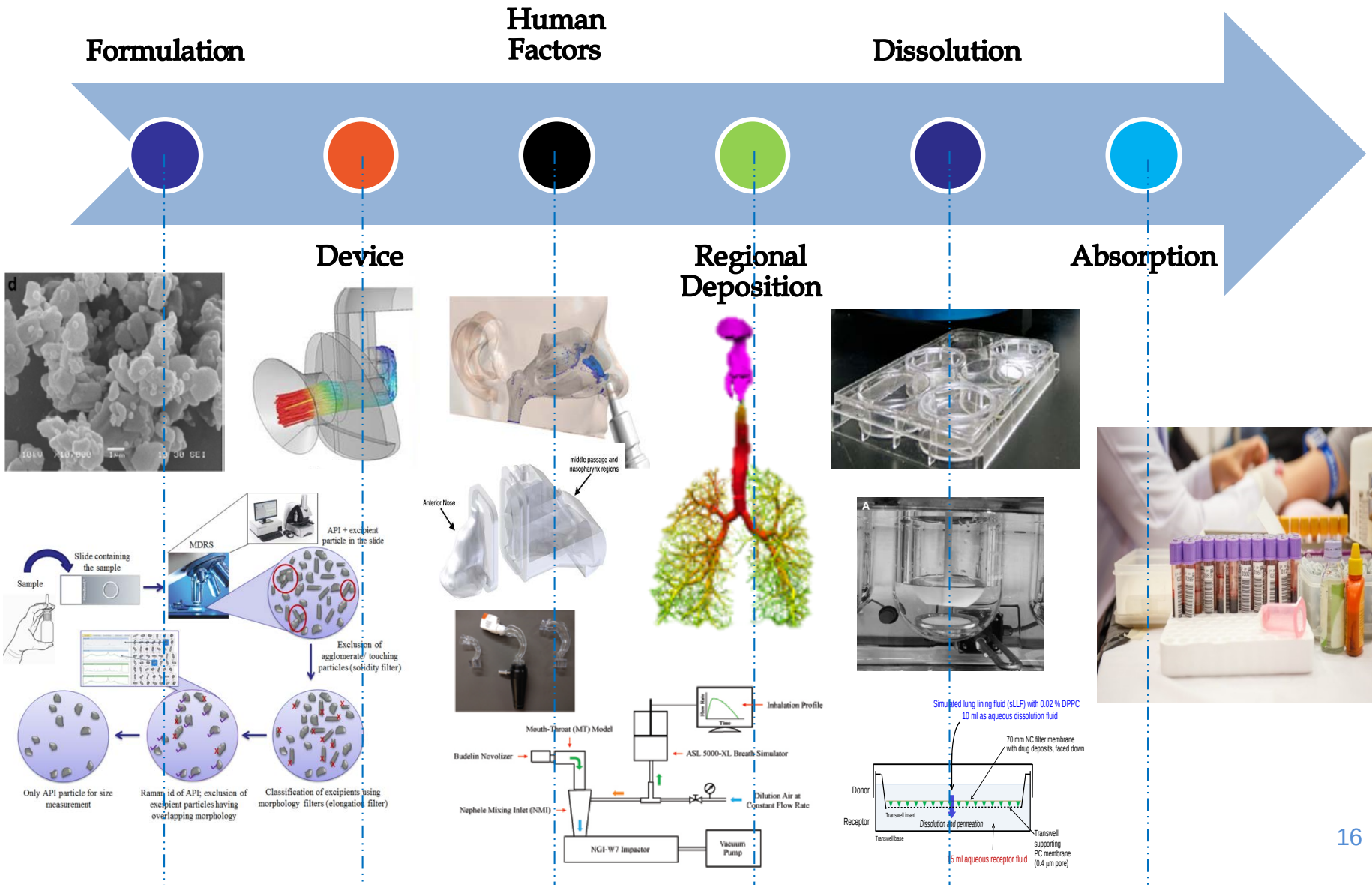
Topical Dosage Forms are Complex

- Complex compositions of matter in the product
  - Immiscible mixtures of several “inactive” ingredients
- Complex states of matter in the product
  - Partially dissolved, partially dispersed drug(s)
- Complex arrangements of matter in the product
  - Multiple phases/components in the drug product
- Complex drug diffusion within the dosage form
  - Potentially complex and dynamic distribution of drug(s)
- Complex drug/device-patient interactions
  - Potentially altered bioavailability at target site of action

Topical Dosage Forms are Locally Acting

- **Equivalence of locally-acting products**
  - inhalation, topical dermatological, nasal, ophthalmic, gastrointestinal, and otic drug products
  - Goal for all is equivalence of drug delivery to the site of action
  - Problem for all is limited direct measurement at the site of action
  - Impact for all is advance the scientific basis of BE and identify more efficient approaches to BE

FDA Research Coordination for Inhaled Drugs



Orally Inhaled Drug Products

Kimberly Witzmann, MD

UPDATE FOR GENERIC ORALLY INHALED AND NASAL DRUG PRODUCTS

Topics

- Generic product bioequivalence
- Bioequivalence for locally-acting drugs
- Components of weight-of-evidence approach
- Challenges for OINDPs
- Product-specific Guidances
- Generic drug-device combination product Guidance

Generic Drug Product Substitutability

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

- **Pharmaceutically Equivalent**

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

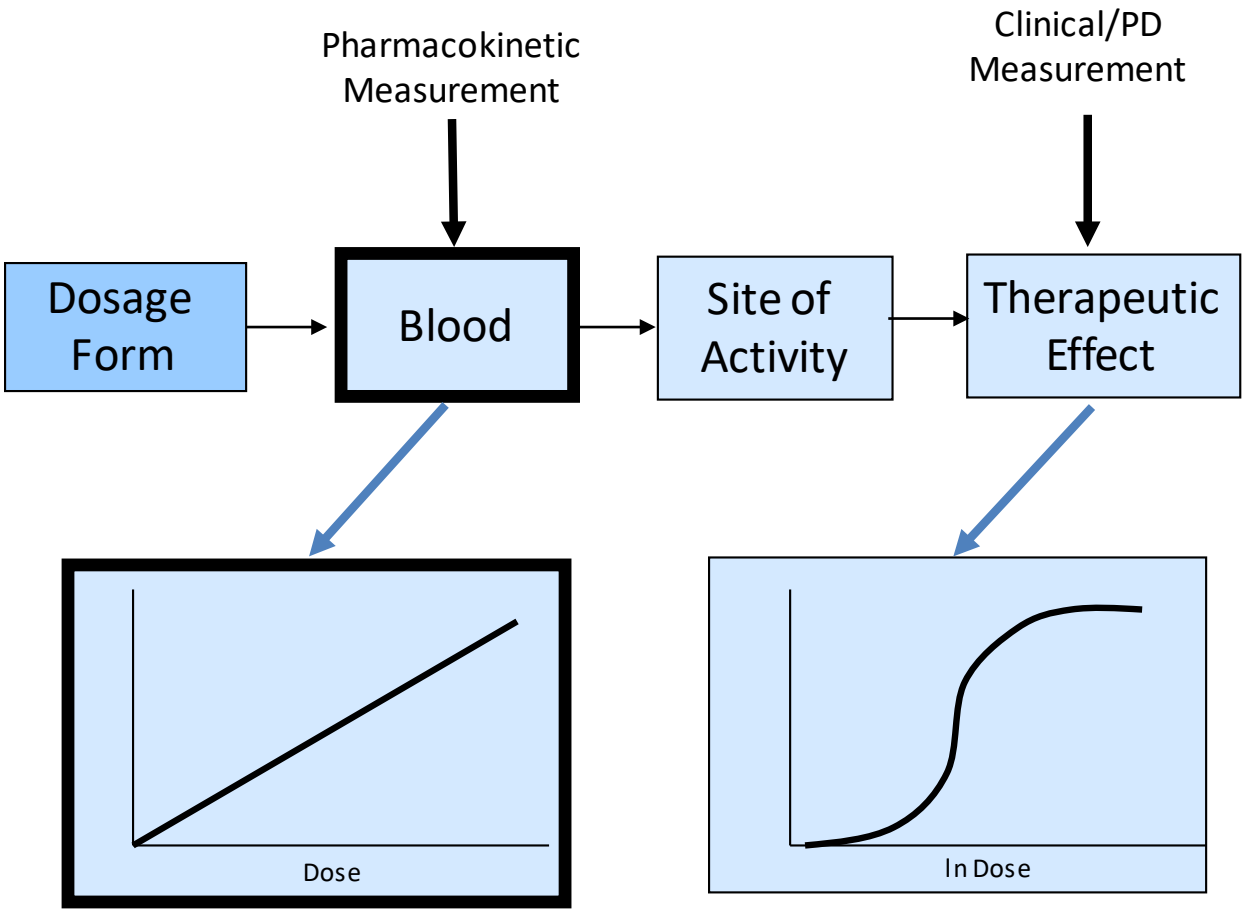
- **Bioequivalent**

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

- **Therapeutically Equivalent**

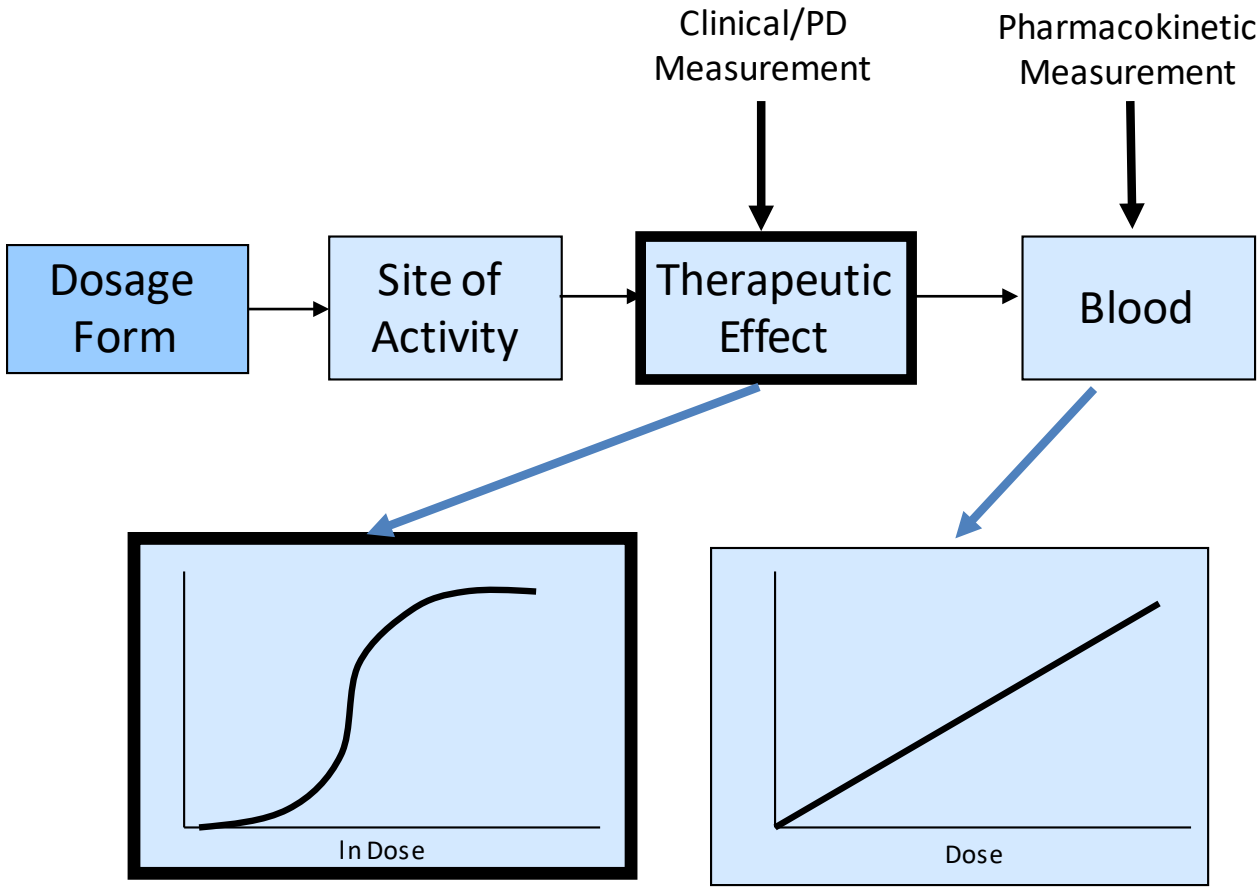
  Can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling

