U.S. FOOD & DRUG ADMINISTRATION

# IMPACT OF EXCIPIENTS ON INHALATION DRUG PRODUCTS

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Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

# Outline

- Regulatory Standards for Bioequivalence
- Differences in Systemically- versus Locally-acting Products
- Specific Bioequivalence Recommendations for OINDPs
- GDUFA Regulatory Science Program
- Excipient Formulation Changes in DPIs
- Excipient Formulation Changes in MDIs
- Conclusions

# 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

- **Therapeutically Equivalent**

  The same safety and efficacy when used in the indicated population according to the labeling recommendations



21 CFR 320- Subpart B; See also FDA's Approved Drug Products with Therapeutic Equivalents (the Orange Book), preface to the 36th edition, at page vii.

# Determination of Generic Drug Product's Equivalence to its Reference Listed Drug

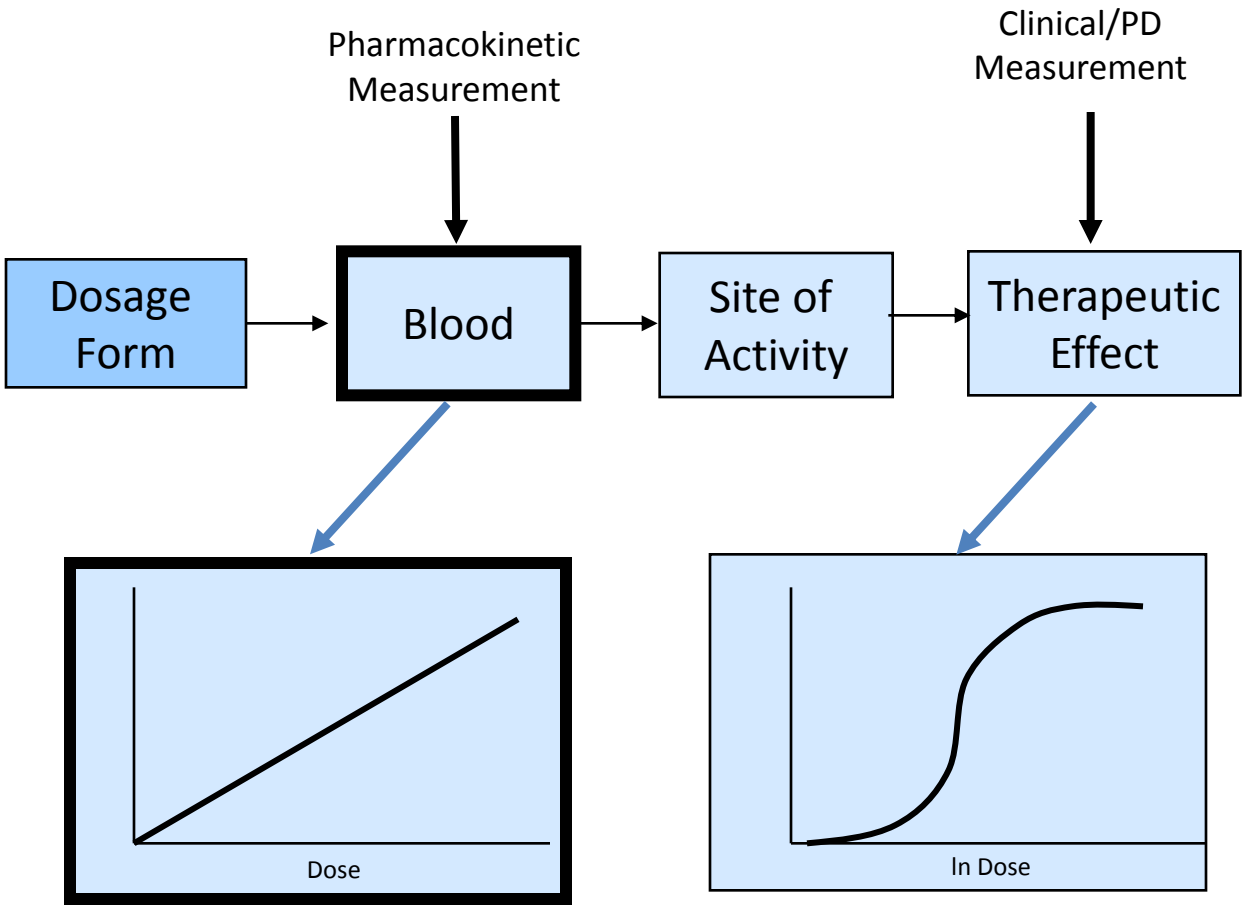
- It is expected that manufacturers conduct testing using the most accurate, sensitive, and reproducible approach
- The choice of methodology used for establishing and ensuring Therapeutic Equivalence throughout product's lifecycle will involve considerations for:
    - Formulation design
    - Product composition
    - Site of action
    - Mechanism of drug delivery and release
    - Ability to measure drug's availability at the site of action
    - Expected and measured therapeutic effects and their relationship to drug concentration
    - Other factors related to patient-product interaction

# Regulatory Science of Bioavailability, Bioequivalence and Product Performance

If your understanding of biopharmaceutics is strong, then you can predict and control bioavailability and bioequivalence through product performance

- Example: For a BCS class I, drug with rapid dissolution, in vivo bioequivalence studies are not needed
- What is the state of biopharmaceutics for non-oral dosage forms?

