# First Generic Drug Approval: Budesonide & Formoterol Fumarate Dihydrate Inhalation Aerosol (RLD: Symbicort): A Quality Perspective

**Fang Yuan, Ph.D.**
Senior Chemist
Immediate Office, Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
CDER | US FDA

Advancing Generic Drug Development: Translating Science to Approval – September 14, 2023

Everyone deserves confidence in their *next* dose of medicine.

**Pharmaceutical quality**

assures the availability, safety, and efficacy of *every* dose

# Learning Objectives

- Discuss potentially overlooked issues in formulation development of generic suspension-based metered dose inhaler (MDI) products
- Highlight a few product characterization studies helpful to verify product design providing consistent delivered dose or identify risk in product design causing inconsistent delivered dose

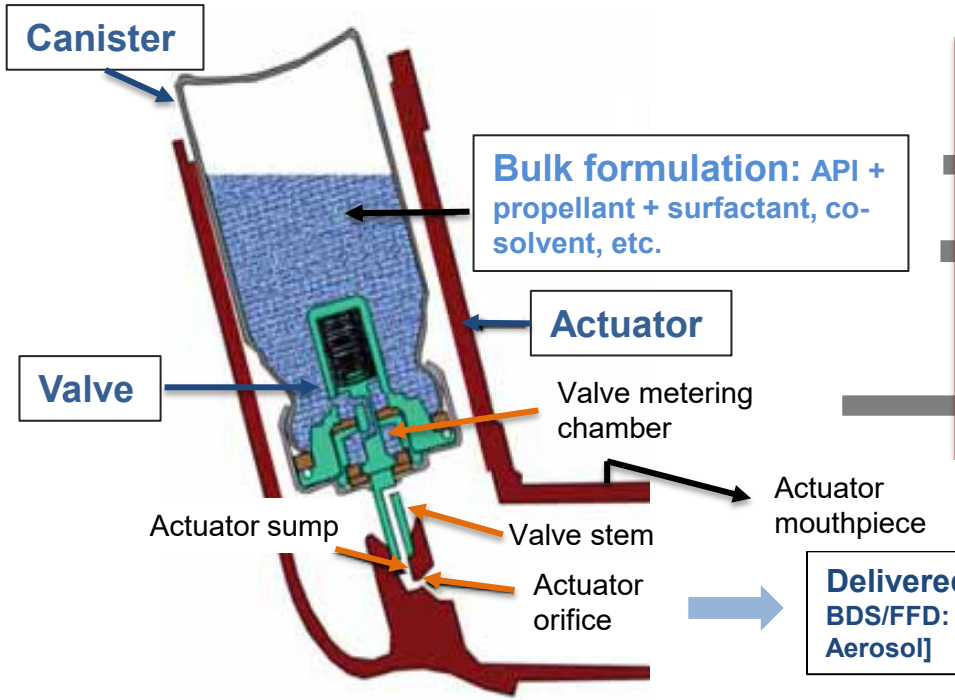
# Budesonide & Formoterol Fumarate Dihydrate Inhalation Aerosol
## (80 µg & 4.5 µg /INH; 160 µg & 4.5 µg /INH)

- **Reference Listed Drug (RLD)**: N21929, Symbicort® approved in 2006, by AstraZeneca LP
- **First Approved Generic**: A211699, Breyna™ approved in 2022, by Mylan Pharmaceuticals Inc. (now Viatris Inc.)
- **Suspension** formulation consists of **two micronized drug substances** [budesonide (BDS) and formoterol fumarate dihydrate (FFD)] suspended in **HFA 227 (propellant)** containing a small amount of **povidone K25 (suspending agent)** and **polyethylene glycol 1000 NF (lubricant)**.

| Drug substance | Dose metered by valve (µg) | Dose delivered from actuator (µg) |
|---|---|---|
| BDS | 91 or 181 | 80 or 160 |
| FFD | 5.1 | 4.5 |

