Quality Consideration for First Generic Tiotropium Bromide Capsule-Based Dry powder Inhalers (DPIs)

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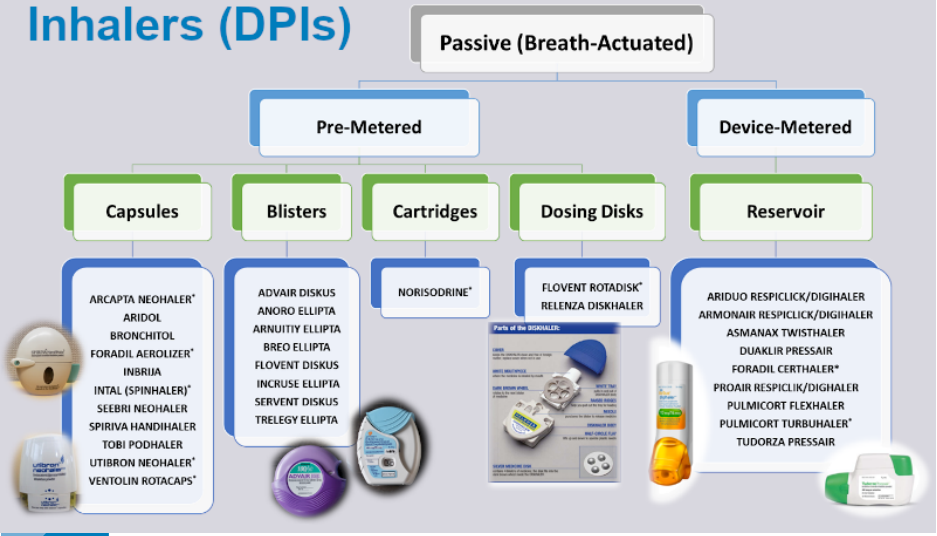
(September 25, 2024)

Advancing Generic Drug Development 2024:
Translating Science to Approval
Day 2, Session 5A: Spotlight Generic Drug Review Challenges and Solutions

Learning Objectives

- Explore the general constrains in DPI formulation/manufacturing.
- Discuss potential development Challenges for Capsule-based DPI Products.
- Share valuable recommendations for highlighted Product Characterization Studies.
- Focus on General Quality Considerations for Primary DPI Stability Batches.

Dry Powder Inhalers (DPIs)



❑ Device constituent parts

Dose container

- Pre-metered: blister, capsule, disc
- Device metered: powder reservoir

- **Can be more complex to review compared to MDI.**
- **Blister and Capsule DPI are the main types submitted to FDA since 2015.**

Generic DPI

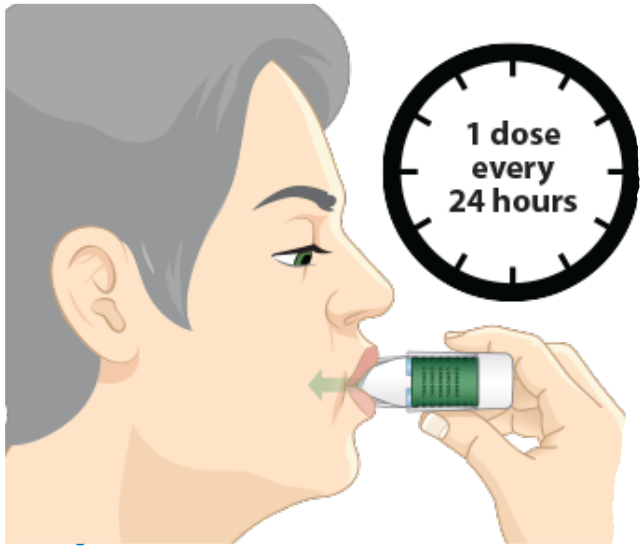
*N.ElGendy, et.al, Advanced Drug Delivery Reviews, 2022, volume 189, p114519

Tiotropium Bromide Inhalation powder, 0.018 mg base/Inh.