# BE for Systemically-Acting Drugs

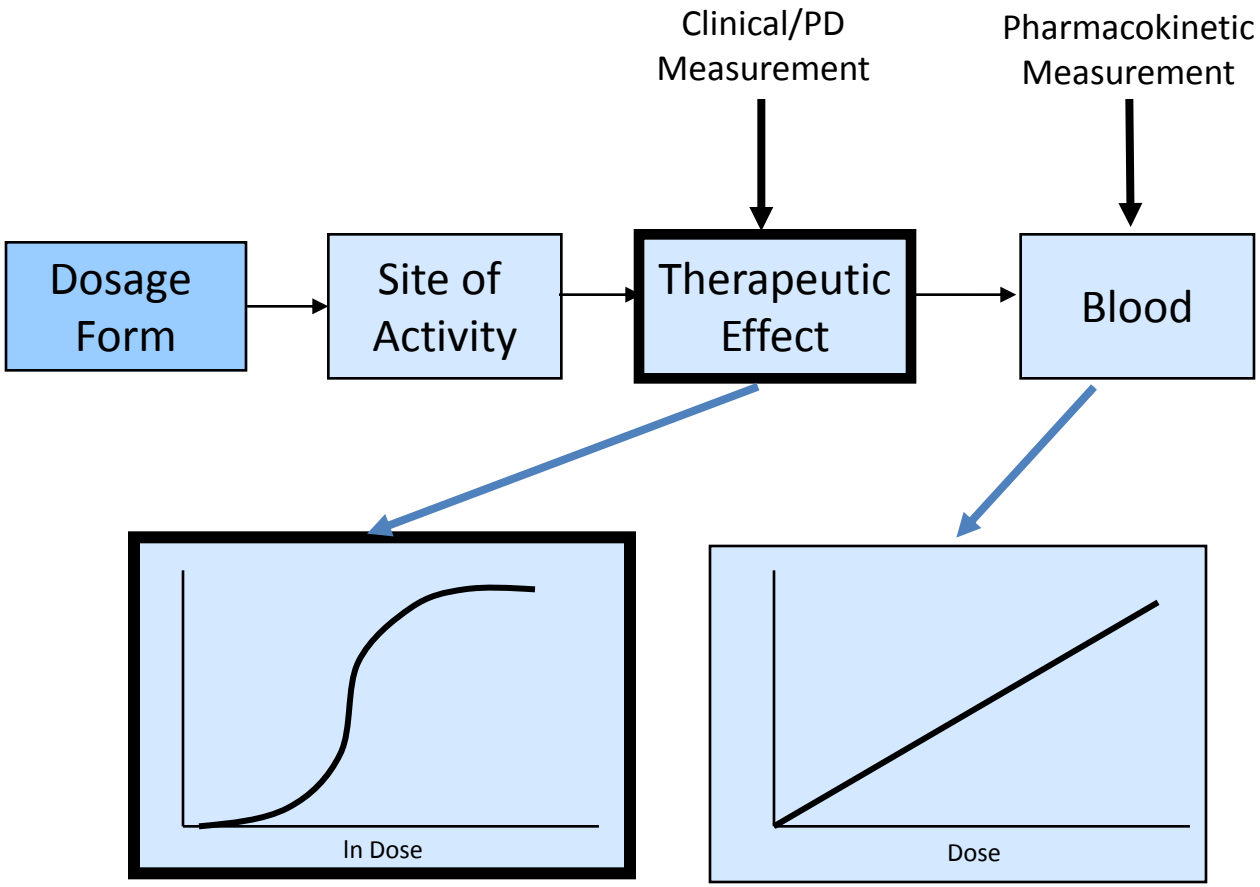



- Delivered to the bloodstream for distribution to site(s) of action in the body
- BE determined with PK studies
  - Relatively short studies
  - Relatively small number of subjects

# Orally Inhaled Drug Products (OIDPs)

- Include Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs)
- Drug delivery is local to site of action (lung tissue), not systemic
- Intended target effect does not rely primarily on systemic absorption
- Challenges to measuring local effect
- Device is integral part of the delivered dose

# BE for Locally-Acting Drugs




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

# Products Delivered to the Respiratory System

- Orally inhaled and nasal drug products
- Factors influencing patient-product interactions and drug bioavailability include:
  - dose percent deposited in the lungs vs. dose percent swallowed and absorbed from the GI tract
  - local solubility/permeability
  - receptor affinity
  - deposition in central vs. peripheral parts of the pulmonary tree
  - pulmonary residence time
  - local clearance (mucociliary transport and RES uptake)
  - device design
  - **effects of formulation differences on product performance**

# Weight-of-Evidence Approach

- Includes the following:
  - In vitro
  - In  vivo PK
  - PD or comparative clinical endpoint study
- 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

