CMC Updates And Other Considerations For Generic Orally Inhaled Drug Products

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Pharmaceutical Quality

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Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Outline

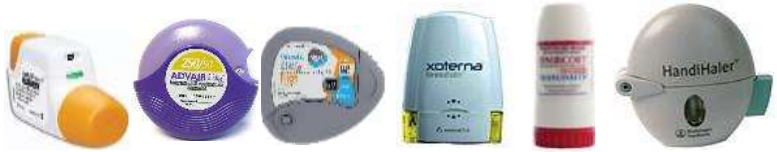
- Overview of orally inhaled drug products (OIDPs): pressurized metered dose inhalations (MDIs) and dry powder inhalations (DPIs)
- Unique quality issues and considerations associated with generic MDI and DPI submissions
- Common quality questions may be beneficial from pre-Abbreviated New Drug Application (ANDA) communication pathways
- Take home messages

Overview Of MDIs And DPIs

MDI	DPI
Locally acting to treat lung diseases (e.g., chronic obstructive pulmonary disease (COPD), asthma, as well as respiratory infections and cystic fibrosis)	
Drug-device combination products: device is integral part of finished product	
Energy to form drug-containing aerosol: Vaporation of propellant	Energy to form drug-containing aerosol: • Passive device: patient inspiration • Active device: compressed gas, battery powered motor driven impeller
Guidance updates: FDA Draft Quality Guidance for MDI and DPI products (April 2018)	
Unique performance critical quality attributes (CQAs): ▫ delivered dose uniformity (DDU): assures accurate delivery dose ▫ aerodynamic particle size distribution (APSD): assures consistent amount of drug to reach desired sites of action	

Overview Of MDIs And DPIs

	MDI	DPI
Formulation	Suspension/solution: micronized active pharmaceutical ingredient (API) suspended or solubilized in residual matrix of liquified propellant, and other excipients (co-solvent, surfactant, etc.)	Dry powder blend: Micronized API dispensed with carrier (and other excipients if needed).
Device constituent parts	Pressurized canister Metering valve Actuator/mouthpiece Dose counter	Dose container • Pre-metered: blister, capsule, disc • Device metered: reservoir Multi-component device assembly (with dose counter and mouthpiece)
Protective packaging system (if necessary)	Protect product from moisture at shelf-life.	



Quality By Design

Finished Product

- Performance CQAs
  - DDU & APSD
  - Spray pattern
  - Shot weight
- Device assembly CQAs
  - Actuation force (MDI)
  - Air flow resistance (DPI)
- Leachables and Other CQAs

In-process Controls

- MDI: homogeneity, fill wt., heat stress, crimp weight and height tests, spray test
- DPI: BU, fill wt./CU of dosage unit, leak test

APIs

- Micronization process
- Physical CMAs
  - PSD, amorphicity, polymorph (MDI suspension and DPI)
  - Solubility (MDI solution)
- Physical stability
- Other CMAs

Excipients

Non-compendial CMAs of

- Propellant for MDI: Boiling point, vapor pressure, purity, etc.
- Carrier for DPI: PSD, other physical attributes, moisture, etc.

Device Constituent Parts

- Critical dimensions
- Dose counter accuracy
- Actuator orifice size
- Valve functionality
- Extractable profile

Quality By Design (Cont'd)

Multi-sources of variability collectively contributed to product quality and performance variability.

- Understand how variability of critical upstream contributors impacts variability of product quality and performance
- Manufacture exhibit batches with incorporation of sufficient variability of critical upstream contributors
  - Manufacturing plan to represent commercial batches
  - Lot-to-lot variability of critical components (API, critical excipients and device constituent parts)
  - Variation range of critical upstream variables (i.e., CMAs of raw materials, CQAs of device constituent parts, CPPs of unit operation)
- Establish final control strategy for CMAs of raw materials and CQAs of device constituent parts / assembly accordingly

Manufacturing Plan For Exhibit Batches

- **Batch scale of exhibit batches**
  - At least one batch at commercial scale
  - Other two batches at least at 1/3 of commercial scale
  - Filling line being 100% completed
  - Selected units for assembly, packaging and stability test represent B, M and E of filling line
- **Three discrete lots of components (API, excipients, and device constituent parts)**
- **Components, formulation and device constituent parts represent those to be used in commercial products**

Underlying Quality Issues

Concerns: May lead to quality and performance issues of future batches!

- **Quality control of raw material, device constituent parts, and device assembly do NOT represent those used for BE and exhibit batches, e.g.,**
  - PSD of micronized API and carrier
  - Diameter / orifice size of mouthpiece / actuator
  - Airflow resistance of DPI device or actuation force of MDI device
- **Completely relying on supplier(s) for routine controls on critical quality aspects without properly qualifying supplier(s)' reliability, e.g.,**
  - Physical stability of micronized API for future lots
  - Critical dimensions of device components
- **Missing proper control on critical quality aspects of components without proper justification, e.g.,**
  - Additional physical attributes (e.g., amorphous content) of micronized materials
  - Relaxation of micronized materials

Quality Considerations For APSD Test

APSD: USP <601> Standard Impactors

Measuring **amount of drug deposits** on the collection surface of each impactor stage following **impactor sizing of aerosol** discharged from the inhaler. Impactor sizing is achieved by cut-off diameter of individual stage, which is determined by **operating flow rate** and **stage setting of a given apparatus**.