# Operating Mechanism of MDI

## Challenge of suspension-based MDI: consistent delivered dose



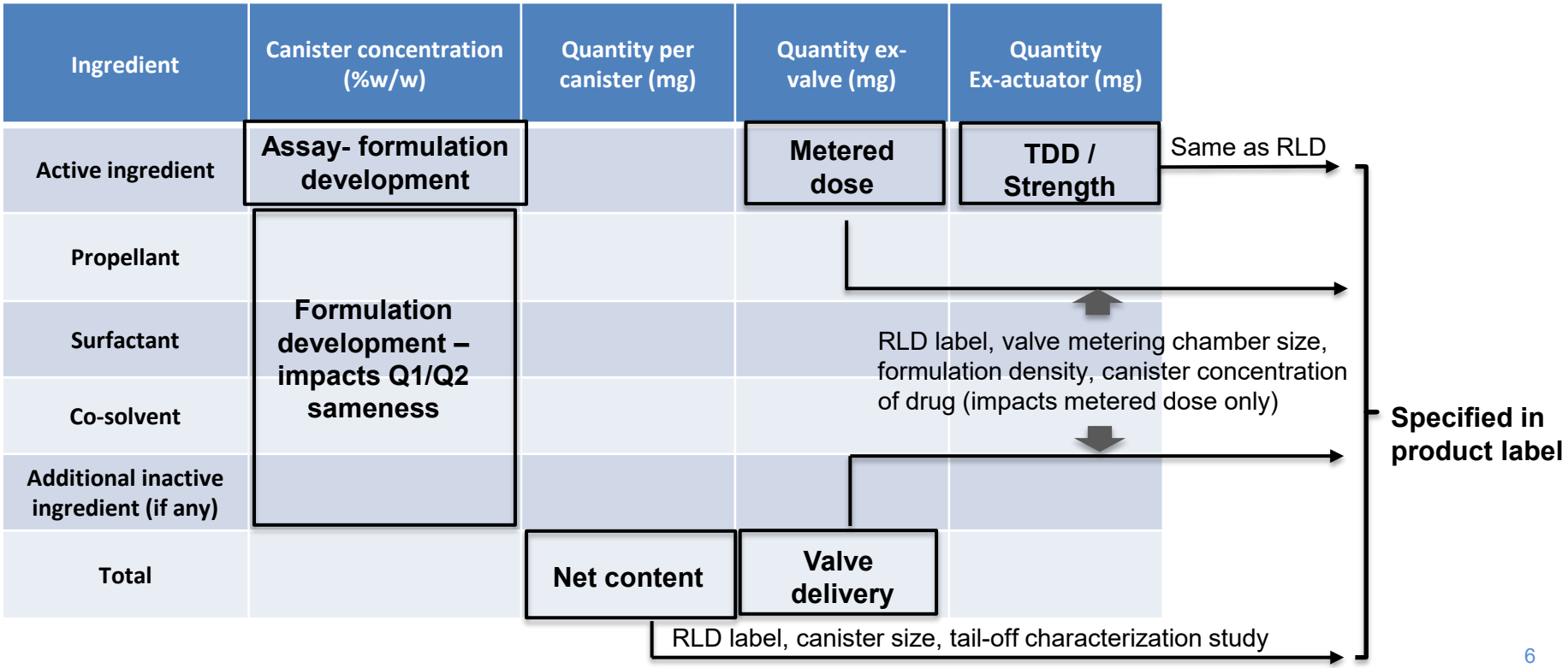

### CQAs impact delivered dose uniformity

- **Assay** (measured as drug concentration in canister)
- **Net content**
- **Metered dose** (e.g., BDS/FFD: 91 µg / 5.1 µg or 181 µg / 5.1 µg for BDS and FFD Inhalation Aerosol)

**Delivered dose** [target delivered dose (TDD) is the strength, e.g., BDS/FFD: 80 µg / 4.5 µg or 160 µg / 4.5 µg for BDS and FFD Inhalation Aerosol]

David Lewis, Metered-dose inhalers: actuators old and new, *Expert Opin. Drug Deliv. (2007) 4(3):235-245*

# Generic MDI Composition Table



# Generic MDI: Formulation Development

- Inactive ingredient canister concentration
  - Q1/Q2 same as RLD: most common
  - NOT Q1/Q2 same as RLD, possibly occurs to inactive ingredients with a very low concentration – **need** additional supporting data (depending on its function in formulation) to demonstrate no impact on product quality and performance
- Active ingredient canister concentration (assay)
  - Based on reverse engineering data from RLD formulation
  - Overage: generally discouraged per ICH Q8 guidance; if used, justify the necessity e.g.,

**Compromise DDU**

- Drug loss during proposed manufacturing process
- **Drug loss due to deposition on device constituent parts through unit life**