Reference Listed Drug (RLD):

- SPIRIVA® HANDIHALER® Inhalation Powder, NDA 021395 by Boehringer Ingleheim Pharmaceuticals Inc., approved in January 2004.

First Approved Generic Spiriva Handihaler (June 20th 2023)



- **LupinHaler™** is the first FDA-approved therapeutically equivalent generic of **Spriva Handihaler®** By Lupin Inc. (ANDA 211287).
- Each capsule contains a dry powder consisting of 18 mcg of tiotropium (22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate.

PSG for Tiotropium Bromide Inhalation Powder

In Vitro Study	Design	BE Analysis
Single Actuation Content (SAC)	• B, M, E lifestages at 20 L/min, 39 L/min, and 60 L/min flow rates • USP <601> Apparatus B • 1 capsule, 2 actuations/capsule, 2 L volume of air per determination	• Population bioequivalence (PBE) of SAC
Aerodynamic Particle Size Distribution (APSD)	• B, E lifestages at 20 L/min, 39 L/min, and 60 L/min flow rates • USP <601> Apparatus 3, 5, or other • Minimum number of capsules • Volume air: 4 L	• PBE of impactor size mass (ISM); CI profiles of individual stages, MMAD, GSD, and FPM are supportive info

Capsule-Based DPI Composition

Ingredient	Quality Standard	Function	Quantity (mg)/ unit (capsule	Concentration (%w/w)
Tiotropium Bromide				
Carrier/Diluent (IID/grade)				
Total				
Capsule Size & composition				
Ink Composition				

Per RLD label

DPI strength: The metered amount of drug from capsule, not the specified TDD*.

Q1/Q2 same as RLD: most common

Capsule shell material may be different in Generic product from RLD (e.g., HPMC vs. Gelatin)

Different moisture content

*__Target delivered dose (TDD):__ The mass of drug delivered from the mouthpiece

- HPMC capsules in Generic DPI product may be acceptable, provided adequate justification/supporting data (e.g., study to demonstrate that fragments generated by piercing/rupturing the capsule are not inhaled by the patient.).

Generic DPI: General Limitation

- **Constraints for formulation design**
  - ❑ Q1 the same; Q2 the same preferred
  - ❑ ***Overage:*** generally discouraged per ICH Q8 guidance; if used, justify the necessity e.g.,
    - Drug loss during proposed manufacturing process
  - ❑ Manufacturability

- **Constraints for device design**
  - ❑ Similar shape
  - ❑ Equivalent design and operating principle
  - ❑ Comparable device resistance

*N.ElGendy, et.al, Advanced Drug Delivery Reviews, 2022, volume 189, p114519

Challenge Question #1

Which of the following examples can justify the proposed Overage in DPI

A. Drug loss during proposed manufacturing process

B. Drug loss due to degradation of the drug substance

C. Drug loss due to deposition on device constituent parts through unit life

Challenges in development of a Generic DPI

- **Consistent DPI performance** (e.g., DDU and APSD) - poses unique challenges related to:

DPI Formulation Development Challenges

Risk:

- Recrystallization of micronized material could lead to uncontrolled particle growth, thereby affecting drug product CQAs (e.g., APSD, DDU).
- Missing proper control on CMAs of drug constituent part of the combination product without proper justification, e.g., amorphous content of micronized materials.

Mitigation Control Strategy:

- Inclusion of an equilibration period/condition.
- Consistency of the micronization process.
- Establish PSD specification based on data of micronized lots used in exhibit batches.
- Continuous in-house control.

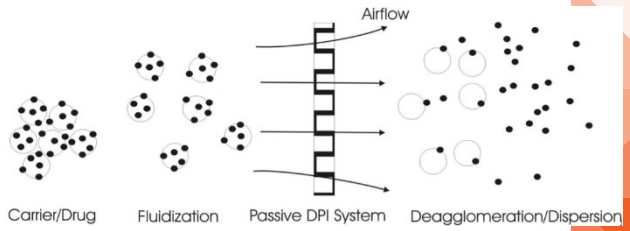
DPI Formulation Development Challenges… Cont'd

Risk:

- **Carrier grade** may lead to particle size growth over time at storage.
- **Carrier's particle morphology** (shape, surface roughness) may affect the adhesive force between API and carrier particles.