# BE Recommendations 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

# 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 provide additional resources, including support for **regulatory science research**
- Largest user fee program to directly support regulatory science research activities

# FDA's Office of Generic Drugs Regulatory Science Program (RSP)

- Research grants and contracts awarded on a competitive basis every year
- Funds allocated under GDUFA to stimulate innovation and growth in the generic drug field

  Identify, study, and implement new methodologies and tools to be used in development and evaluation of quality and equivalence of new generic drug products in all therapeutic areas and various product categories
- FDA holds an annual public meeting with stakeholders, including industry, academia, patient advocates, professional societies and others, to provide an opportunity for public input on research priorities in generic drug development and regulation

# GDUFA Regulatory Science Program

- Supports access to generic drugs in all product categories
  - inhalation, nasal, topical dermatological, ophthalmic, liposomal, sustained release parenteral
- Development of new tools to evaluate drug equivalence and support drug development
  - Simulation tools to predict drug absorption
  - Advanced analytical methods for product characterization
  - In vitro methods to predict in vivo performance

# FY15 Locally-Acting Orally Inhaled and Nasal Drug Products

- Intent is to develop Product-Specific Recommendations
- Clinically relevant in vitro methods to predict regional deposition and local bioavailability of OINDPs, assist in assessment of BE, and serve as pharmaceutical development tool
- Three research aims to develop
  - Predictive dissolution methods
  - Predictive lung deposition models
  - Clinically relevant in vitro performance tests incorporating mouth-throat models
- Additional research interests
  - **Effects of device design and formulation factors on performance of DPIs and MDIs**
  - If PK studies can provide information about local sites of action in lung for DPIs, and in nose for nasal suspensions

# Projects and Collaborators

- Evaluation of Formulation and Device Changes on In Vitro Performance of Dry Powder Inhalers
  - Study PI: Robert Price (University of Bath)
  - Contract #: HHSF223200910017C

- Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance
  - Site PI: Guenther Hochhaus (University of Florida)
  - Grant #: U01FD004943

# Evaluation of Formulation Changes on *In Vitro* Performance of Dry Powder Inhalers

- FY-09 Critical Path Project, contract # HHSF223200910017C:
  - Awarded to University of Bath

- The goal of this project was to utilize quality by design (QbD) approach to identify critical formulation attributes of a test DPI that could be adjusted to achieve equivalent in vitro performance to the reference DPI, given that the test and reference DPI devices have the same dosing format (e.g., pre-metered single dose units) and similar device resistance.



Shur J, Saluja B, Lee S, Tibbatts J, Price R. Effect of device design and formulation on the in vitro comparability for multi-unit dose dry powder inhalers. The AAPS Journal. 2015:1-12.

# Methods

- Several T formulations were prepared to investigate the effect of particle size and surface properties of the API and carrier lactose as well as cohesive and adhesive properties of the DPI formulation on the in vitro comparability of T and R DPIs.
- The T DPI device was modified to achieve comparable specific resistance and airflow path between T and R devices.



Shur J, Saluja B, Lee S, Tibbatts J, Price R. Effect of device design and formulation on the in vitro comparability for multi-unit dose dry powder inhalers. The AAPS Journal. 2015:1-12.

# Formulation Characteristics

## Characterization of micronized fluticasone propionate (FP)

| FP batches | Particle size distribution (μm) | | | Specific surface area ($m^2/g$) | CAB ratio |
|---|---|---|---|---|---|
| | $d_{10}$ | $d_{50}$ | $d_{90}$ | | |
| A | 1.20 (1.15–1.26) | 2.00 (1.94–2.04) | 5.72 (5.70–5.74) | 7.95 (7.88–8.04) | 0.94 (0.93–0.95) |
| B | 1.20 (1.18–1.22) | 2.72 (2.70–2.74) | 5.17 (5.15–5.19) | 6.85 (6.78–6.89) | 0.82 (0.81–0.83) |
| C | 0.96 (0.94–0.98) | 2.65 (2.60–2.72) | 7.41 (7.38–7.43) | 7.76 (7.64–7.79) | 0.65 (0.63–0.66) |
| D | 0.98 (0.95–0.99) | 2.73 (2.68–2.74) | 5.25 (5.19–5.27) | 6.54 (6.51–6.56) | 0.42 (0.41–0.43) |

Range, min–max is shown in the parenthesis ($n$=3)

## Characterization of milled (ML001) and sieved (SV003) lactose

| Batch | Particle size distribution (μm) | | | % <5 μm |
|---|---|---|---|---|
| | $d_{10}$ | $d_{50}$ | $d_{90}$ | |
| ML001 | 2.77 (2.76–2.78) | 33.32 (33.28–33.34) | 148.07 (147.89–148.15) | 14.45 (14.35–14.51) |
| SV003 | 15.51 (15.48–15.53) | 56.80 (56.32–56.84) | 92.59 (90.39–93.43) | 6.48 (6.42–6.53) |