BE for Systemically Acting Drugs



- Delivered to the bloodstream for distribution to site(s) of action in the body
- BE determined with PK studies
  - Relatively short studies
  - Relatively small number of subjects

BE for Locally Acting Drugs



- Not intended to be absorbed into the bloodstream
- Delivered directly to sites of action (lung)

OINDPs: Weight-of-Evidence Approach

- Includes the following:
  - Qualitative and Quantitative sameness of formulation
  - In vitro comparative studies
  - In vivo PK studies
  - PD or comparative clinical endpoint study
  - Device substitutability
- Incomplete understanding of the relevance of results from BE studies to drug concentrations at local site of action in lung
- Residual uncertainties regarding sufficiency of correlation of in vitro to in vivo PK data to establish BE

Bioequivalence for Generic OIDPs

Formulation and Device

- Q1 and Q2 same
- Similar size and shape
- Same basic operating principle
- Same number of doses

In Vitro Performance

Equivalent Systemic Exposure

- Based on PK (AUC and Cmax) data
- For all strengths

Equivalent Local Delivery

Based on PD endpoints showing dose-response/ Clinical PD BE study

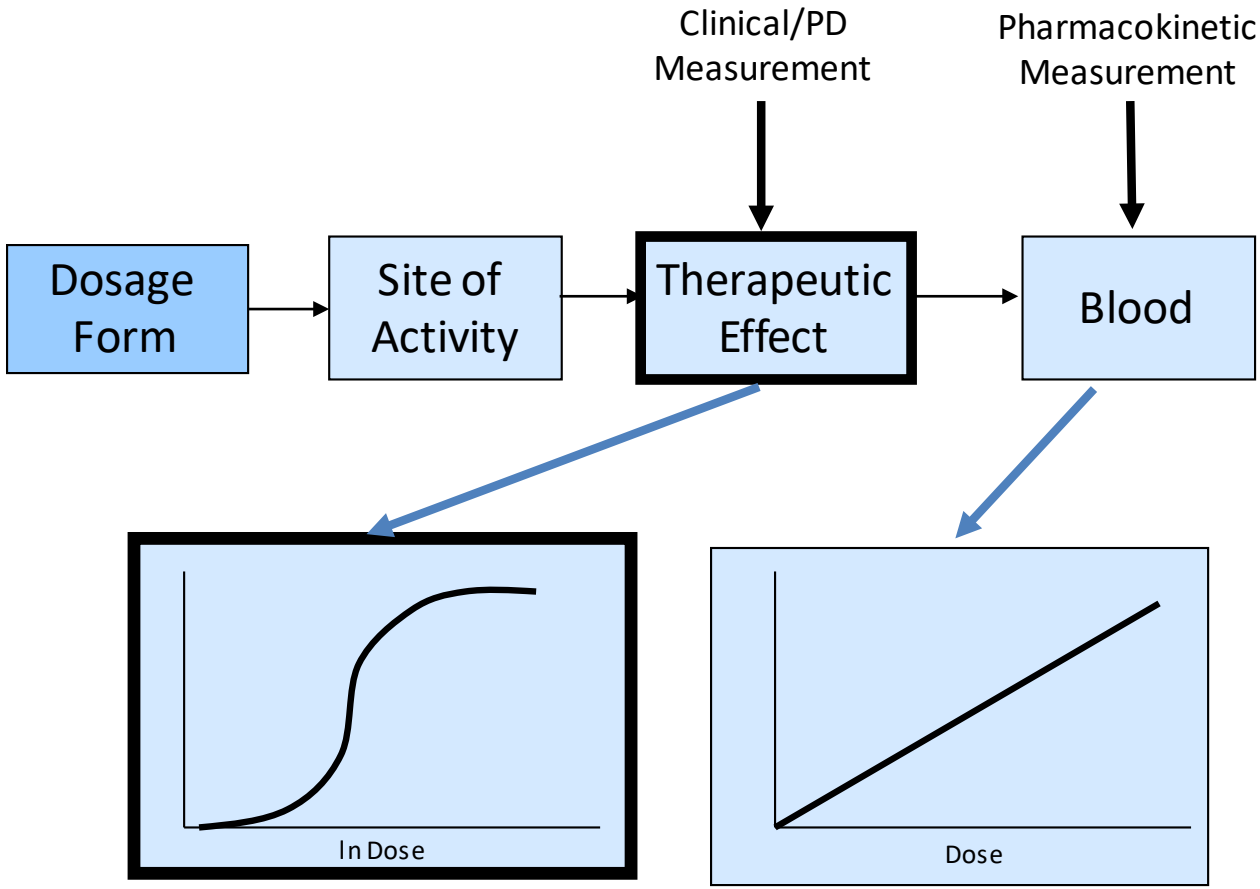
Formulation Considerations

- 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 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 dependent on, and sensitive to, product- and process-related factors
  - Physicochemical properties of API(s) and carrier
  - Device properties
  - Process conditions

Pharmacokinetic Studies



The sampling site for PK studies (plasma) is downstream of the site of action (the lung)

In Vivo Pharmacokinetics

PK BE study objective

- Reliable and sensitive method to determine differences in drug product characteristics
- Single-dose studies in healthy subjects for all strengths
- Dose based on minimizing the number of inhalations, but justified by assay sensitivity
- Relation between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood, **therefore all strengths are needed**

In Vivo Pharmacodynamics

- Dose-response PD BE study preferred over a BE study with a comparative clinical endpoint
- PD study used if there is adequate dose-response (short-acting β-agonists)
- Dose-response ensures the sensitivity of a PD study to distinguish potential differences between test and reference products
- Establishing dose-response for inhaled corticosteroids has been challenging
- Comparative clinical studies for products which do not demonstrate adequate dose-response

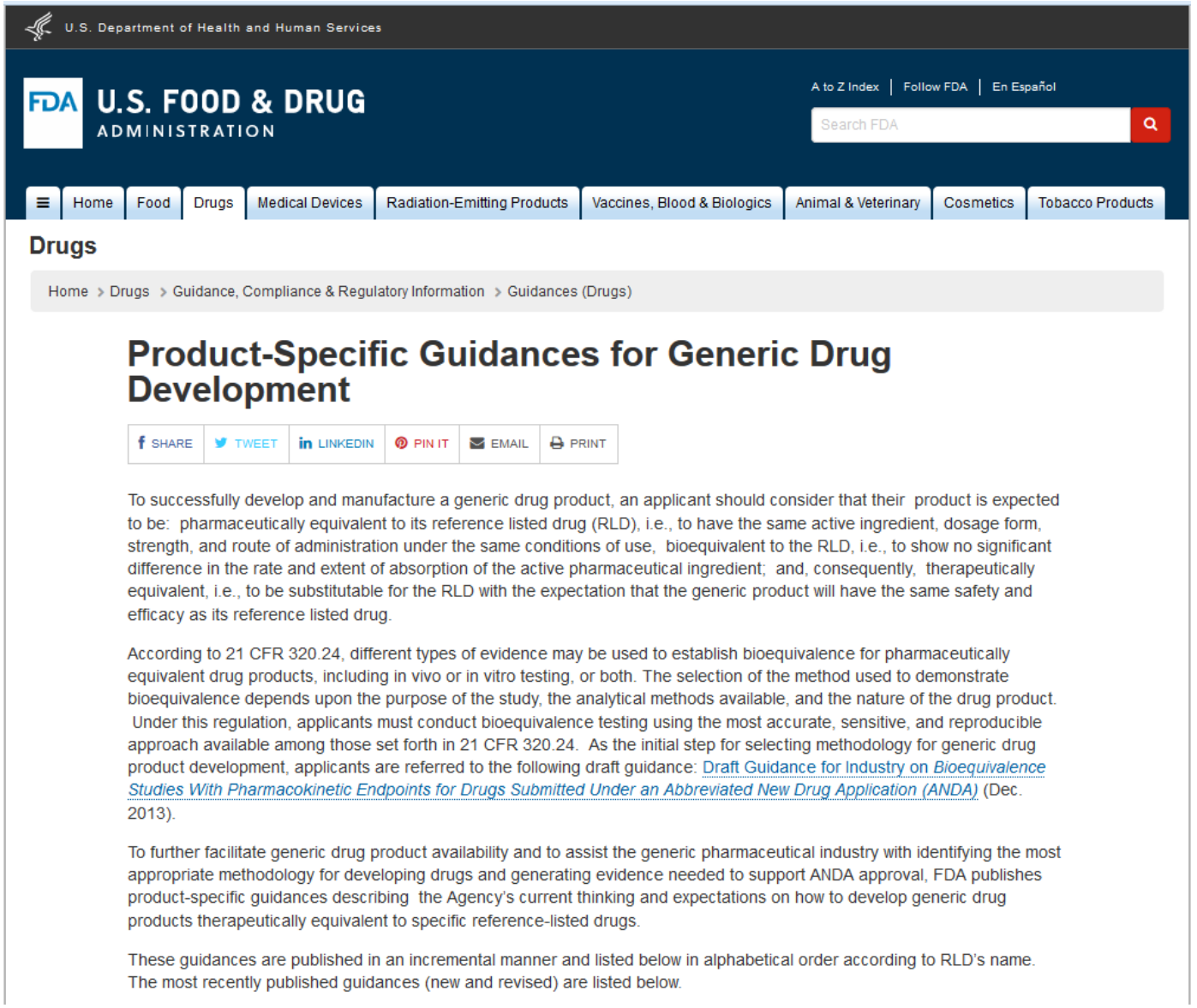
Comparative Clinical Endpoint Study

- Different from NDA Phase 3 study
- Three arms: Test, Reference, placebo control
- Comparison demonstrates sensitivity
- Lowest labeled dose
- Relies on RLD for safety and efficacy
- Study in one indicated population
- BE met if 90%CI for T/R ratio for endpoints falls within 80.00-125.00%

Comparative Clinical Endpoint Study

- Less sensitive than other methods for BE
- Patients are more variable
- Must meet the established BE limits
- May require several hundred patients
- Study duration may be several weeks depending upon the approved labeling
- Expensive to conduct
- Product-Specific Guidances based on data from RLD programs

Product-Specific Guidances



U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Guidance, Compliance & Regulatory Information > Guidances (Drugs)

Product-Specific Guidances for Generic Drug Development

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use, bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

According to 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the initial step for selecting methodology for generic drug product development, applicants are referred to the following draft guidance: Draft Guidance for Industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

To further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference-listed drugs.

