Product Quality Consideration for Orally Inhaled Drug Products (OIDPs)

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Disclaimer

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Outline

- Overview of Metered Dose Inhalation Aerosols (MDIs) and Metered Dose Inhalation Powders (DPIs)
  - Quality by Design (QbD) consideration
  - Lifecycle Management
  - CQAs for MDI & DPI/Linking CMAs and CPPs to CQAs
  - Product/Device Development Considerations
  - Process Development Considerations
  - Control Strategy
- OIDPs (MDIs & DPIs): General Quality Expectations
- OLDP/OTR Collaboration
- Conclusion
Overview of MDIs & DPIs

**METERED DOSE**

**INHALATION AEROSOLS (MDIs)**
Deliver medication to the lungs in the form of a short burst of aerosolized formulation.

MDIs generally do not exhibit great diversity in device design and operating principles.

Use energy stored in a liquefied gas propellant under pressure for generating aerosols.

The MDI Aerosols consists of four major components,

- Formulation: drug substance(s), either dissolved or suspended, in a (1) liquefied propellant, (2) mixture of liquefied propellants, or (3) mixture of solvents, propellants, and/or other excipients.
- Container or canister
- Metering valve (including its components), which is crimped onto the container, and
- any additional accessories (e.g., integrated spacer), as well as protective secondary packaging (e.g., an overwrap).

**METERED DOSE**

**INHALATION POWDER (DPIs)**
Deliver medication to the lungs in the form of a dry powder formulation (micronized drug particles attached to larger carrier particles).

DPIs do not contain propellants.

Energy source: Active and Passive breath actuated.

Available as “Pre-metered” or “Device-metered DPIs” have an internal reservoir containing sufficient quantity of formulation for multiple doses.

DPI products consist of a formulation and container closure system components,

- The formulation contains drug substance and excipients including a drug carrier (e.g., lactose).
- Container closure system consists of the device and any protective secondary packaging (e.g., an overwrap).
QbD consideration for OIDPs

- **Combination product (CP)** [21CFR 21 CFR § 3.2(e) (1)] comprised of two or more regulated components, i.e., drug/device..that are physically, chemically, or otherwise combined or mixed and produced as a single-entity; -Examples MDIs & DPIs
  - Components [21 CFR § 820.3(c)] means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

- Inherent complexity of oral inhalation drug products (MDIs and DPIs), consisting of different constituent parts (drug, device) and with the desired product quality including performance been function of varied drug product critical quality attributes (CQAs) (for example, drug substance, excipients, device/container closure system), Quality by Design approach is highly recommended for such products.

- **Quality by Design (QbD)** provides not only scientific, risk based, holistic, proactive approach to enhanced product development/understanding (product formulation, process, and device) but also ensure consistent desired product quality including performance over the product life-cycle, including continual improvement.
Lifecycle Management

Invest in QbD as it offers a holistic approach to lifecycle management.

Regardless of the method used (e.g., ICH Q9/Q10 or ISO 14971), the basic risk management process steps remain the same: assess the product’s risk(s) (safety profile) to ensure the benefits outweigh the risks, and life cycle management updates for the combination product.

‘The key to successful lifecycle management of drug products.’ 

Slide courtesy: Susan Rosencrance
MDI & DPI: DP CQAs

**DS CQAs**
- Assay, impurities and degradants, delivered dose, aerodynamic particle size distribution (APSD), spray pattern, leachables, alcohol/excipient content, foreign particulate matter, moisture content, net content and device characteristics such as component dimensions, force distance to advance dose counter (MDI), specific resistance to air flow (DPI).

**DPIs- Device/CCS CQAs**
- Device components (canister, actuator, valve and its components):
  - Materials used
  - Geometry and dimensions
  - Secondary packaging

**Excipient CQAs**
- Assay, boiling point and vapor pressure, moisture content, density, impurity profile, particle morphology (e.g., shape, crystal habit, texture, surface area, rugosity), flow properties, amorphous content, microbial limits, pyrogens or bacterial endotoxins, and PSD.

**Lot-to-lot variability (DS, excipients, device components)**

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Coated/Surface properties
- APSD, spray velocity, SP
- Orifice size
  - APSD can be affected by surface properties
  - Adherence of DS to walls

Material used
- Direct contact with formulation or patient, thereby potentially affecting product safety and performance.
- Organic propellant (HFA) leading to leaching of valve compounds

Material used
- Direct contact with formulation or patient, thereby potentially affecting product safety and performance.