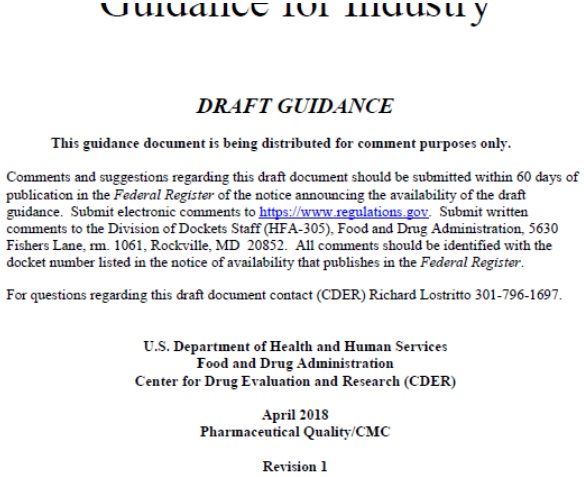
# Challenge Question #1

**Which of the following Critical Quality Attributes can impact Delivered Dose Uniformity of MDIs?**

A. Assay
B. Leachables
C. Net content
D. Metered dose

# Product Characterization Studies

**Product characterization studies can be more than a tool verifying final product design!!!**



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 https://www.regulations.gov. Submit written comments to the Division of Dockets Staff (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) Richard Lostritto 301-796-1697.

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

**April 2018**
**Pharmaceutical Quality/CMC**

**Revision 1**

| Studies | MDI |
|---|---|
| In-Use Period | X |
| Temperature Cycling | X |
| Priming and Repriming | X |
| Effect of Patient Use | X |
| Effect of Storage and Shaking (suspension formulated MDIs only) | X |
| Effect of Orientation of the Device on Delivered Dose | |
| Drug Deposition on Mouthpiece and/or Accessories | X |
| Cleaning Instructions | X |
| Profiling of Actuations Near Device Exhaustion | X |
| Effect of Varying Flow Rate on DPI Performance | |
| Effect of Flow Rate and Inhalation Delay on MDIs with Spacers | X |
| Robustness | X |

# Highlighted Product Characterization Studies

- **Drug Deposition on Mouthpiece and/or Accessories Characterization Study**

  **Recommendation:** assess drug deposition on internal and external surfaces of individual device constituent parts (mouthpiece, valve components, sump, canister, etc.) through the unit life, ideally by cleaning intervals based on cleaning instruction in label; and compare the data between the generic and RLD products (as needed)

- **Cleaning Instruction Study**

  **Recommendation:** assess product performance through unit life at simulated patient use condition (i.e., strictly following the cleaning intervals and cleaning procedures described in package insert)

**Rationale of recommendation:** To help identify potential risk / root cause leading to trending / inconsistency of delivered dose through unit life and provide scientific basis to optimize / justify the selected device constituent parts and / or product formulation

# Highlighted Product Characterization Studies Cont'd

- **Profiling of Actuations Near Device Exhaustion study (a.k.a., tail-off study)**
  - Justifies the minimum net content
- **Effect of Storage and Shaking Study**
  - Justifies canister concentration of suspending agent (especially in the case of non-Q1/Q2 sameness)

# Challenge Question #2

**Which of the following statements regarding product characterization studies are correct?**

A. To support labeling instructions
B. To verify robustness of product design
C. One-time studies – never needs to repeat
D. Either using development batches or exhibit batches

# Resources

- Draft Guidance for Industry: *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations* (April 2018)
- Draft Guidance on *Budesonide; Formoterol fumarate dihydrate* (June 2015)
- USP General Chapter <5> *Inhalation and Nasal Drug Products – General Information and Product Quality Tests*
- USP General Chapter <601> *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests*

# Closing Remarks

Some considerations to minimize risk of inconsistent delivered dose through unit life over shelf-life of generic suspension-based MDI products

- Cautiously select device constituent parts to minimize drug particles build-up during use
- Do **NOT** overlook potential impact of drug deposition in device constituent parts on the delivered dose uniformity
- Leverage certain product characterization studies to quickly identify risk / root cause of inconsistent delivered dose (if occurs) and optimize product design at early phase of development if possible

# THANK YOU!

**Fang Yuan, Ph.D., Senior Chemist**
Immediate Office, Office of Lifecycle Drug Products
Office of Pharmaceutical Quality | CDER | US FDA


FDA
U.S. FOOD & DRUG
ADMINISTRATION