# In Vitro Comparison of T and R DPI Formulations (A, B, C, D) Using Sieved (SV) Lactose

| | Accuhaler® | | | | SV A | | | | SV B | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Flow rate (L/min) | ED (μg) | ISM (μg) | FPM (μg) | MMAD (μm±GSD) | ED (μg) | ISM (μg) | FPM (μg) | MMAD (μm±GSD) | ED (μg) | ISM (μg) | FPM (μg) |
| 30 | 83.8 (79.4–85.2) | 17.0 (14.5–18.4) | 15.4 (12.7–17.1) | 4.3±2.2 | 80.4 (77.8–83.0) | 16.0 (14.2–19.2) | 13.3 (11.4–14.9) | 3.2±2.3 | 83.0 (79.1–85.8) | 14.1 (12.2–16.5) | 11.3 (9.1–13.1) |
| 60 | 88.7 (83.9–91.2) | 21.4 (20.3–22.1) | 19.9 (18.8–20.9) | 3.5±2.2 | 82.8 (79.1–84.6) | 20.7 (18.4–23.2) | 19.0 (17.2–21.2) | 3.6±2.1 | 86.0 (82.8–89.3) | 19.0 (17.1–21.5) | 16.3 (14.6–18.1) |
| 90 | 88.8 (85.3–91.7) | 21.1 (20.3–21.5) | 20.6 (19.1–21.9) | 3.3±2.2 | 82.3 (79.4–85.2) | 24.1 (21.4–26.5) | 20.2 (17.4–22.6) | 2.6±2.2 | 86.6 (82.6–90.5) | 23.1 (21.2–24.9) | 20.2 (18.4–22.1) |

| | SV B | SV C | | | | SV D | | | |
|---|---|---|---|---|---|---|---|---|---|
| Flow rate (L/min) | MMAD (μm±GSD) | ED (μg) | ISM (μg) | FPM (μg) | MMAD (μm±GSD) | ED (μg) | ISM (μg) | FPM (μg) | MMAD (μm±GSD) |
| 30 | 2.8±2.3 | 81.6 (78.0–83.1) | 14.0 (12.2–16.2) | 11.3 (9.2–13.2) | 2.9±3.3 | 82.3 (80.5–84.1) | 14.0 (12.8–16.2) | 11.3 (9.4–13.6) | 2.9±2.1 |
| 60 | 3.1±2.1 | 84.7 (81.9–87.5) | 18.3 (16.3–20.8) | 14.5 (11.7–17.3) | 2.5±2.1 | 86.5 (82.8–89.6) | 16.2 (14.4–18.2) | 13.1 (11.9–15.2) | 2.7±2.1 |
| 90 | 3.1±2.0 | 83.3 (81.8–84.8) | 18.9 (16.4–20.9) | 16.3 (14.4–18.9) | 2.9±2.0 | 90.7 (86.5–94.9) | 20.4 (18.2–22.3) | 17.4 (15.4–19.1) | 2.8±2.0 |

Range, min–max is shown in the parenthesis ($n$=3)

For the same flow rate, there were differences in in vitro metrics (e.g., MMAD) according to different formulation characteristics.

# In vitro comparison of T and R DPI formulations (A, B, C, D) using milled (ML) lactose

| Flow rate (L/min) | Accuhaler® ED (µg) | Accuhaler® ISM (µg) | Accuhaler® FPM (µg) | Accuhaler® MMAD (µm±GSD) | ML A ED (µg) | ML A ISM (µg) | ML A FPM (µg) | ML A MMAD (µm±GSD) | ML B ED (µg) | ML B ISM (µg) | ML B FPM (µg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 83.8 (79.4–85.2) | 17.0 (14.5–18.4) | 15.4 (12.7–17.1) | 4.3±2.2 | 81.1 (78.4–83.9) | 19.9 (17.4–21.5) | 17.7 (15.4–19.2) | 4.1±2.2 | 84.2 (80.9–87.5) | 19.4 (14.5–18.4) | 17.2 (12.7–17.1) |
| 60 | 88.7 (83.9–91.2) | 21.4 (20.3–22.1) | 19.9 (18.8–20.9) | 3.5±2.2 | 91.3 (88.8–93.2) | 31.5 (28.6–34.1) | 26.7 (24.8–28.7) | 3.0±2.1 | 85.1 (83.2–86.9) | 27.1 (25.2–29.1) | 22.1 (19.9–24.5) |
| 90 | 88.8 (85.3–91.7) | 21.1 (20.3–21.5) | 20.6 (19.1–21.9) | 3.3±2.2 | 85.0 (79.4–89.6) | 35.1 (31.9–37.6) | 31.9 (28.5–33.1) | 2.9±2.2 | 94.9 (92.2–96.2) | 33.0 (30.2–36.2) | 27.1 (24.2–29.2) |

