Device Change Management for Inhaled Products

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# Topics to be covered

- Update on ISO/TC 084/WG 15: Device Change Management
- Guidelines for development of drug products- Quality by Design (QbD) (ICH 8, 9 and 10)
- Combination products – Inhaled products are a combination of a medical device and medicine
- Focus on Metered Dose Inhaler (MDI) products – Post approval changes
- Quality attributes of MDI products
- Impact of device changes on product attributes and management of these changes through aspects of a QbD approach
- Examples
  - Introduction of a dose counter
  - Changes to MDI canister internal coating
  - MDI valve design
  - Indirect device impact (changes to formulations, analytical methods, processes, complaints, inspections. Recalls, OOS results)
## Post Approval Changes – Application of QbD principles

1. **Product development occurred before or after implementation of QbD principles**
2. **Control strategy is in place**
   - Control of input materials
   - In-process controls
   - Controls around container closure systems
   - Controls around analytical methods
   - FMEAs conducted
   - Risk assessments have been conducted
   - Regular review of trending, control charts, process capability etc.
3. **Device changes – change management process**
   - Need to revisit elements of the control strategy
   - Understand impact from a FMEA perspective. Perform a product risk assessment.
   - Manage changes proactively
Schematic Diagram of a Metered Dose Inhaler
## Quality Attributes of a Metered Dose Inhaler Product

<table>
<thead>
<tr>
<th>Quality Attributes</th>
<th>Critical Quality Attributes</th>
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<tbody>
<tr>
<td>- Appearance and Color</td>
<td>- Particle size distribution, fine particle dose</td>
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<tr>
<td>- Water or Moisture content</td>
<td></td>
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<td>- Dehydrated alcohol content</td>
<td>- Dose content uniformity through container life</td>
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<tr>
<td>- Microscopic evaluation</td>
<td>- Content uniformity of dose</td>
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<tr>
<td>- Spray pattern</td>
<td>- Identification</td>
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<tr>
<td>- Plume geometry</td>
<td>- Microbial limits</td>
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<tr>
<td>- Valve delivery – Shot weight</td>
<td></td>
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<tr>
<td>- Weight of canister contents</td>
<td>- Foreign particulate matter</td>
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<tr>
<td>- Drug content in a canister</td>
<td>- Leachables</td>
</tr>
<tr>
<td>- Leak Rate</td>
<td>- Impurities and degradation products</td>
</tr>
</tbody>
</table>
Interactive Nature of Inhaled Drug Products

- Components
- Formulation
- Inhaled Drug Product
- Processes
- Methods

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Device Change Management
Example: Dose Counters and Dose Indicators in MDIs

- Around the nozzle block of the actuator
- On top of the can
- Counters and Indicators
Impact of addition of dose counter or dose indicator

Changes to device deposition

Addition of a Dose counter or Dose indicator

- Patient Handling Studies
- Valve function
- Counter robustness

Impact on automated analytical methods (DTU & CI)

- Material changes
- Electrostatics
- Extractables

Impact on filling process

- Ex-Device dose
- Throat deposition
- Delivered dose
- Changes in deposition on CI stages
- Overages

Air flow changes
Example: Change in can coating formulation

- Change in solvent used in the coating formulation.
- Driven by environmental, health, safety concerns
- May need to consider a change in polymers used in the coating material

Impact on:
- Control strategy
- Coating process
- Coating quality – conformity and pinholes
- Extractables and leachables
- Drug deposition on can wall
- Overages
- Delivered dose and Cascade impaction results
Cross-Sectional view of a Metered Dose Inhaler Valve
(Courtesy Aptar Pharma)
Complexity of MDI Valve and its Assembly Process
(Courtesy Aptar Pharma)
Impact of change in valve design

- Valve design changes can be driven by a multiplicity of factors
  - Problems that arise due to propellant leakage
  - Valve function issues
  - Change in valve seal properties
  - Shot weight changes
  - Change in materials – shrinkage, extractables, dimensional controls

- Impact on product critical and quality attributes and critical process parameters
  - Changes in delivered dose and Cascade impaction results
  - Changes in leak rate
  - Changes in valve frictional behaviour

- Analysis and management of valve design changes
  - Optimization of crimp parameters
  - Addition of lubricants to the valve
  - Changes in valve dimensions
  - Assessment of valve functionality
Conclusions

- Inhaled products are a very complex dosage form
- Device changes occur all the time and many of them are mandatory
- Impact of device related changes can be significant
- Change management entails the use of a structured FMEA and Risk analysis based approach
- Device changes can alter existing control strategy
- Changes are very time consuming, labor intensive and require regulatory submissions of various types
- In the pharmaceutical industry we have transitioned and implemented good Quality Management Systems.
- ISO standards for “Device change management” are not expected to alter to any significant extent the currently existing quality control measures
Thank you