Material used
- Drug particle surface interactions, such as adhesion onto mouthpiece surfaces, affect delivered dose and APSD

Geometry
- Device resistance, air flow, shear, turbulence generated within device and thus drug delivery

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Office of Pharmaceutical Quality
CQA of one step can become a CMA for a downstream unit operation.

CQAs = f\left( CPP_1, CPP_2, CPP_3,... \right) 
CMA(API)_1, CMA(excipient)_2, CMA(device)_3,...)
PRODUCT/DEVICE DEVELOPMENT CONSIDERATIONS

MDIs

- *Device* (canister, valve components, actuator, and dose counter) and its components
  - Adhesion of suspended drug particles to various CCS components
  - Formulation components such as organic co-solvents, could potentially solubilize constituents of the container closure system. Therefore, **prudent to employ materials that reduce possibility of leachables** in the drug product.

- *Suspension based MDIs*, potential for **settling, creaming, or aggregation** of drug substance

- *Properties/amount of propellants*: fill volume, formulation homogeneity (for suspension) and fill weight are likely to have significant impact on the delivered dose.

DPIs

- *Selected carriers* (e.g., lactose): affects APSD, promote uniformity, flowability, reproducibility of delivered dose, fine particle of DP (reducing agglomeration of DS)

- *Interparticulate interactions* between the drug substance and excipients and with the container closure/device components **at a microscopic level** (e.g., cohesive and adhesive properties, surface activity, specific surface area, static charge properties of the formulation) can also be important.

- *Selection of device, additional protective components* (e.g., desiccants, foil overwraps) affecting moisture ingress into device.
The crystallinity of the drug substance can be affected by mechanical processing, including micronization. This can lead to the generation of amorphous particles that are thermodynamically unstable, with a tendency to convert to a more stable crystalline state upon storage. This recrystallization of micronized material could lead to uncontrolled particle growth, thereby affecting drug product CQAs (e.g., APSD, DDU). Therefore, a conditioning step should be considered following micronization to allow conversion of amorphous to crystalline form under controlled conditions of temperature and humidity.
MDI

- Typical manufacturing operations for an MDI are sequential mixing of the drug substance(s), propellants and co-solvents, filling, device assembly, and packaging.

- Filling process is considered critical and better understanding of the filling process can be obtained by designing experiments to study the impact of deliberate variations in the PP. For example, the filling operation of an MDI can be optimized by evaluating the change in concentration of the drug substance in the formulation tank during the filling process (due to the volatility of the propellants) and determining the amount of propellant to be added to maintain the concentration of the drug substance.

- Adequate mixing and circulation within the formulation tank, filling tank, and filling heads.

- Ensure Uniformity of suspension product fill into individual units, Sampling Strategy: testing should be conducted on the test canisters selected in a randomized manner from the test batch, including units from the beginning, middle and end of the production run.

DPI

- Typical manufacturing operations for a DPI are dry powder blending or spray drying of the drug substance(s) and excipients (carrier), blister or capsule filling (reservoir filling for device-metered DPIs), device assembly, and packaging.

- Equipment (e.g., blender type), process parameters (e.g., blending time, blender speed, blender fill level), and environmental conditions - Blend uniformity (drug particle cohesiveness, low dose, affect flowability). Final blend properties (e.g., bulk density, particle size, flowability) can impact the process parameters for filling capsules, blisters, and reservoirs. Traditional methods (sample thief) or Online technologies (NIR).

- Significant changes proposed for proposed commercial and used during exhibit should be clearly identified and risk-based approach used to further justify such differences.

- Demonstrate (for each product strength) that the difference would not result in change or affect any performance related quality attributes at product release and shelf-life.
ICH Q10, a control strategy is a “planned set of controls, derived from current product and process understanding that assures process performance and product quality.” The overall purpose of the control strategy is to ensure that the CQAs are within the appropriate range, limit, or distribution to assure drug substance and drug product quality.
OIDPs (MDIs & DPIs): General Quality Expectations
**MDIs- General Recommendation**

**Recommendations for a Test MDI device**

*For assurance of substitutability of the T and R:*

- Same number of doses
- Same external design & operating procedure (patient instruction)
- Similar cleaning instructions and frequency
- Similar actuation force
- Similar size of the canister and actuator
- Inclusion of a dose counter*
- Appropriateness of a lock-out mechanism

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DPI- General Recommendation

**Recommendations for a Test DPI device**

For assurance of substitutability of the T and R:

- Same source for respiratory drug delivery (i.e., a breath-actuated device)
- Same metering principle (i.e., pre-metered single unit-dose, pre-metered multiunit-dose or device-metered multi-dose)
- Contain same number of doses
- Same external design & operating procedure (patient instruction).
- Internal operation/device function can be different as long as it doesn’t affect patient experience (similar device resistance).
- Similar size and shape to the R product
- Comparable device resistance to the R product
Formulation Considerations (Q1/Q2)

- Recommended that the T formulation be Q1 and Q2 *(exception allowed for DPIs*) the same R formulation.
  - Q1 (qualitative sameness) same inactive ingredient(s) as the reference product.
  - Q2 (quantitative sameness) concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference product.