| Flow rate (L/min) | ML B MMAD (µm±GSD) | ML C ED (µg) | ML C ISM (µg) | ML C FPM (µg) | ML C MMAD (µm±GSD) | ML D ED (µg) | ML D ISM (µg) | ML D FPM (µg) | ML D MMAD (µm±GSD) |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 4.0±2.2 | 87.1 (82.8–91.3) | 25.3 (22.9–27.5) | 21.3 (17.9–23.6) | 3.5±2.2 | 82.0 (79.9–83.5) | 38.0 (36.4–39.2) | 35.6 (32.8–37.5) | 4.9±2.1 |
| 60 | 2.7±2.1 | 82.8 (79.7–85.6) | 37.3 (35.5–39.1) | 32.0 (29.8–34.3) | 2.8±2.3 | 93.9 (82.8–91.3) | 47.6 (42.8–51.8) | 40.0 (35.6–44.3) | 2.8±2.2 |
| 90 | 2.5±2.1 | 92.3 (90.5–94.1) | 40.7 (38.5–42.5) | 35.9 (32.2–36.1) | 2.9±2.1 | 99.5 (95.6–103.4) | 37.2 (34.3–39.5) | 34.3 (31.9–36.8) | 3.2±2.0 |

Range, min–max is shown in the parenthesis ($n$=3)

For the same flow rate, there were differences in in vitro metrics (e.g., MMAD) according to different formulation characteristics.

# Research Conclusion

- This investigation illustrated the importance of enhanced device and formulation understanding, to enable fabrication and refinement of the T DPI device and selection of formulation components, respectively, to provide a closer match to the aerosolization performance of the R DPI at multiple flow rates.

# Comprehensive Evaluation of Formulation Effects on MDI Performance

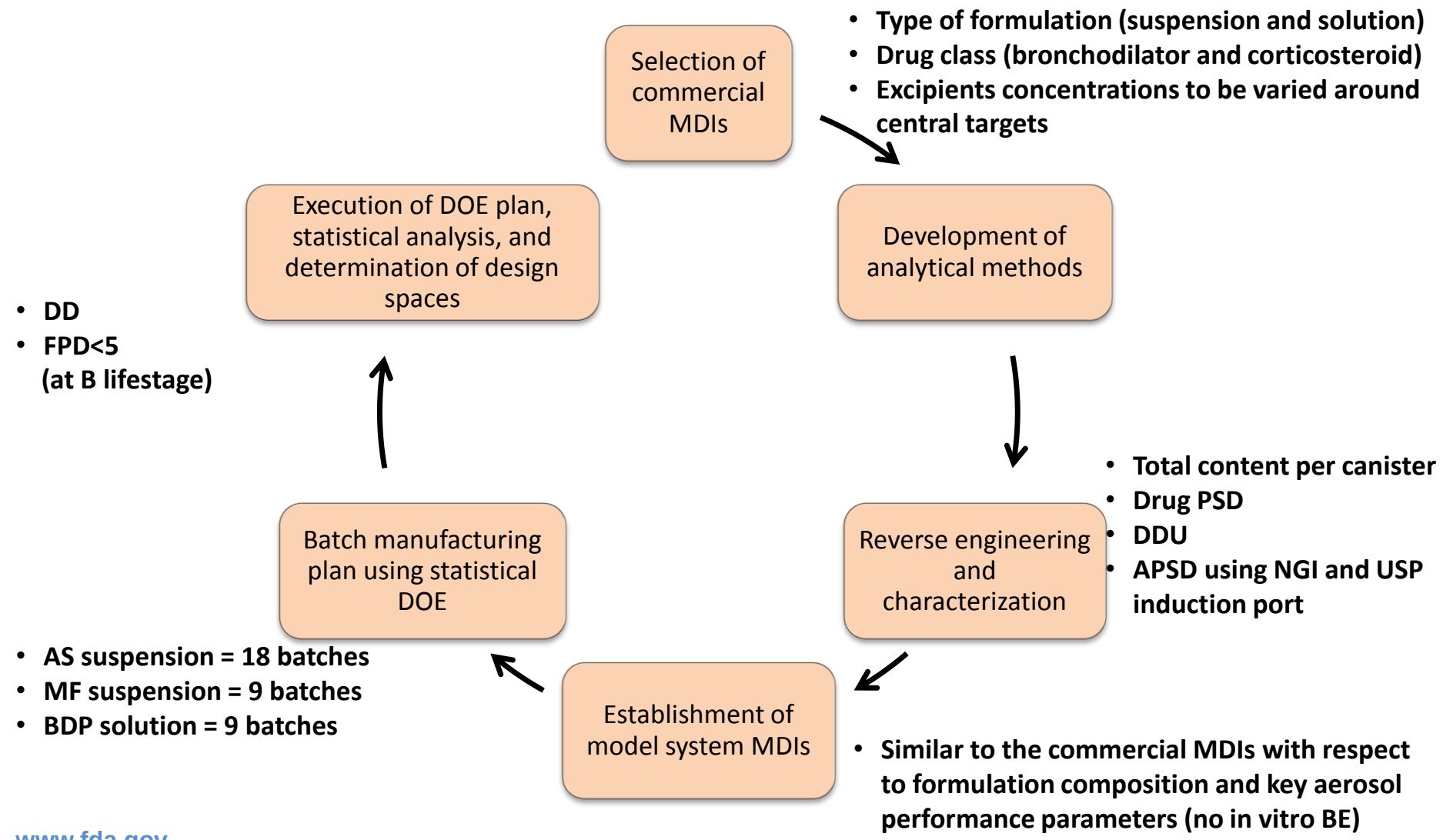
- FY-13 grant # U01FD004943:
  - Awarded to Cirrus Pharmaceuticals (present: Recipharm)
  - Expanded to University of Florida