These guidances are published in an incremental manner and listed below in alphabetical order according to RLD's name. The most recently published guidances (new and revised) are listed below.

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Product-Specific Guidances

Contains Nonbinding Recommendations

Draft Guidance on Budesonide

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:	Budesonide
Dosage Form; Route:	Powder; inhalation
Strength:	0.09 mg/INH 0.180 mg/INH
Recommended Studies:	In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing budesonide.

Product-Specific Guidances for OINDPs

- Inhaled DPI and MDI products
- Locally-acting nasal suspension products
- Drug-device combination products
  - Naloxone nasal (4/17)
  - Epinephrine auto-injector (12/16)
- GDUFA research program informs PSG creation

DPIs

Fluticasone propionate/ SX
Fluticasone furoate/ vilanterol
Fluticasone furoate
Formoterol fumarate
Indecaterol maleate
Umeclidinium bromide
Budesonide

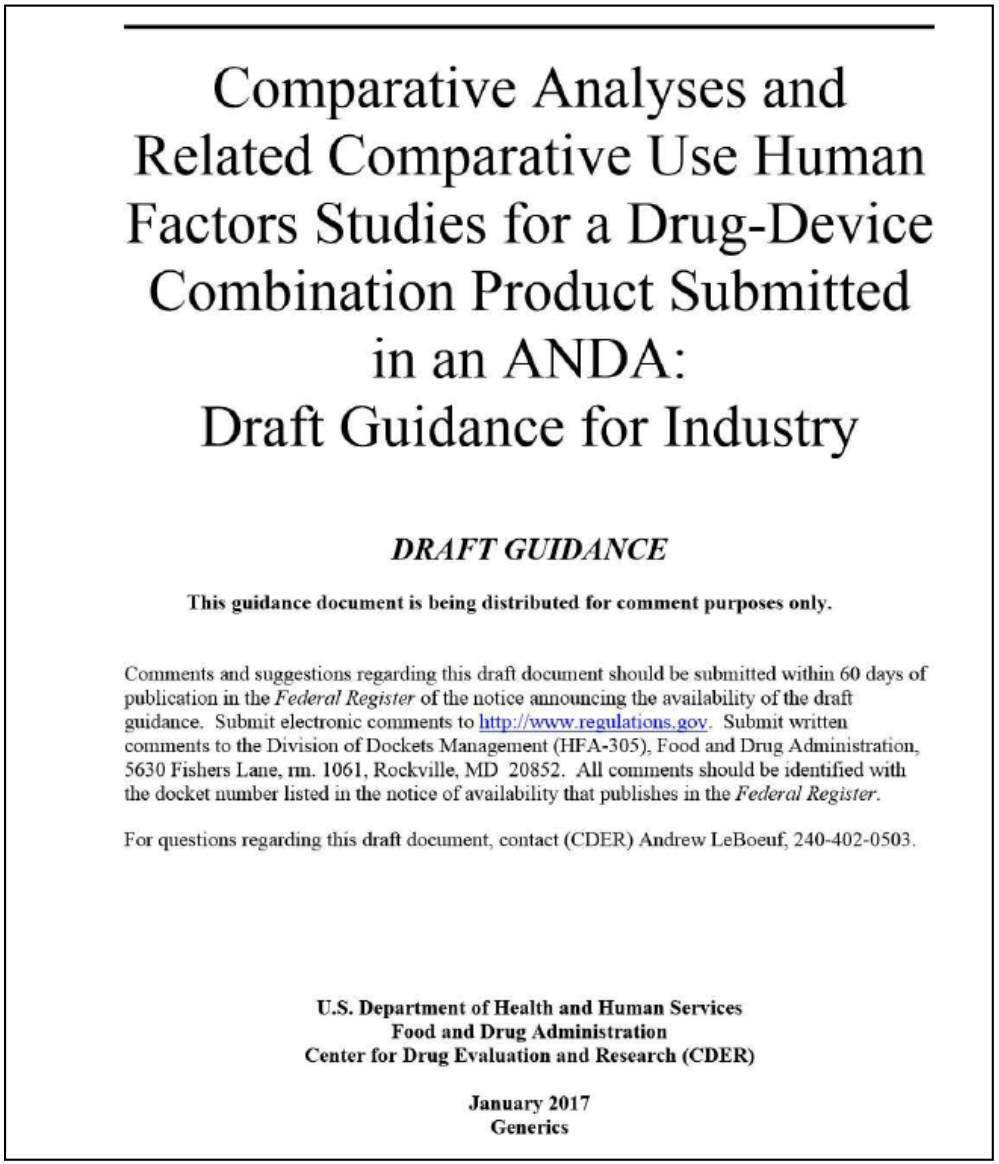
MDIs

Albuterol
Ipratropium
Levalbuterol tartrate
Aclidinium bromide
Budesonide/formoterol
Beclomethasone dipropionate
Ciclesonide
Mometasone furoate
Mometasone /formoterol

Nasal

Fluticasone propionate Rx.
Fluticasone propionate OTC
Triamcinolone
Mometasone
Ciclesonide
Olopatadine
Azelastine/ Fluticasone
Naloxone

New Generic Guidance



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

General Principles

- Drug products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent (TE) to their RLD
- A generic drug-device combination product classified as therapeutically equivalent to the RLD can be expected to produce the same clinical effect and safety profile as the RLD under conditions specified in labeling
- Proposed generic drug-device combination product and its RLD do NOT need to be IDENTICAL in all respects
  - However, applicants should generally seek approval of a presentation approved for the RLD
- Considerations
  - Performance characteristics
  - User Interface

General Principles

In general, the FDA expects that the end-users can use the generic drug-device combination product when it is substituted for the RLD

- Without additional intervention of the health care provider and/or
- Without additional training prior to the use of the generic combination product

Threshold Analyses

Labeling Comparison

- Side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent part(s) of the generic drug-device combination product and its RLD

Comparative Task Analysis

- Comparative task analysis between the proposed generic drug-device combination product and its RLD
- Critical tasks are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care

Physical Comparison of Delivery Device Constituent Part

- Examine (e.g., visual and tactile examination) the physical features of the delivery device constituent part for the proposed generic drug-device combination product and compare them to those of the RLD

Assessment of Identified Differences

Minor Differences

- Guidance describes a design difference as minor if the differences in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD, *do not affect an external critical design attribute.* External critical design attributes are those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product.

Other Differences

- FDA may not view a design difference as minor if any aspect of the threshold analyses suggests that differences in the design of the user interface of a proposed generic combination product as compared to the RLD *may* impact an external critical design attribute that involves administration of the product.

Assessment of Identified Differences

In instances when differences other than minor differences are identified:

- Consider re-design of the user interface to minimize differences from the RLD
- Potential need for additional information and/or data to support the ANDA submission
- Draft guidance recommends that potential applicants contact FDA through a pre-ANDA submission/controlled correspondence *before* conducting comparative use human factors studies

Summary

- Presented generic product bioequivalence
- Explained the determining factors of bioequivalence for locally-acting drugs
- Described the components of the weight-of-evidence approach
- Identified challenges for OINDPs
- Reviewed product-specific Guidances
- Introduced a new Guidance for generic drug-device combination products

Denise Conti, PhD

EMERGING TECHNOLOGIES FOR BIOEQUIVALENCE OF ORALLY-INHALED AND NASAL GENERIC DRUG PRODUCTS

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)

- Title III of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144)
- 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**
- User fee program which directly supports regulatory science research activities

GDUFA Regulatory Science Program

- Competitive research grants and contracts 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

GDUFA Regulatory Science Program

- Supports access to **generic drugs in all product categories**
  - Inhalation and nasal
  - Topical dermatological and transdermal
  - Ophthalmic
  - Liposomal
  - Sustained release parenteral
- Develops **new methodologies and tools** to evaluate drug equivalence and support generic drug development
  - Computational simulations to predict drug absorption
  - Advanced analytical methods for product characterization
  - In vitro methods to predict in vivo performance

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

- Performance is governed by complex interactions between formulation, device, and patient factors
  - In vitro methods have limited predictability
  - Bioequivalence (BE) demonstration is very challenging
  - In vivo studies are time-consuming and expensive
- Current regulatory pathway for BE demonstration utilizes the weight-of-evidence approach
- The Office of Generic Drugs continues to explore **new methods** to make development and BE demonstration more cost- and time-effective

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

- Goal: 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)

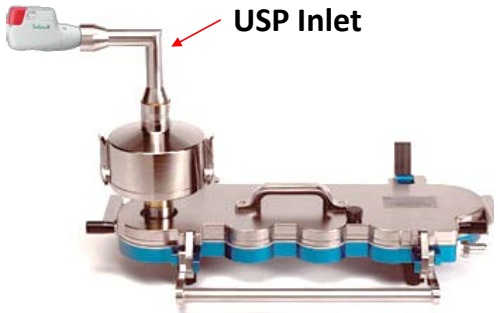
Why should we perform more realistic APSD in vitro tests for OIDPs?