Mitigation Control Strategy:

- Adjust ratio of fine to coarse grade Carrier
- Continuous in-house control for particle size and morphology



*Changning Guo, Oral Presentation 'Quality and Performance Testing for Orally Inhaled and Nasal Drug Products (OINDP)', Sep 24-29 (2019), US FDA/CDER /OPQ/OTR/DPA, St.Louis, MO

DPI Manufacturing Challenges 'Blend Uniformity'

Risk: Blend uniformity (low drug load) and flowability (due to excipient lot-to-lot variability)

Mitigation Control Strategy:

- Equipment (blender type)
- Critical process parameters (blending time/speed, blender fill level); excipient CMAs; environmental conditions; conditioning/hold/equilibration time after blending
- Final blend characterization (uniformity, bulk density, particle size)

DPI Manufacturing Challenges 'Powder Filling'

Risks:

- Fill weight variation and segregation of API and excipients lead to content uniformity, APSD, and DDU failures.
- Moisture affects APSD and DDU

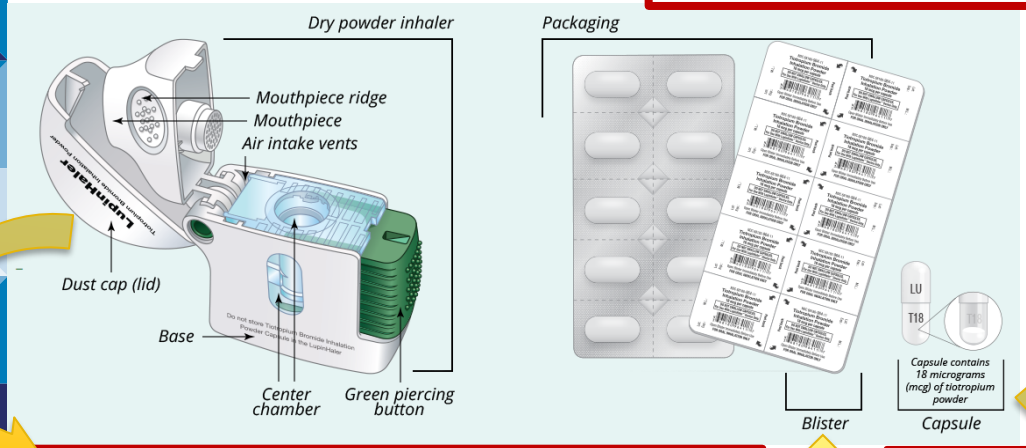
Mitigation Control Strategy:

Identification of CPPs and characterization of fill weight, content uniformity, moisture, APSD and DDU from filled units through **stratified sampling* during development**

*** Refer to ASTM E2709 and ASTM E2810 for reference on establishing stratified sampling strategy, statistical test, and acceptance criteria for the in-process content uniformity test.**

DPI Container Closure System Challenges

Capsule, Blister, Device



Capsule dimension is critical for adequate insertion in the inhalation device, piercing, and drug delivery - DP specifications should include testing for capsule dimensions (lock length).

Inhaler device specifications: include critical functional parameters (e.g., Flow resistance, Cap Opening Force, Button push-in Force, Mouthpiece Opening Force, Chamber Opening Force, Device dimensions, etc.).

Blister foil and overwrap pouch provides protection from moisture permeation for blend formulation at in-use period and shelf-life. Functional layers of the foils should be controlled for thickness of individual functional layers, to assure consistent quality of primary and secondary packaging components.

https://www.lupin.com/US/lupinhaler/

Challenges…Device Constituent Part Components

- ❑ **Needle Diameter**
- ❑ **Mesh composition for capsule rattle**

Investigate the potential effect of the needle diameter and the mesh material on the product performance and powder residue in the capsule after DDU/APSD testing

- ❑ **Button push-in force**

To be determined over the lifetime of the inhaler containing a capsule in the chamber for consistency

- ❑ **Cap opening force**

Demonstrate if this force changes over the use of the device and if so, whether the changed/reduced force is sufficient to keep the cap closed

Challenge Question #2

Which of the followings are considered Formulation Development challenge for DPI?