- This project investigates the effect of excipient concentrations on the aerosolization performance of typical hydroflouroalkane (HFA)-based MDI formulations and evaluate the sensitivity of the in vitro methods in detecting excipient concentration changes.



https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-013.html

# Overview of the Systematic Approach






Conti, D. S.; Holt, J.; Sheth, P.; Sandell, D.; Hickey, A.; Saluja, B. "The Effects of Formulation Factors on the Aerosolization Performance of Metered Dose Inhalers." In: AIChe Annual Meeting, 2016, San Francisco, CA, United States. Poster presentation

# MDI Batch Manufacturing Plan

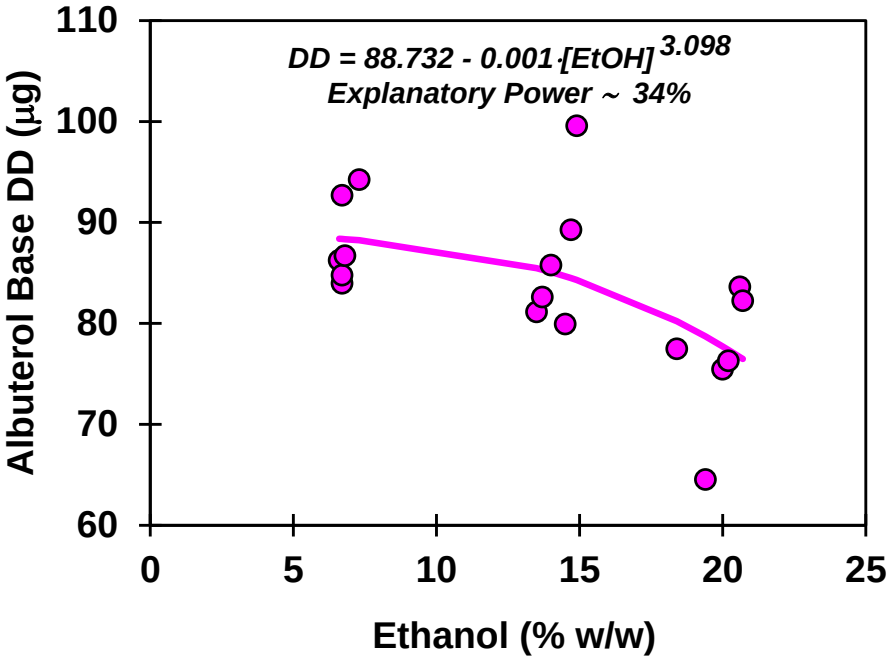
- The levels of excipients [ethanol (EtOH) and oleic acid (OA)] and drug PSD D50 were varied according to a reduced factorial statistical design of experiments (DOE) approach. The following ranges were studied:

| MDI Formulation | PSD D50 (µm) | EtOH (% w/w) | OA (% w/w) |
|---|---|---|---|
| AS suspension | 1.4 – 2.5 | 7 – 20 | 0.005 – 0.1 |
| MF suspension | 1.1 – 2.0 | 0.45 – 3.6 | 0.001 – 0.025 |
| BDP solution | N/A | 7 – 9 | 0 – 2 |

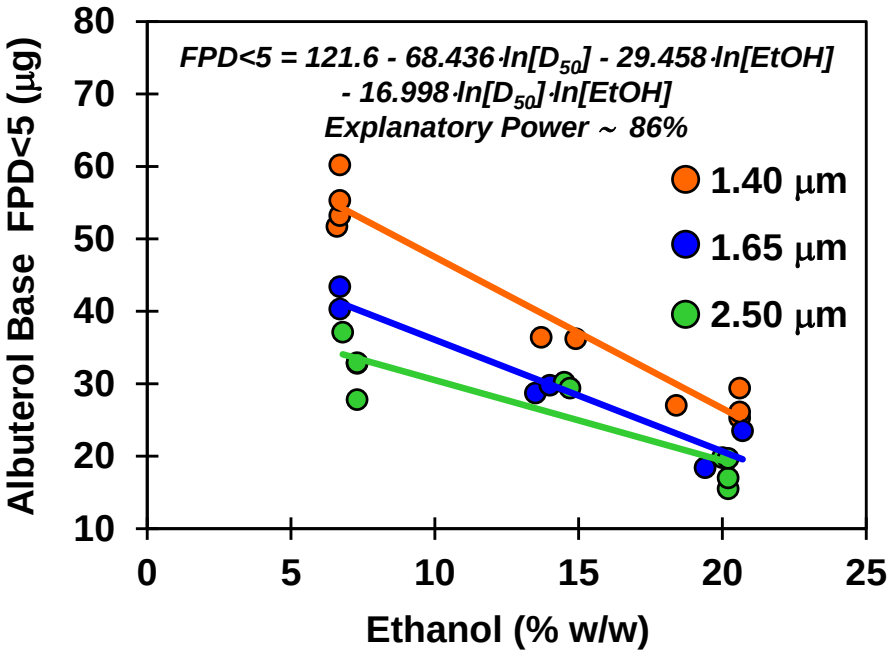


Conti, D. S.; Holt, J.; Sheth, P.; Sandell, D.; Hickey, A.; Saluja, B. "The Effects of Formulation Factors on the Aerosolization Performance of Metered Dose Inhalers." In: AIChe Annual Meeting, 2016, San Francisco, CA, United States. Poster presentation