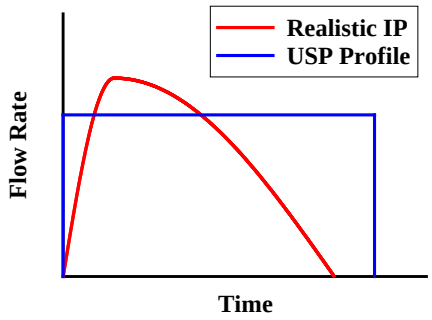
- APSD defines where the particles are likely to be deposited following inhalation
  - 1 - 5 μm: Lungs
  - > 5 μm: Oropharynx and swallowed
  - < 1 μm: Exhaled
- Current in vitro methods for APSD determination are designed for **quality control** and may not be predictive of deposition in vivo
- USP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

Andersen Cascade Impactor (ACI)

Next Generation Impactor (NGI)

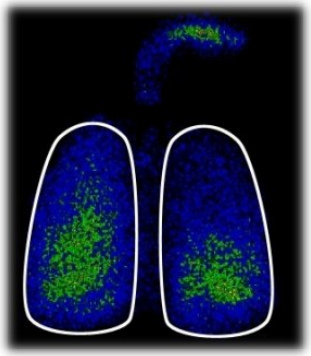
http://www.copleyscientific.com/downloads/brochures





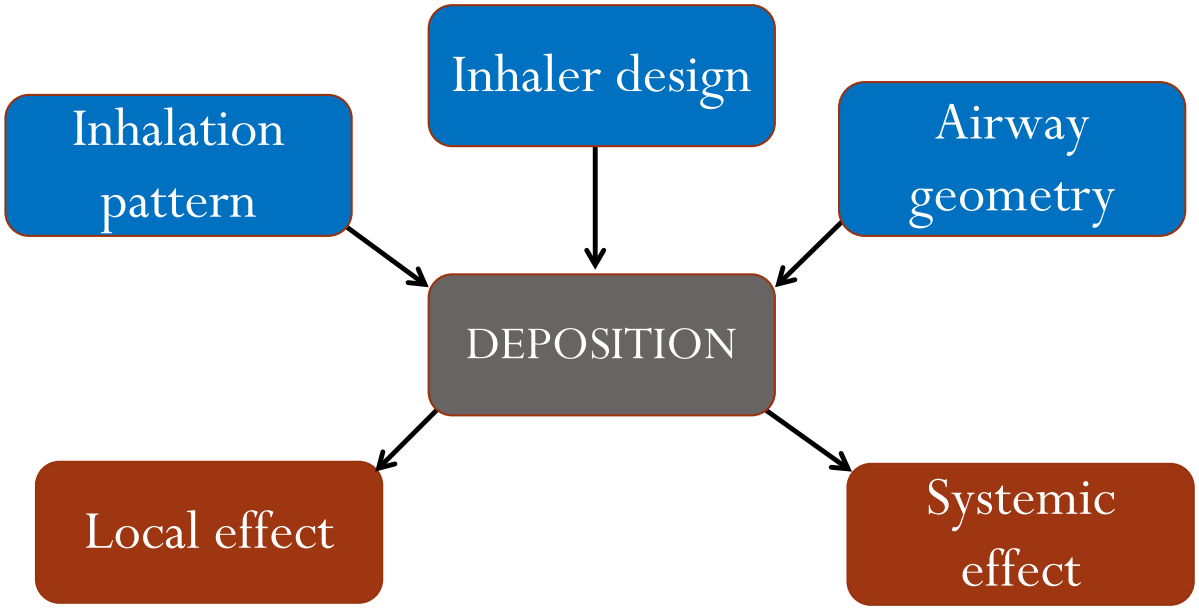
Why should we perform more realistic APSD in vitro tests for OIDPs?

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



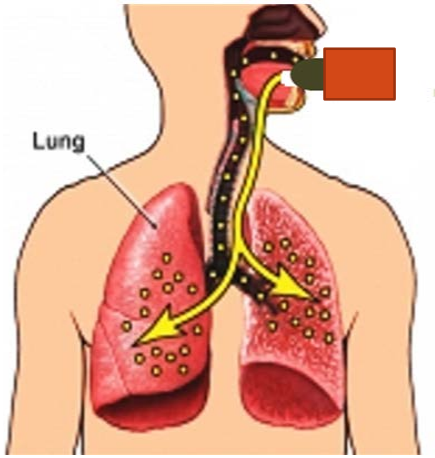
http://www.flowcaps.com/trial.htm

- Several factors influence the fate of inhaled medication



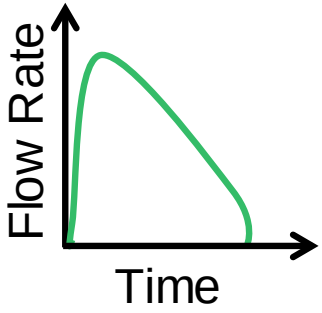
Clinically Relevant APSD In Vitro Test

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

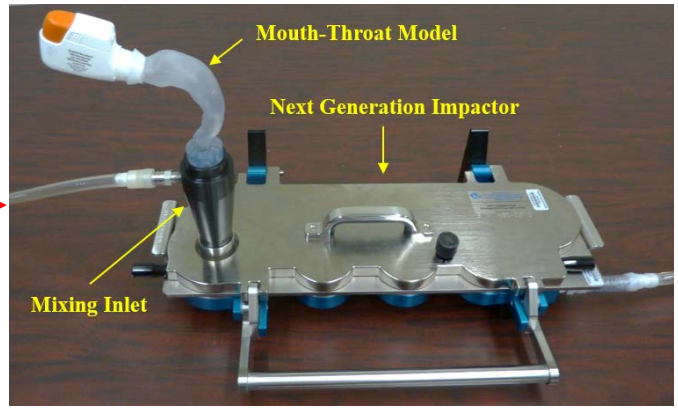


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Physical mouth-throat (MT) models



Representative inhalation profiles (IP)

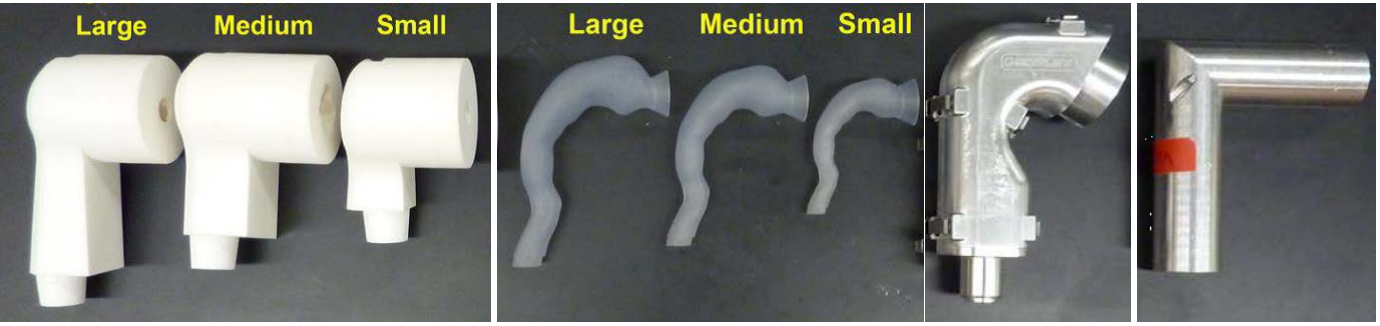


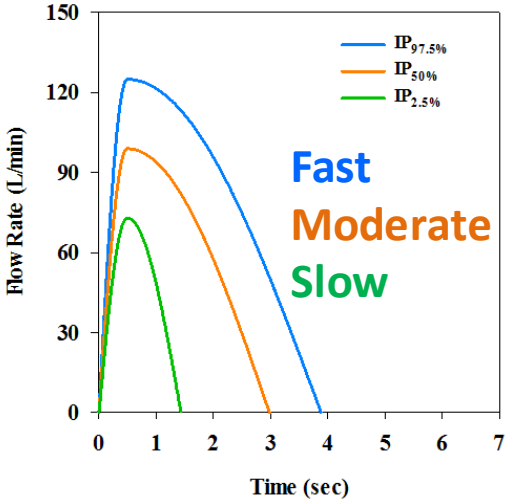
In vitro APSD method more predictive of in vivo deposition