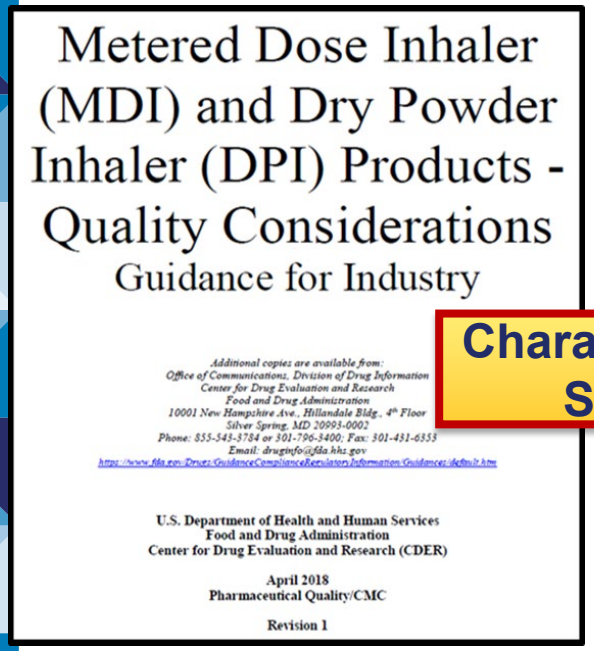
A. Fill weight

B. Excipient grade

C. Device resistance

D. Amorphous content of spray dried API

Drug Product Characterization Studies



Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

Characterization Studies

DPIs
- In-use period - Temperature cycling - Effect of patient use - Effect of orientation of the device on delivered dose - Drug deposition on mouthpiece and/or accessories - Cleaning instructions - Effect of flow rate on DPI performance - Robustness

To demonstrate the robustness and performance of the product and to support labeling information.

Product Characterization Studies…Cont'd

- **Recommendation:**
  - DPI product units used for the characterization studies should be stored under conditions consistent with the storage conditions identified in the labeling.
  - To support the proposed shelf life at the intended storage conditions, some characterization studies (e.g., in-use period, cleaning, robustness) should be conducted on DPI product units at the beginning and near the end of the proposed shelf life.

Highlighted Drug Product Characterization Studies

Robustness:

- Assess the physical robustness of capsules following dropping or vibration of the blister card (e.g., any damage to the capsule or powder spillage from the capsule, changes in the capsule lock length).

Cleaning Instruction Study:

- Determine drug residual at the end of the experiment for each unit in addition to visual inspection for capsule fragments and particle residual.

Fragment Study:

Assess the puncturing and fragmentation behavior of the proposed HPMC capsule in comparison to the gelatin capsule in the RLD.

Highlighted Characterization Studies…. Cont's

Effect of Patient Use Study:

- Inspect partially used product units from clinical studies (inhalers, blister cards and capsules) for external damage.

- Evaluate the functionality and piercing mechanism of the clinical returned inhalers for any mechanical defects or failures (e.g., lack of rattling sound, opening and closing of the mouthpiece to load capsules, depression of the piercing button, piercing of capsules, etc.).

Challenge Question #3

Which of the following product characterization studies should be conducted on DPI product units at the beginning and near the end of the proposed shelf life?