- *Q1/Q2 sameness determination does not take into consideration any differences in the amount of active pharmaceutical ingredient(s) (APIs) between the test and reference formulations.*

- *API overage is strongly discouraged; please refer to Guidance for Industry: Q8(R2) Pharmaceutical Development (2009) for Agency’s recommendation on overage.*

*Cannot exceed the levels used in other FDA approved products administered by the same route of administration (i.e., inhalation)*
Recommendation for Submission Batch Size (MDIs and DPIs)

Due to complexity of these dosage form, Agency’s current thinking regarding the exhibit batch size,

- Recommend a minimum of three submission/stability batches *(each strength)*, of which one batch (100%) should be manufactured at the proposed commercial scale and other two batches are at least one-third (1/3) of the proposed commercial scale.
All three submission batches of each strength should be completely filled into canister.

One of the three primary batches of each strength (regardless of scale – commercial or pilot) should be packaged fully (assembly of the filled canister units into actuators and heat sealing each actuator-canister assembly in a foil pouch with desiccant).
Partial packaging for the other two batches is acceptable, as long as the fully packaged products canisters selected for testing are representative of the whole batches i.e. sampled from beginning, middle and end of filling process.

Finished product selected for stability testing from all three batches (each strength) should be representative of the respective whole batches of inhaler units, i.e., sampled from beginning, middle and end of inhaler incorporation process.
All three submission batches of each strength should be completely filled into individual blister strips.

One of the three primary batches of each strength (regardless of scale – commercial or pilot) should be packaged fully into finished products with the whole package system. (i.e., blister strips being assembled into inhaler device, further packed into the foil laminate overwrap).

Partial packaging for the other two batches is acceptable, as long as samples selected for testing are representative of the whole batches i.e. sampled from beginning, middle and end of blister filling process.

Finished product selected for stability testing from all three batches (each strength) should be representative of the respective whole batches of inhaler units, i.e., sampled from beginning, middle and end of inhaler incorporation process.
Number of Device/Excipient Lots:

Device/Formulation components variability:

- Recommended to incorporate different batches of CCS in the three exhibit batches.
- In addition, for suspension MDI products, the three exhibit batches should be manufactured, preferably from three different batches of the drug substance and critical excipients.
- For DPI three discrete lots of APIs and proposed diluents be used for manufacturing registration stability batches of finished product, to show the impact of lot-to-lot variability of each ingredient on the quality, stability, and performance characteristics of finished drug product.
  
  - For instance the particle size and surface morphology of Lactose Monohydrate will significantly affect the efficiency of redispersity of API particles in an inhaled stream. Therefore, it is considered as critical excipient, for which a minimum of 3 lots should be used to manufacture the stability batches to show the impact of lot-to-lot variability of Lactose Monohydrate on the quality and performance characteristics of drug product.

Number of API lots: Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products Q&A (May 2014)

Section C Q&A 4: “A minimum of two lots of the drug substance should be used to prepare the three primary batches of drug product. For nasal aerosols and nasal sprays, you should use three different lots of drug substance.”
OLDP in collaboration with OTR and other stakeholders is continuously engaged in regulatory research and scientific advancements for OIDPs, to support science and risk based review process/regulatory decisions, to assure that quality drugs are available to the American public.

‘One Quality Voice’
Conclusion

- With the inherent complexity of these drug products (drug/device combination product), MDIs and DPIs pose unique challenges, however, a systematic QbD approach for product development will efficiently bring competitive products to market while,
  - identifying the key target profile and critical quality attributes of the product.
  - identifying development risks, challenges, and knowledge gaps during the formulation, process, device development.
  - maintaining products quality and performance through the expiration dating period under patient-use conditions,
  - maintaining product quality and performance over the product life cycle, including continual improvement.
- OIDPs (MDIs & DPIs) recommendations are to ensure consistent drug product quality assessment for such complex generic drugs.
- OLDP in collaboration with OTR and other stakeholders is continuously engaged in regulatory research and scientific advancements for OIDPs, to support science and risk based review process/regulatory decisions.
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Additional Questions:
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