Cascade Impactors for DPIs

- USP <601> Apparatus 3 / Andersen Cascade Impactor (ACI) with pre-separator
- USP <601> Apparatus 5 / Next Generation Impactor (NGI) with pre-separator

Cascade Impactors for MDIs

- USP <601> Apparatus 1 / Andersen Cascade Impactor (ACI) without pre-separator
- USP <601> Apparatus 6 / Next Generation Impactor (NGI) without pre-separator

Existing USP Monographs For MDIs/DPIs

- Fluticasone Propionate Inhalation Aerosol
- Fluticasone Propionate Inhalation Powder
- Fluticasone Propionate and Salmeterol Inhalation Aerosol
- Fluticasone Propionate and Salmeterol Inhalation Powder
- Salmeterol Inhalation Powder

APSD Test

- Type of impactor and accessories
- Setup parameters: airflow rate and duration (for DPI)
- No. of unit doses per determination
- Groupings of impactor stage

Acceptance Criteria

- Method-specific
- Product-specific

- **Challenge: feasibility of cross-comparison between APSD specifications**
- **If USP drug product monograph exists and contains APSD specification,** conformance with USP monograph requirement is generally recommended. Otherwise, communicate with assessment disciplines as early as possible at development stage.

APSD Test Method

- USP References: USP <601>
- Provide **sufficient details**: The equipment (e.g., induction port, adapter for mouthpiece) and assembly, cut-off diameters, run conditions, setup parameters (e.g., flow rate, duration), # of doses per determination, # of determinations per batch, plates coating solution, stage sample collection (e.g., volume of diluent for individual stage, final concentration of drug substances in samples), quantification analytical procedure, environmental conditions (e.g., temperature, humidity), etc.
- **Mass balance (MB)**: Expectation of reasonable acceptance criteria and values reporting. Atypical MB value may be caused by quality aspects of MDI / DPI units. **APSD determination with an atypical MB should be properly investigated,**
  - to exclude possibility of quality issue of the tested dose units
  - to assure any system suitability issue is resolved before retest on additional dose units
  - to avoid abuse of retest procedure

APSD Test Method (Cont'd)

- **Number of doses per determination** (relying on sensitivity of the quantification analytical procedure): generally recommend minimum number of actuations/unit doses, justified by sensitivity of the quantification analytical procedure. Excessive number of unit doses causes bias the results by masking individual unit doses variability. **If necessary, applicants may seek assessment discipline's feedbacks at method development stage.**
- **Number of determination**: Appropriate number of DPI / MDI units (n ≥ 4 per batch).

APSD Test Acceptance Criteria

- Quality acceptance criteria for APSD control mass deposition of drug at groupings of impactor accessories and stages / cups.
- Groupings are product-specific and method-specific: generally three or four groupings, e.g.,
  - Grouping 1: Non respirable fraction (e.g., > ~5 mcm, varying dependent upon the selected impactor and operating flow rates)
  - Grouping 2: Fine particle fraction (e.g., ≤ ~5 mcm)
  - Grouping 3: Slightly coarse fraction within the fine particle fraction (e.g., 3-5 mcm, or 1-5 mcm)
  - Grouping 4: Sub-micron fine particle fraction (e.g., ≤ ~1 mcm)
- Groupings and acceptance criteria are expected to control complete particle size profile and have discriminative power to detect shifts at stability.

APSD: Stability Trend & Equilibration

Equilibration / quarantine period for DPI

- APSD is typically companied with **stability trend throughout shelf-life**, especially for DPI. **Trend is more significant at early time points.**
- To assure consistent performance of commercial product in the market, an appropriate quarantine period is necessary to allow DPI's APSD profile reaching equilibrium at appropriate storage condition before release to market.
- Acceptance criteria are intended to assure marketed product (i.e., post equilibration throughout shelf-life) with consistent and adequate APSD profile. **Hence, the APSD testing results on products before completion of equilibration may not be considered appropriate justification for the proposed commercial acceptance criteria.**
- Date of manufacture (date of dispensing): **Not affected** by quarantine period

Common Quality Issues May Be Beneficial From PANDAs / CCs

- Pre-market changes and ridging study plan
- APSD and/or DDU methods development
- Considerations on establishment of APSD and DDU specification limits
- Product characterization study design/plan

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Pre-market Changes

Bridging study package is commonly required from both BE and Quality.

Changes may occur after manufacture of BE and exhibit batches

- Suppliers of API / critical excipients / device
- Formulation e.g., grade (or ratio of fine particle size grade) of carrier for DPI, concentration of MDI suspension/solution
- Device constituent parts: e.g., dimensions, materials of construction, manufacturing process (such as equipment. site)
- DP manufacturing process: e.g., site / equipment

Key to avoid major deficiency is proper communications!!!

Proper Communication

- **When**
  - Identify such potential issues **as early as possible**
  - Communicate **as soon as possible**
  - If issues occur after filing original ANDA submission, communicate via additional pathways.
- **How**
  - Present issues **without holding back important information**
  - Provide **intended changes, rationale, and proposal of bridging study plan**
  - Seek assessment discipline's feedbacks
- **Then what**
  - Prepare submission package **per agreement with Agency**
  - Make a reference communication history with Agency in submission

Take Home Messages…

- Develop generic MDI and DPI products with science and risk based approach
- Establish control strategy for components and finished products based on scientific evidence gathered from thorough characterization of BE and exhibit batches.
- Communicate timely and effectively with the Agency about issues that may result in major deficiency.


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