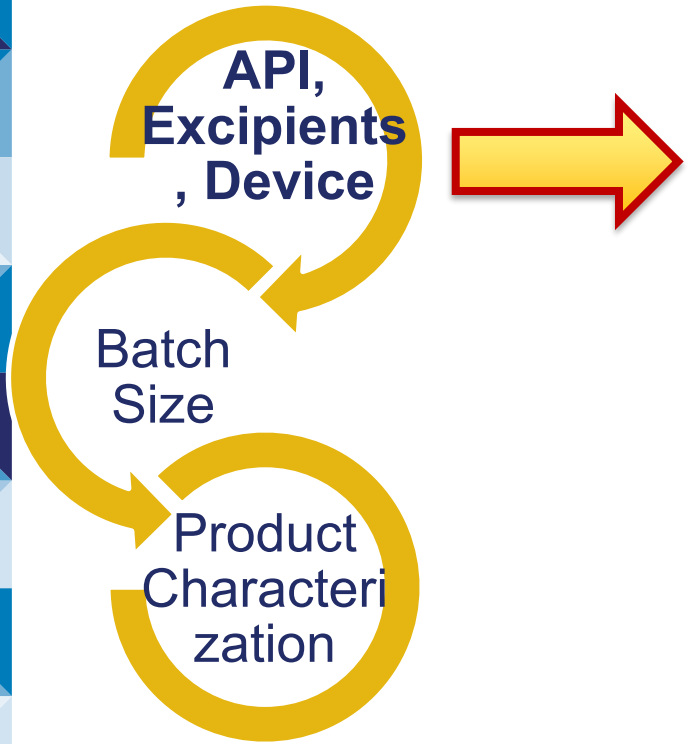
A. Cleaning instruction

B. Temperature Cycling

C. Robustness

D. In-use period

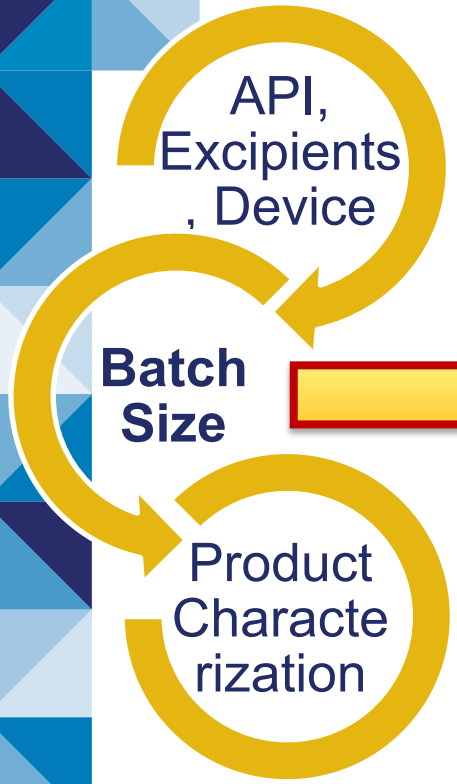
General Quality Considerations for Primary DPI Stability Batches



Three different lots be used for three primary stability batches:

- ❑ Drug substance (discrete lots),
- ❑ Device constituent part components and,
- ❑ Critical Excipients.

Continue…..



- Given the complexities and potential risks involved in scaling up the manufacturing process for DPI products, recommend stability data submitted from three batches at the proposed production scale.
  - However, at a minimum one batch at the proposed commercial production scale and other two should be of at least one-third (1/3) of the proposed commercial.

Continue…..

- Conducted on the to-be-marketed configurations and versions of DPI products.
- Three batches with reasonable sample size to support reliability, reproducibility of product quality and performance.

Resources

- Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations (April 2018).

- 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

DPI product review can be more complex than MDI

- Thoroughly characterize and understand the quality of the batches used in your exhibit stability
- Identify cause of inconsistent DPI performance and optimize product design at early phase of development to minimize risk
- Establish control strategy based on scientific evidence gathered from thorough characterization of batches

Acknowledgements

OPQ/OPQA I/ODPA V

- Yue (Helen) Teng, Ph.D
- Dhaval Gaglani, M.S.
- Colleagues in Unit 2

OPQ/OPQR II

- Jason Rodriguez, Ph.D
- Changning Guo, Ph.D
- Nicholas Holtgewe, Ph.D

OPQ/ OPMA

- Sharmista Chatterjee, Ph.D
- Chengjiu Hu, PhD
- Shu-Wei Yang, Ph.D
- Vicky He , Ph.D

OGD/ORS/DTP I

- Past and present members of the Nasal and Inhalation Products Team

Questions?

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