# Albuterol Sulfate Suspension

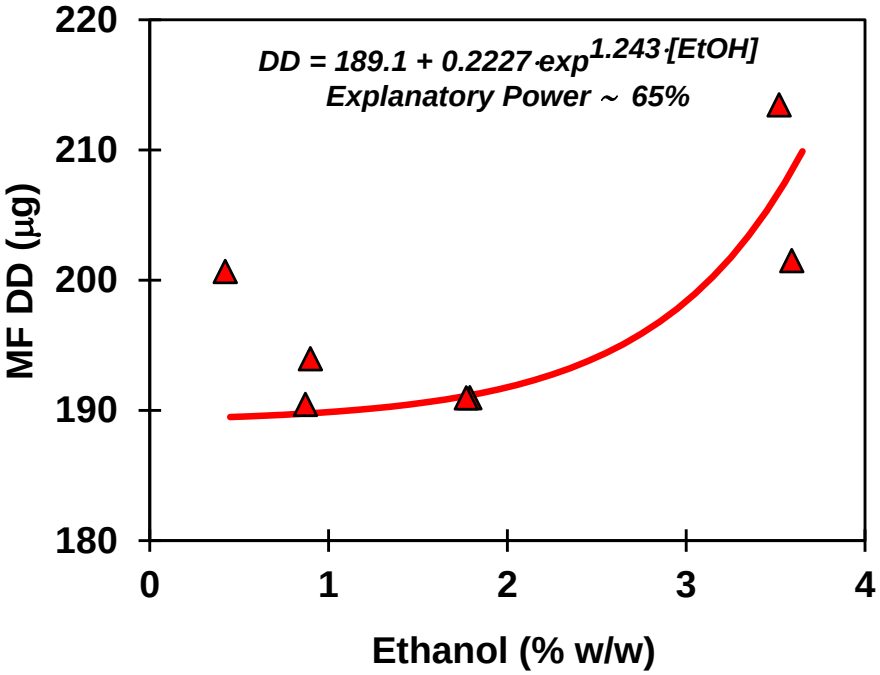


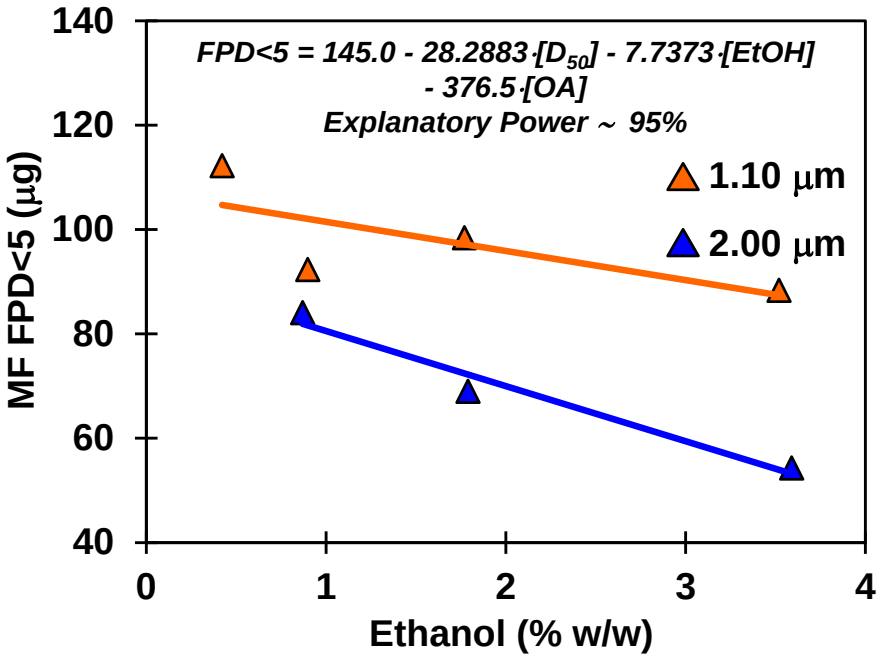

As the level of ethanol increased from 7% to 20% w/w, the DD of albuterol decreased by 13%.




As the level of ethanol increased from 7% to 20% w/w, the FPD<5 of albuterol decreased by 51% (1.40 µm), 50% (1.65 µm) and 45% (2.50 µm).