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

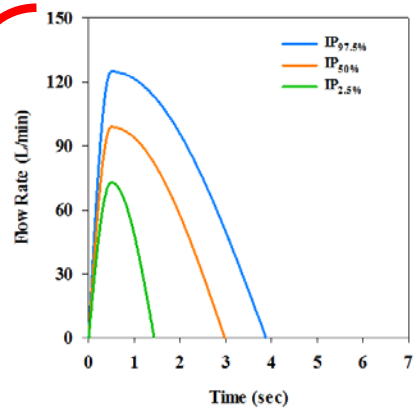
Compressed Air 140 L/min

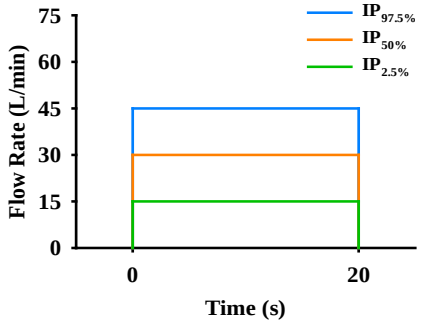
Nephele III Mixing Inlet

140 L/min

Modified NGI with W7 Impactor

Vacuum Pump





Fast

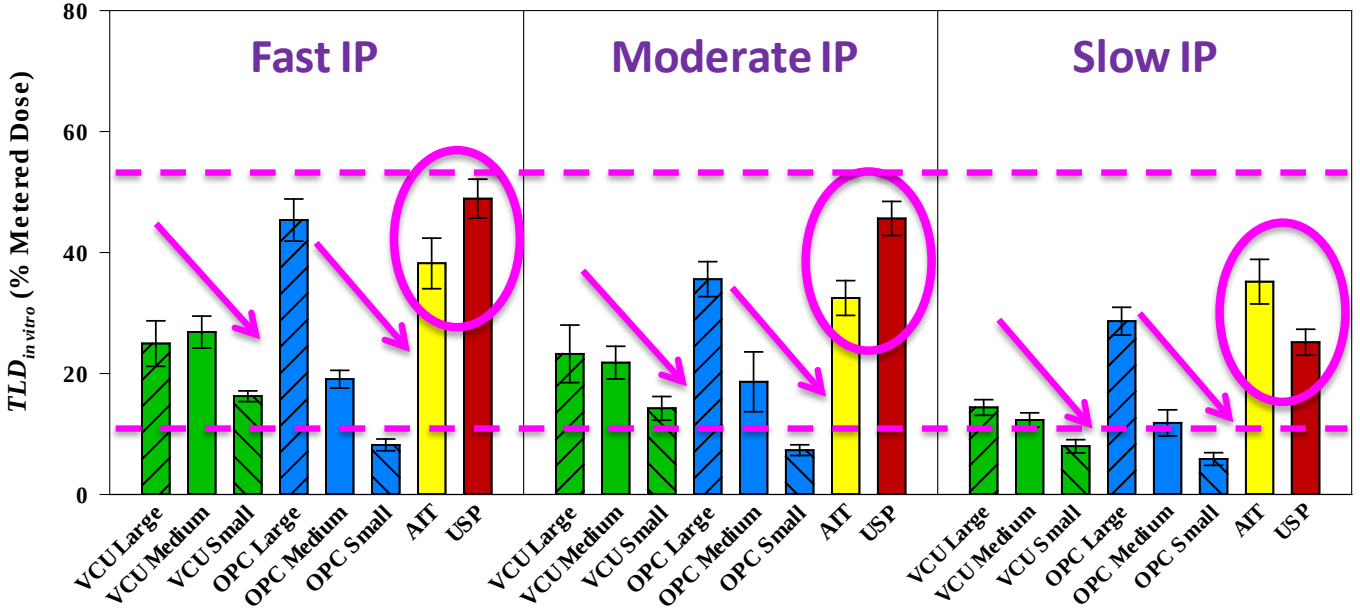
Moderate

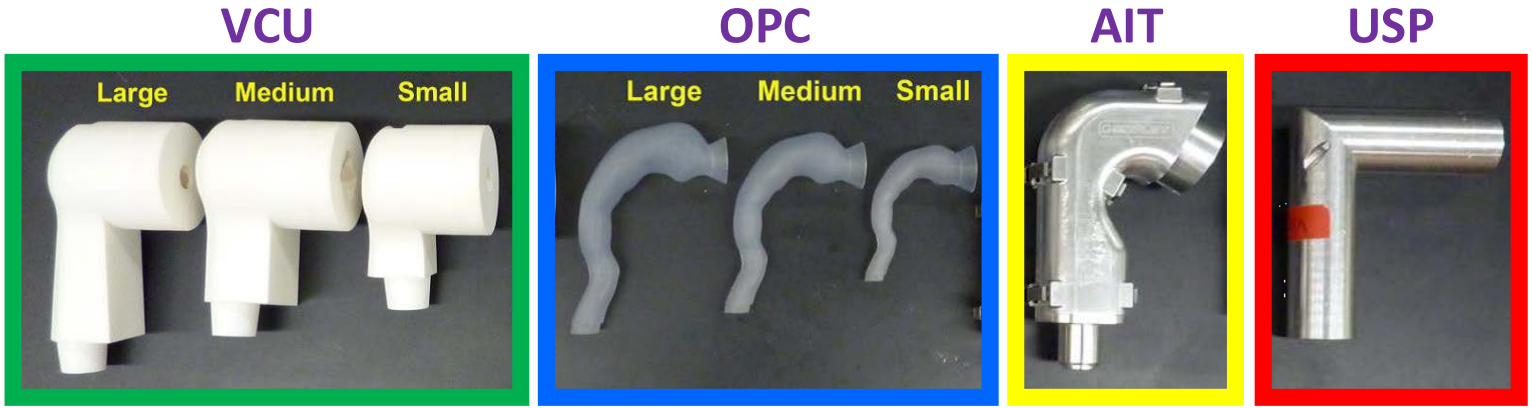
Slow

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

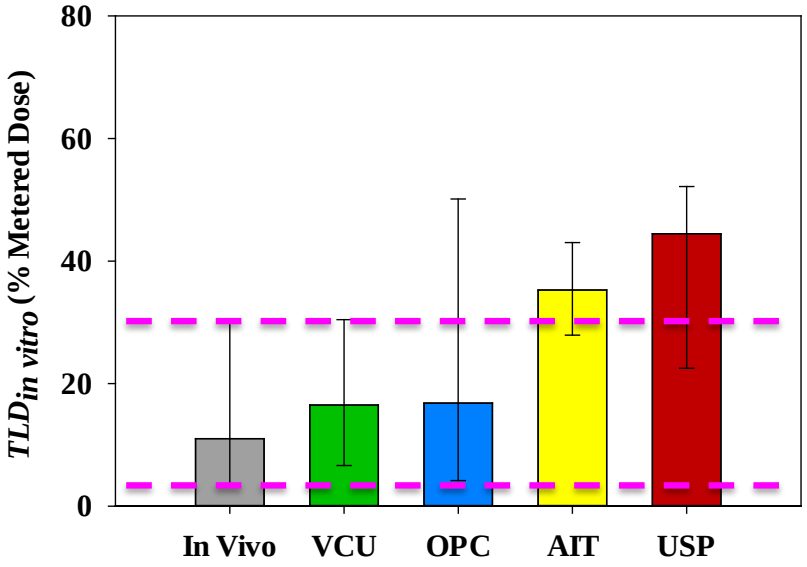


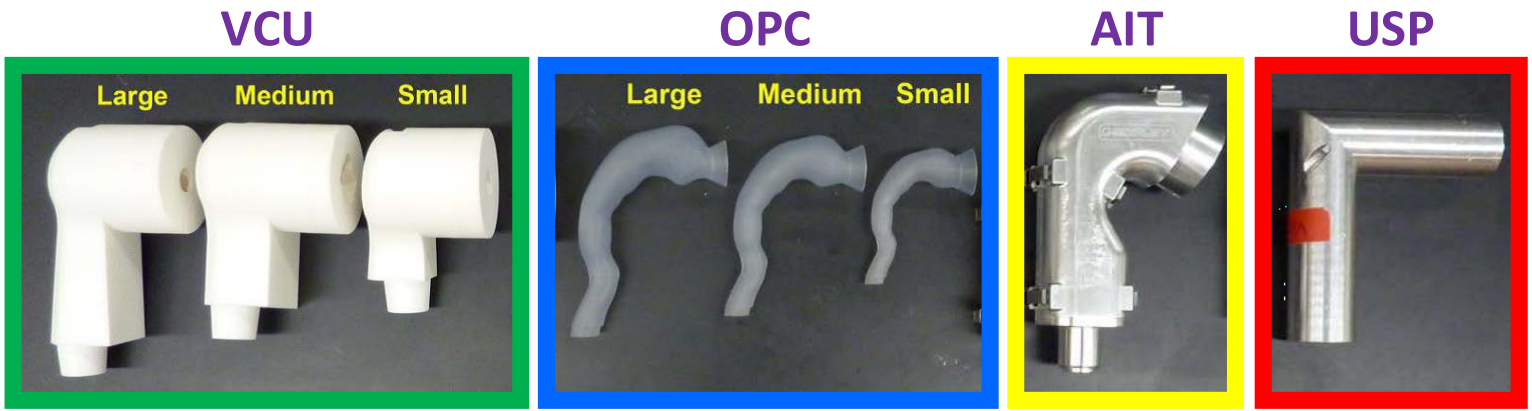


MDI Results

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

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





Conclusions

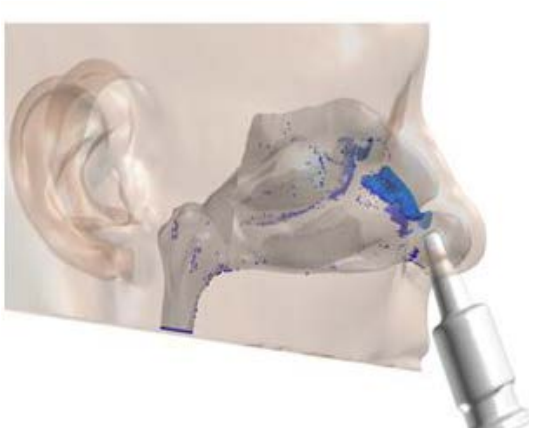
- A more realistic APSD in vitro test for OIDPs provides a **better prediction** of where inhaled particles may be deposited in the lungs compared to the current APSD in vitro test which uses the USP inlet
- Importance for **generic** OIDPs
  - Product development
  - Quality control
  - Faster, less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

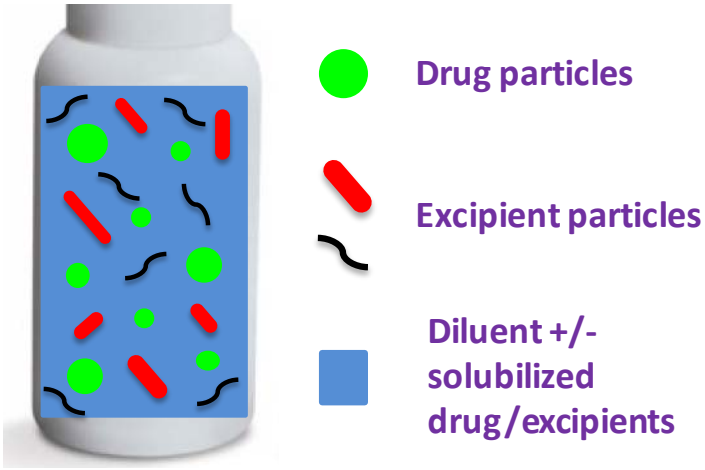
Research Initiatives for OINDPs

- 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



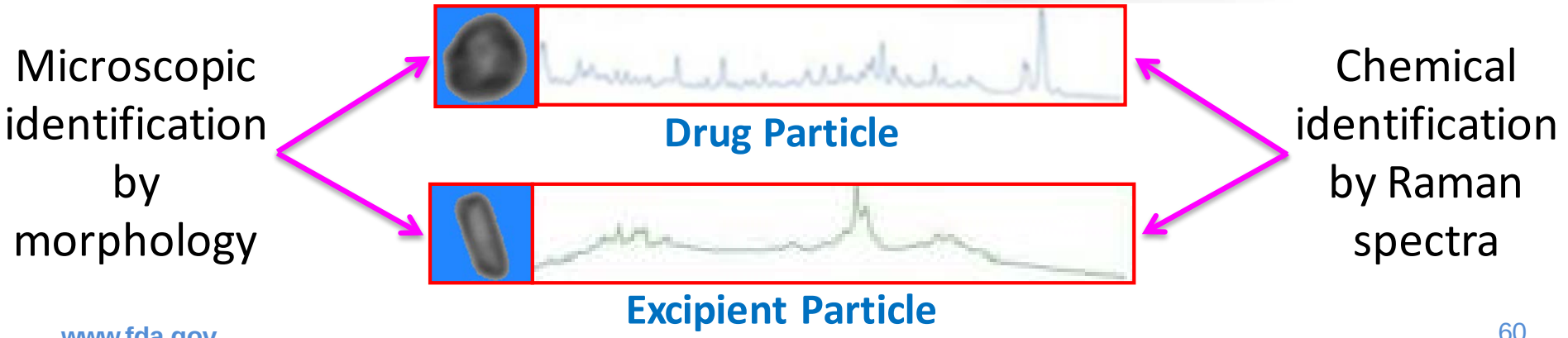


- Drug particle size distribution (PSD) in suspension formulations has the potential to influence **the rate and extent of drug availability** to nasal sites of action and systemic circulation
- Inability to adequately characterize drug PSD in aerosols and sprays using **common analytical methods**