# Mometasone Furoate Suspension

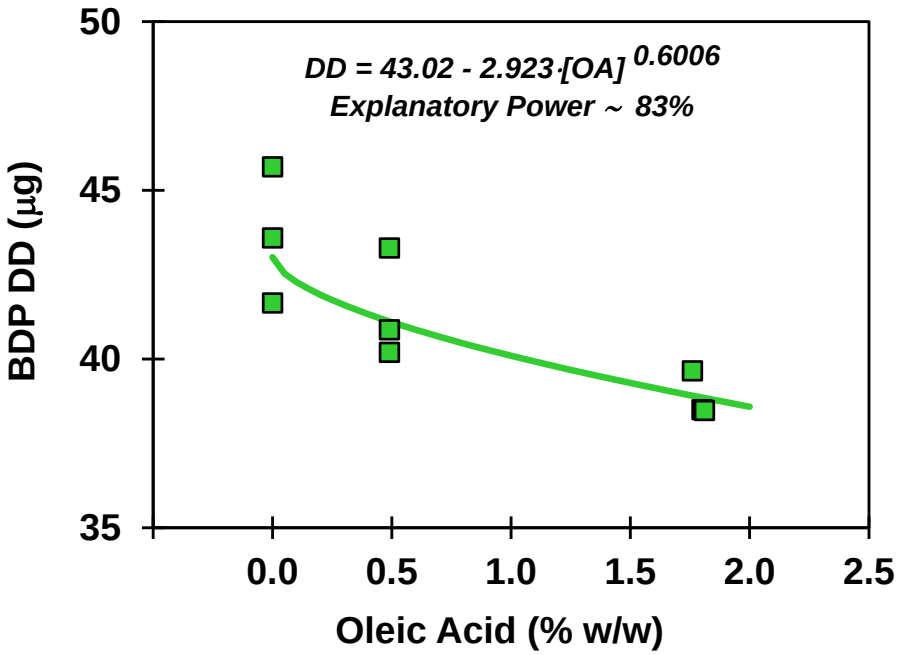


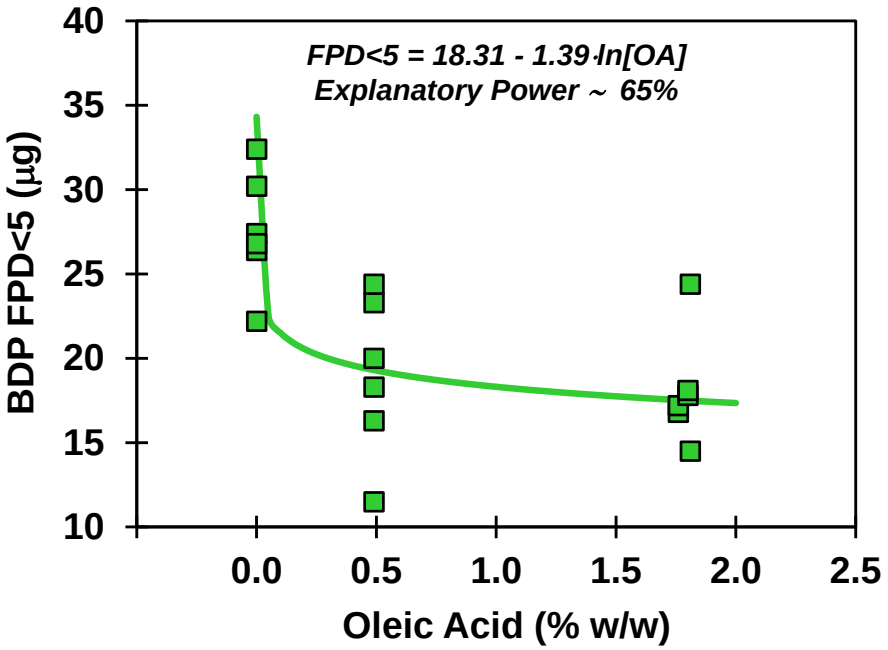




As the level of ethanol increased from 1.8% to 3.6% w/w, the DD of MF increased by 9%.

As the level of ethanol increased from 0.45% to 3.6% w/w (1.1 µm) and from 0.90% to 3.6% (2.0 µm), the FPD<5 of MF decreased by 21% and 35%.

# Beclomethasone Dipropionate Solution




As the level of oleic acid increased from 0% to 2% w/w, the DD of BDP decreased by 11%.

As the level of oleic acid increased from 0% to 2% w/w, the FPD<5 of BDP decreased by 34%.

# Research Conclusions

- The changes in API PSD had statistically significant effects on the APSD performance of suspension MDI formulations studied, but not on DD.
- The changes in concentrations of excipients (ethanol and oleic acid) showed, in some cases, statistically significant effects on DD and APSD performance of suspension and solution MDI formulations studied. However, several cases without effects were also found, despite some large changes in concentrations of inactive ingredients studied.
- The possible effects of varying these characteristics must be studied on a case-by-case basis.

# Discussion

- Complexity of bioequivalence for inhalation products
- Rationale for why weight-of-evidence approach is currently used
- Importance of the GDUFA Regulatory Science Program
- Demonstrated that excipient changes can lead to performance parameter differences in dry powder and metered-dose inhalation products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