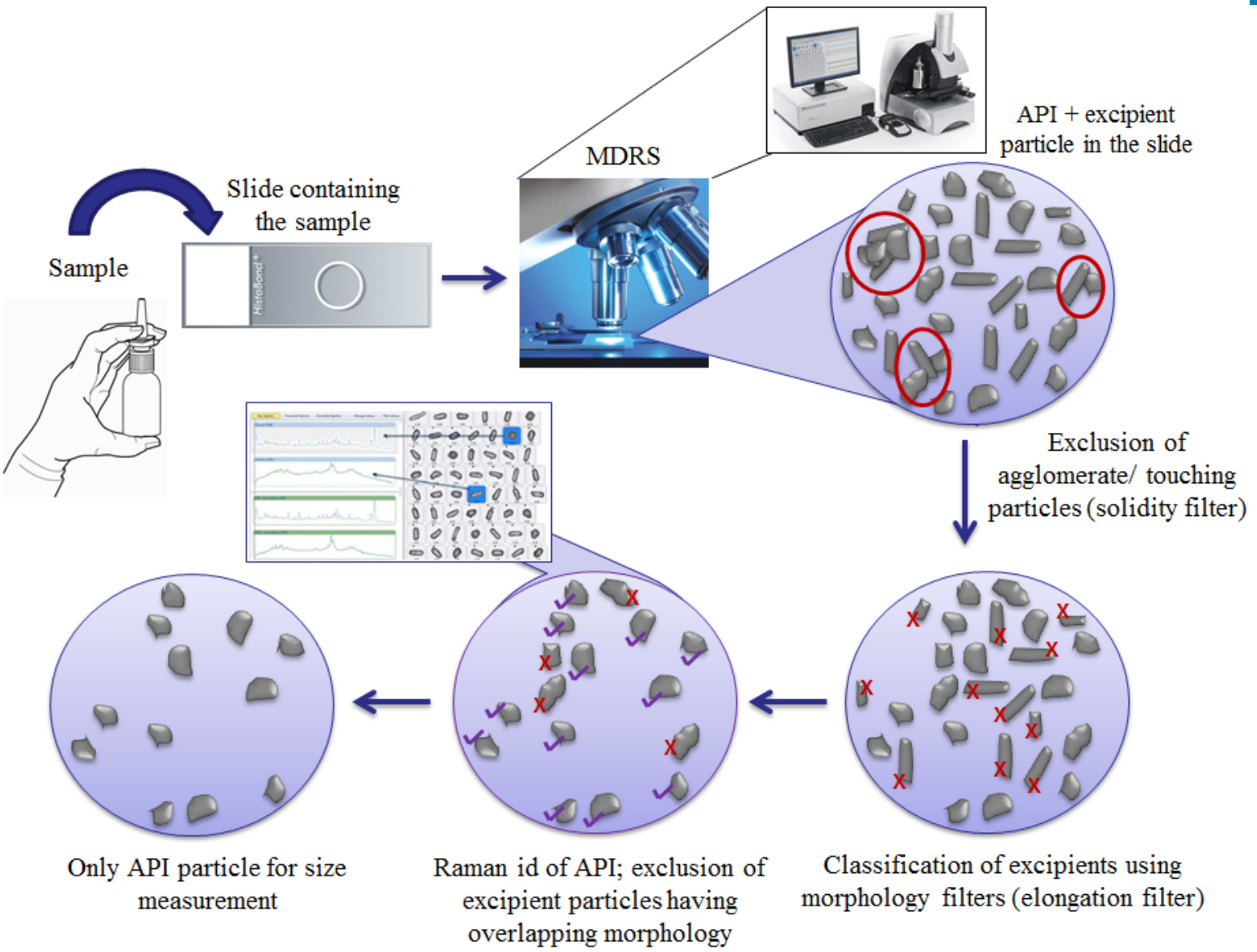
MDRS for Nasal Spray Suspensions

- 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?

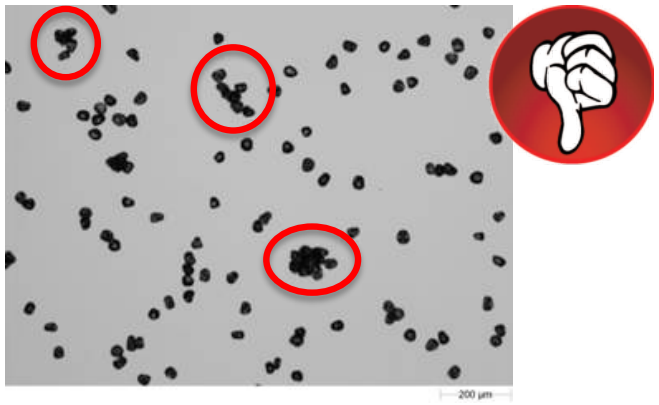


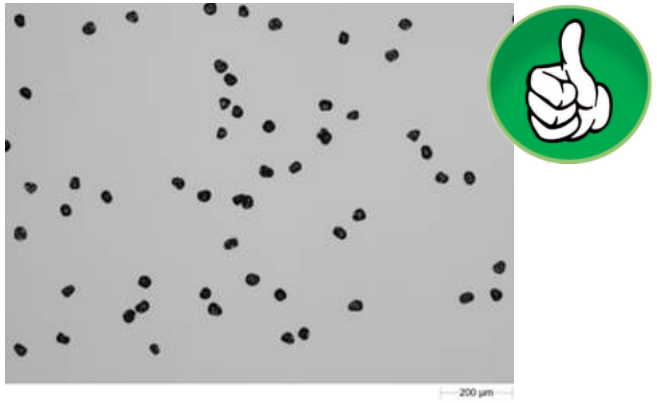
Courtesy of Dr. Abir Absar, Ph.D. (FDA/OCP)

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

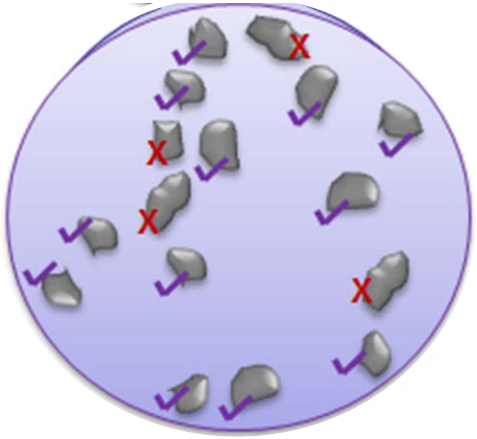
Circularity = 0.47
Convexity = 0.7
Elongation = 0.24

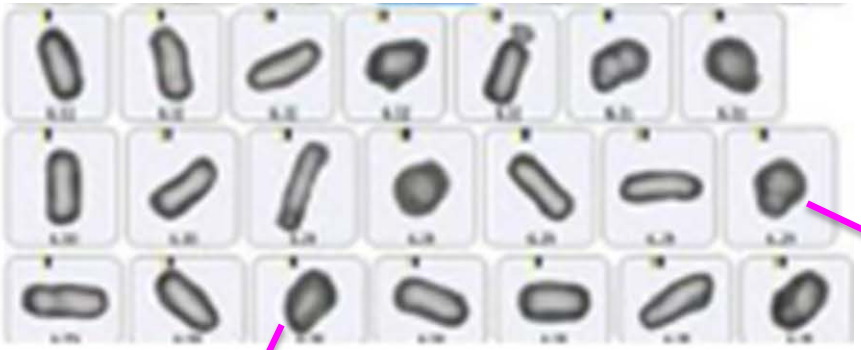
Circularity = 0.21
Convexity = 0.73
Elongation = 0.83

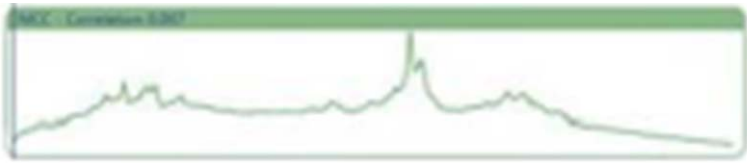
Circularity = 0.52
Convexity = 1
Elongation = 0.79

Chemical Identification by Raman Spectra

- Identifies particles with overlapping morphological features







Conclusions

- An **advanced analytical method** for measuring drug PSD in nasal 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
  - Stimulates **innovation and growth** in the generic drug field
  - Develops **new methodologies and 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
  - 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
  - An **advanced analytical method** for measuring drug PSD in nasal suspension products, **such as MDRS**, enables a comparison of drug PSD in the generic and reference products

Thank you!

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

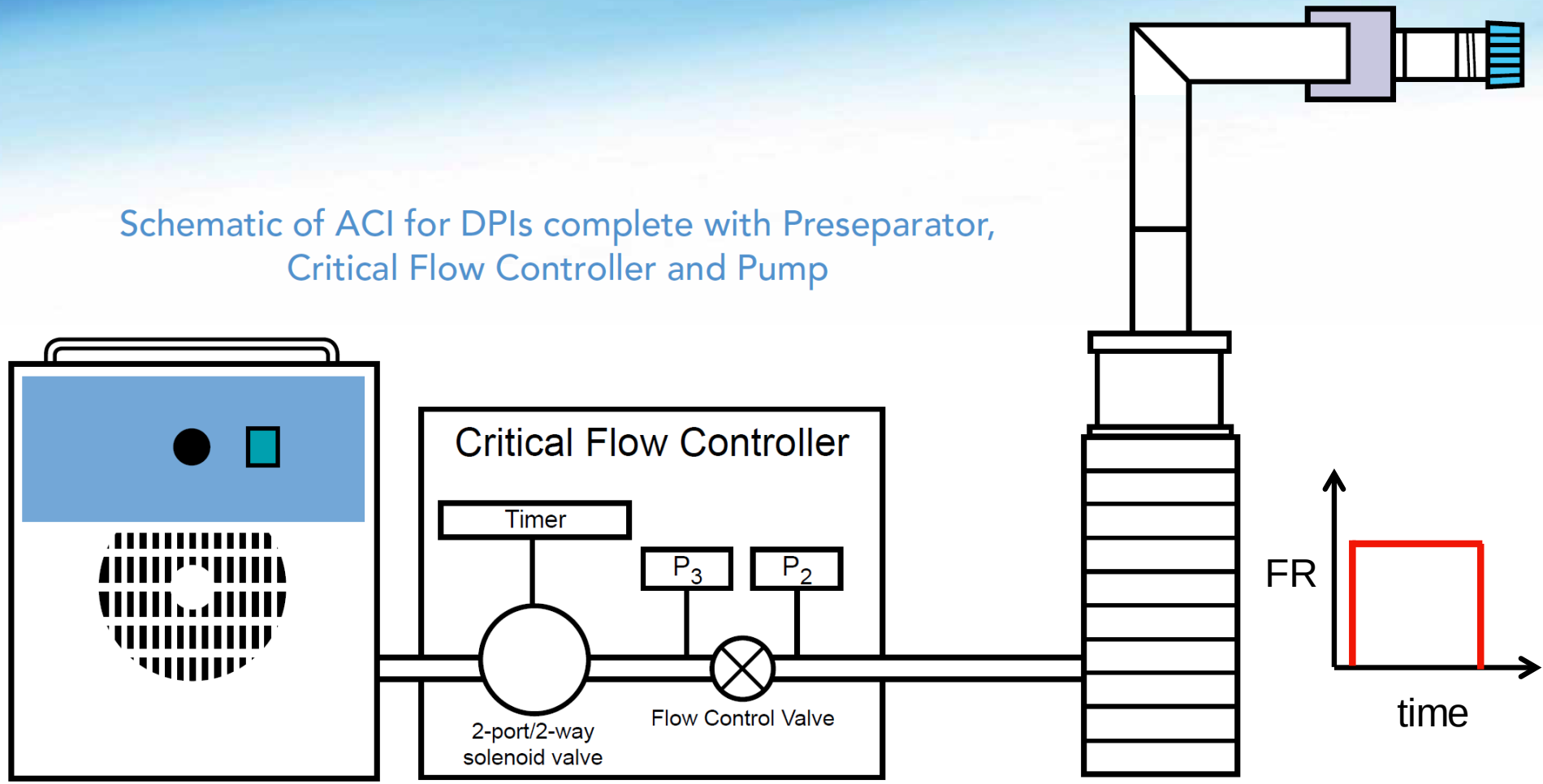

FDA
U.S. FOOD & DRUG
ADMINISTRATION

QUESTIONS?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Back-up Slides

Operating Principle of Cascade Impactors

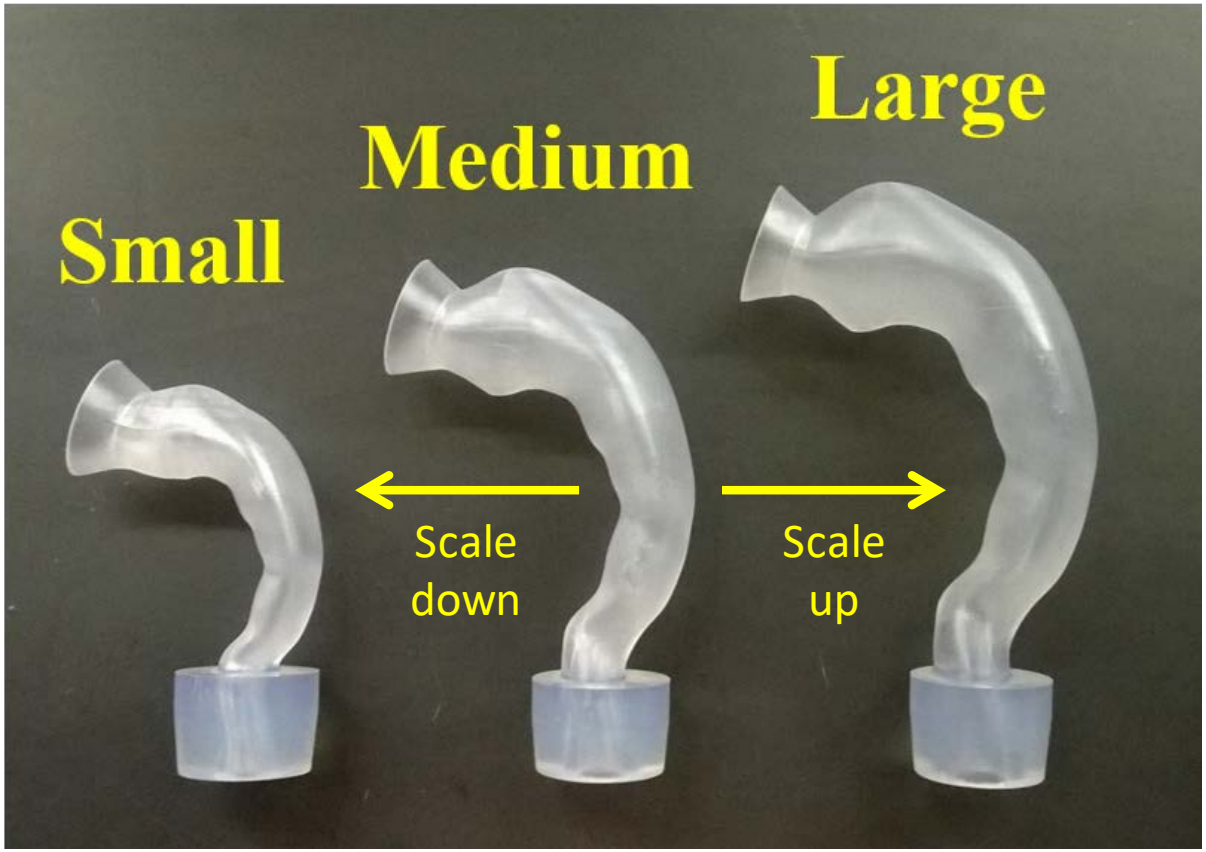


NGI Cutoff Diameters

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

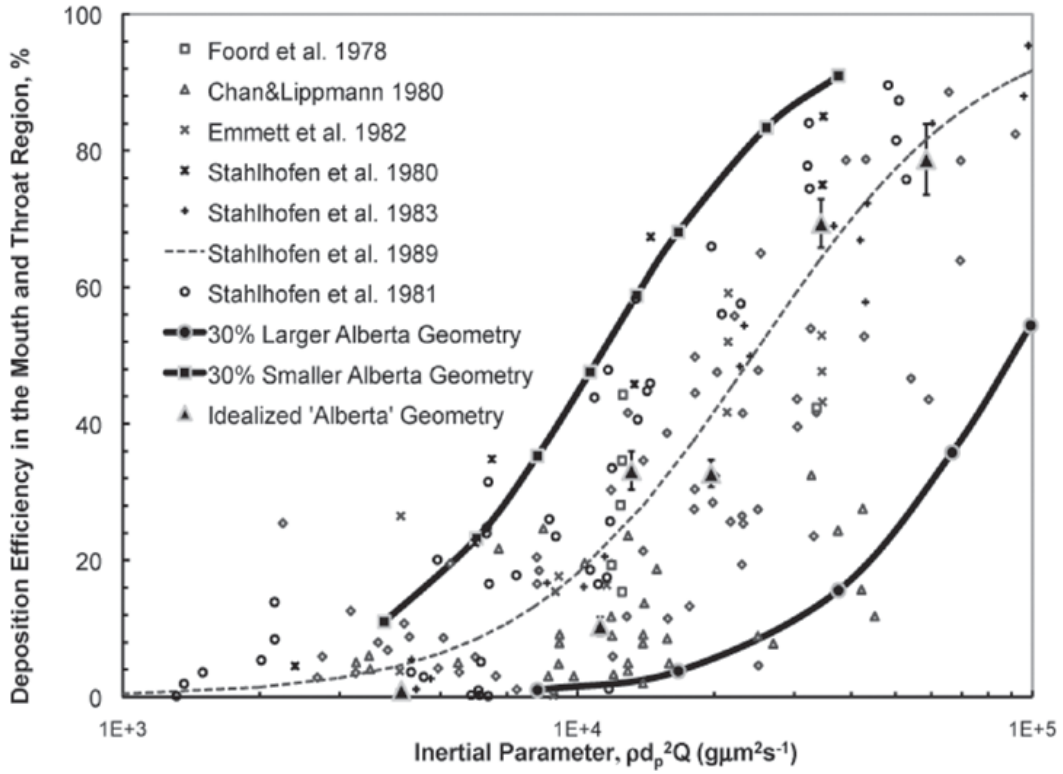
VCU Models

Scaling average model to capture anatomical variability



Alberta Idealized Throat (AIT) Model

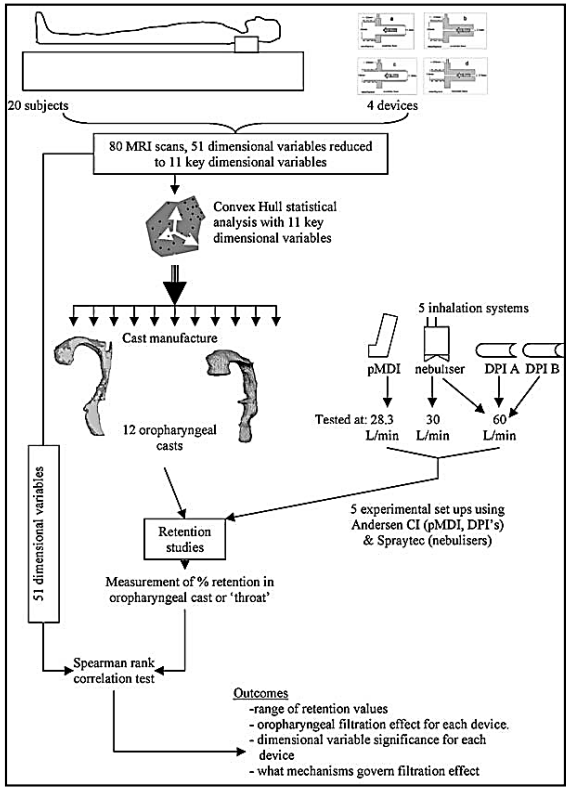
Scaling average model that span the aerosol deposition behavior



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

Oropharyngeal Pharmaceutical Consortium (OPC) Models

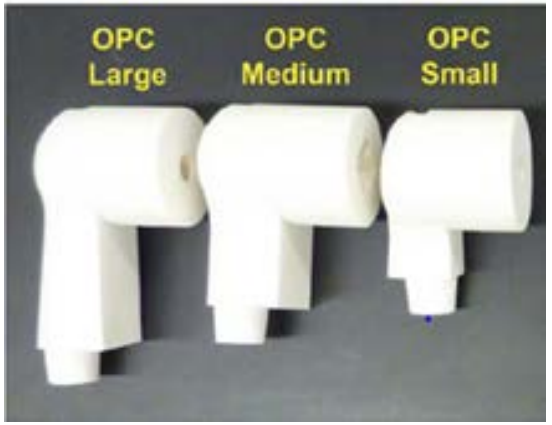
Scanning several airway geometries under different inhalation conditions



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

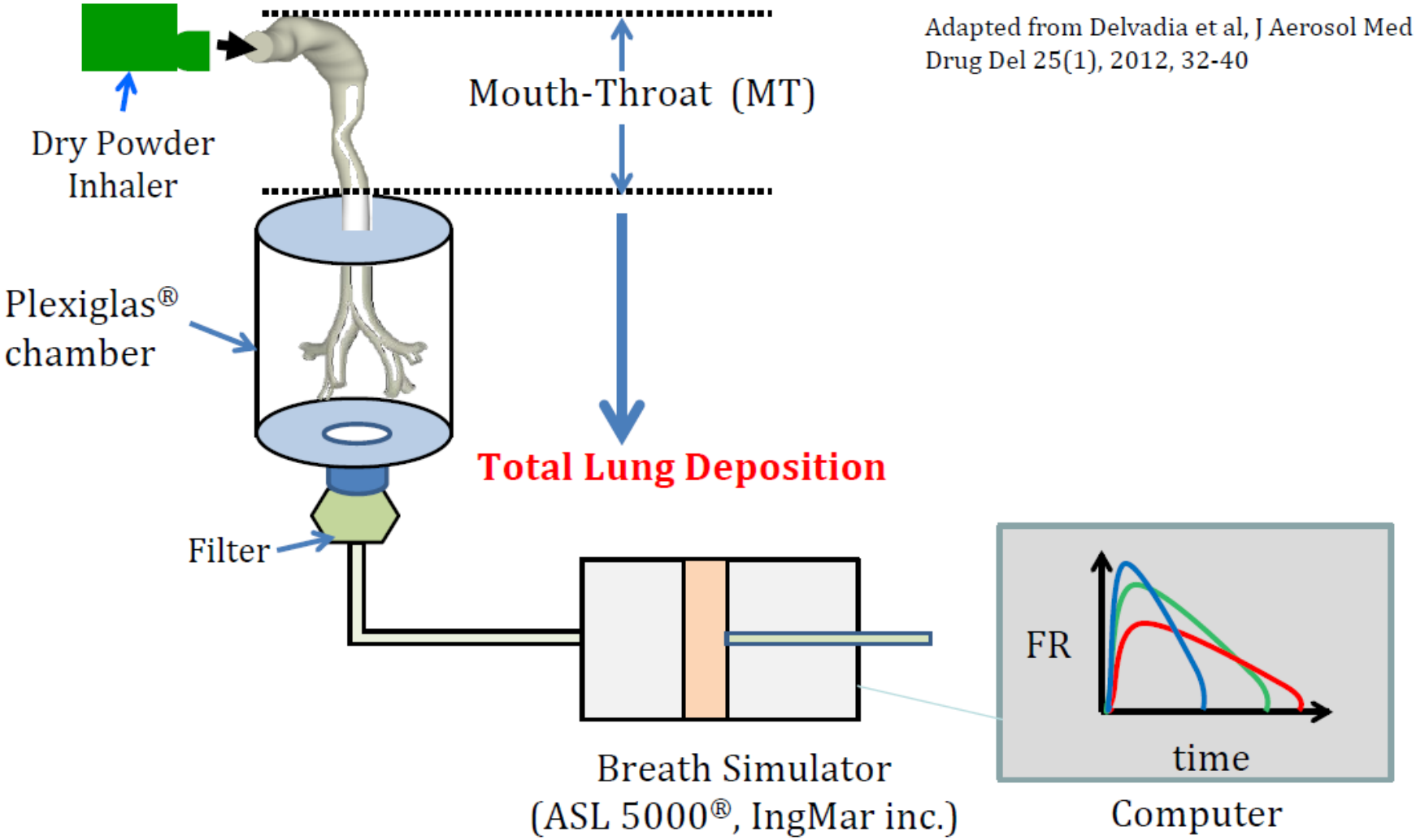
Pick representative models

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



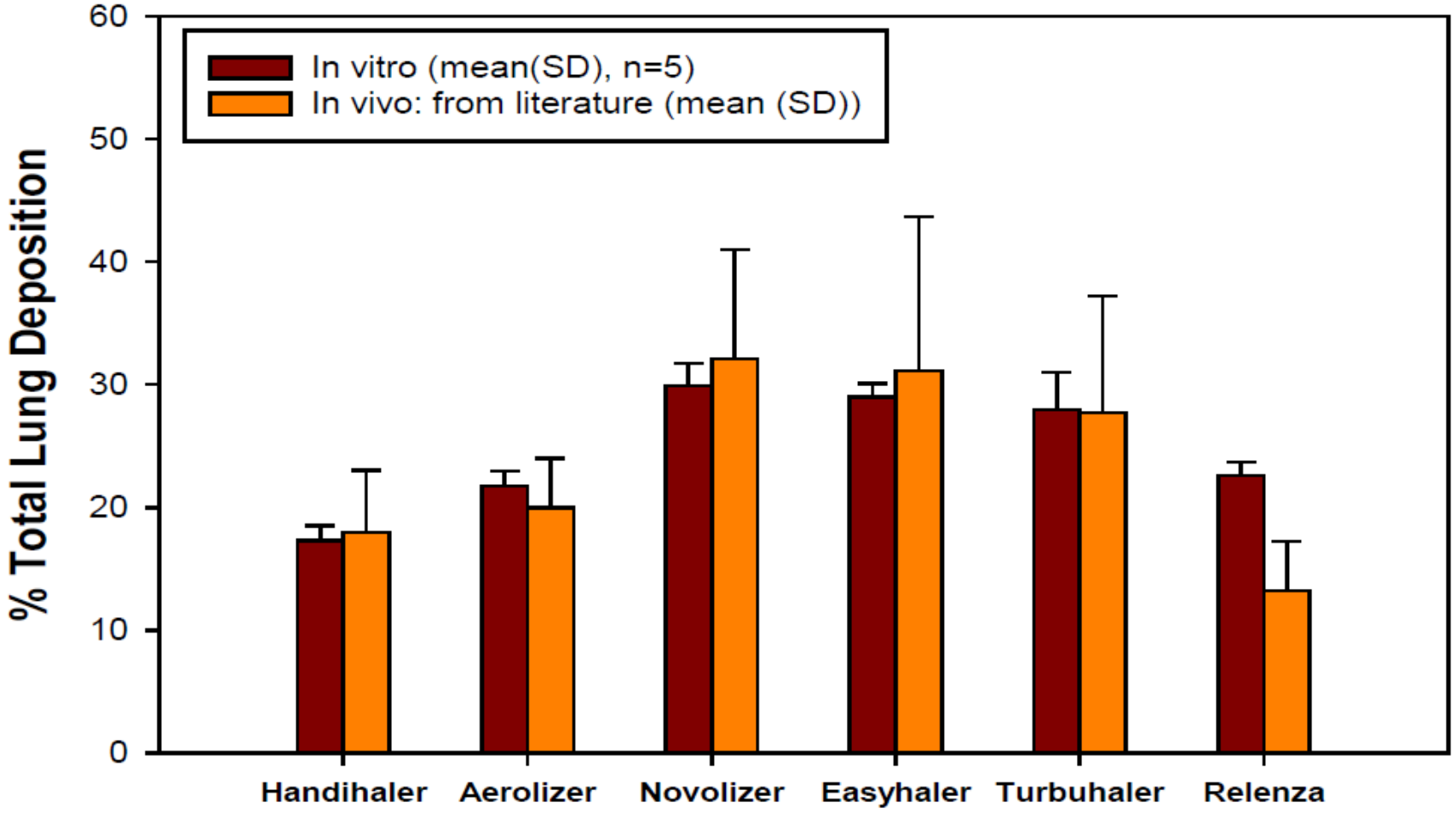
Adapted from Byron et al., RDD 2013, Vol 1, 85-92

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

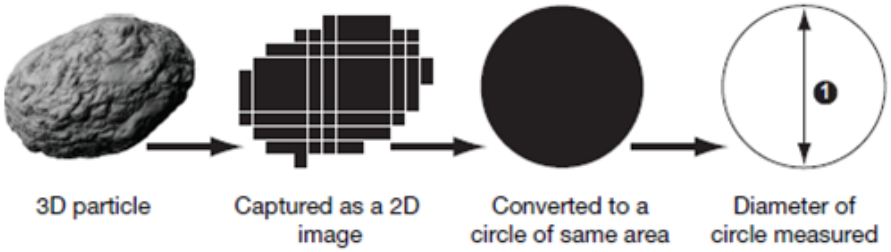
In Vitro – In Vivo TLD Comparison



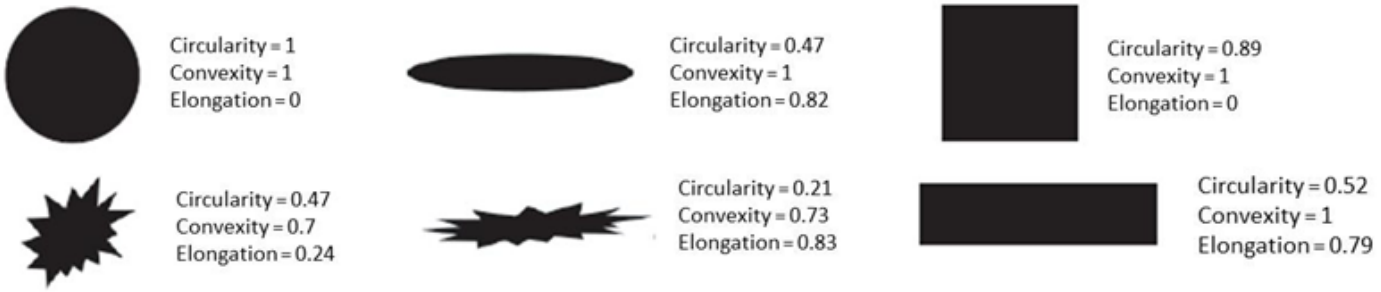
Based on results published in Delvadia et al, J Aerosol Med Pul Drug Del 25(1), 2012, 32-40 and Delvadia et al, J Aerosol Med Pul Drug Del 26(3), 2013 ,138-144

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

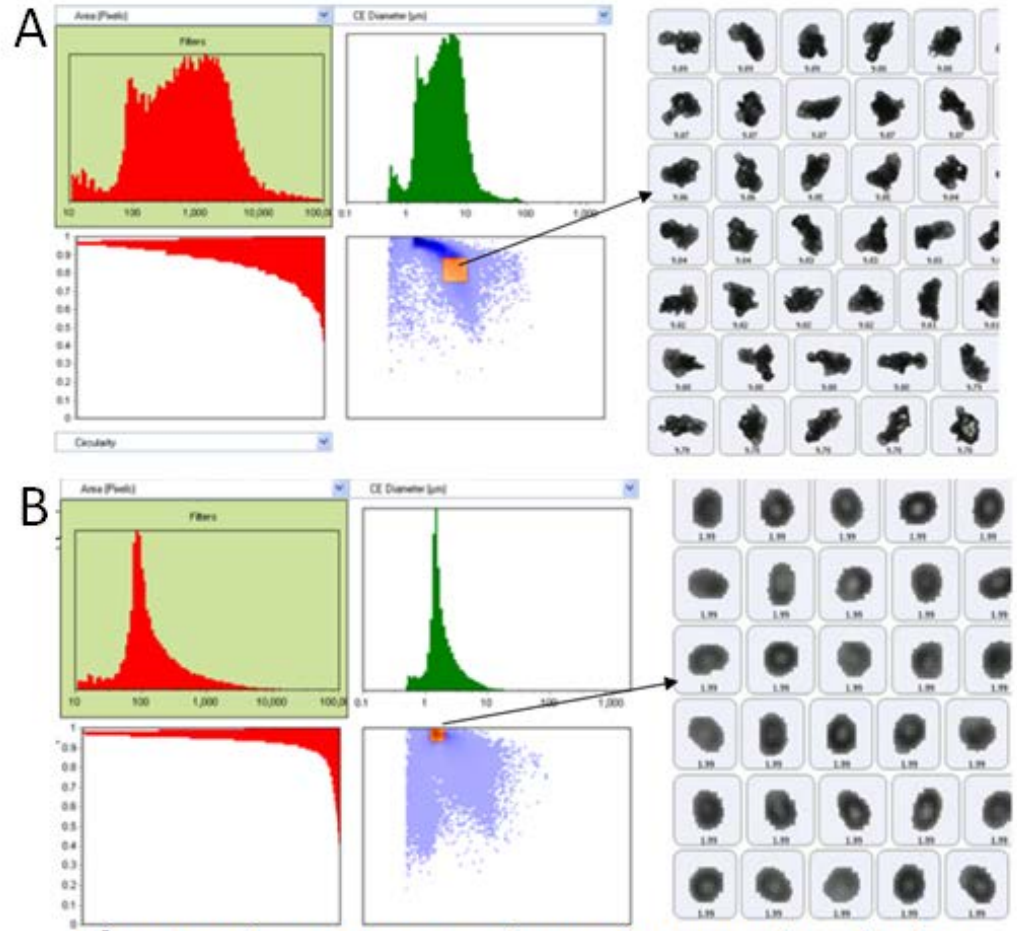


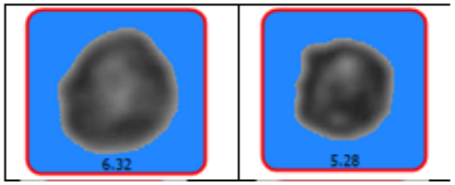
Fig: Agglomerates show lower circularity and higher CE diameter

MDRS: Classification of Particles

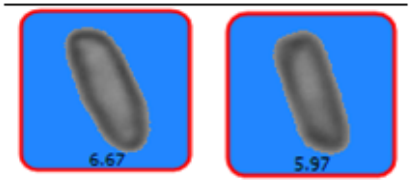
- Classify the particles based on morphological features
- Use of morphology filters – circularity, elongation, convexity/solidity

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