

Control Strategies for APSD

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on behalf of the
IPAC-RS Cascade Impactor Working Group

Overview

- Control Strategy: Model & Concepts?
- Elements of Control Strategy
- Elements of Control Strategy for Metered Dose Inhaler (MDI)
- Factors affecting APSD of an MDI
- Overall APSD Risk Assessment Steps.

Control Strategy

- “The Control Strategy is a comprehensive plan for ensuring the final product meets critical requirements, and therefore the needs of the patient”

- *“PQLI Control Strategy Model and Concepts”, Bruce Davis et.al., J. Pharm Innov (2008) 3:95-104*

- AIM / EDA is one element of overall control strategy

Definitions

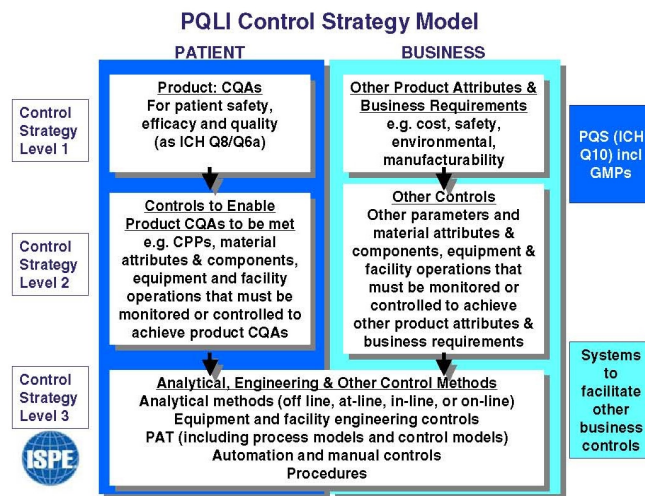
- PQLI: Product Quality Lifecycle Implementation.
- CQAs: Critical Product Attributes.
- QRM: Quality Risk Management.
- CPP: Critical Process Parameter
- PQS: Pharmaceutical Quality System

Definitions

- AIM-QC = abbreviated impactor for OIP quality control
- APSD = aerodynamic particle size distribution
- CI = full resolution cascade impactor
- EDA = efficient data analysis
- FPM = fine particle mass (absolute) of APSD
- ISM = impactor sized mass
- LPM = large particle mass (absolute) of APSD
- MMAD = mass median aerodynamic diameter
- SPM = small particle mass (absolute) of APSD

- *SOD: spray orifice diameter*

PQLI Control Strategy Model & Concepts



"PQLI Control Strategy Model and Concepts", Bruce Davis et al., *J. Pharm Into* (2008) 3:95-104

Elements of Control Strategy

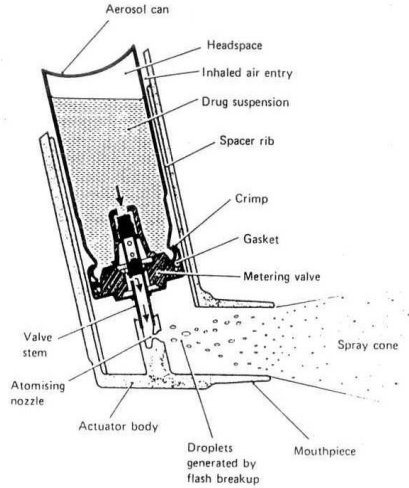
Elements of Control Strategy can include:

- Control of input material attributes (e.g. drug substance, excipients, primary packaging materials)
- Product specifications
- Facility controls (e.g. environmental systems and operating conditions)
- Control of unit operations that have an impact on downstream processing or end product quality
- Other

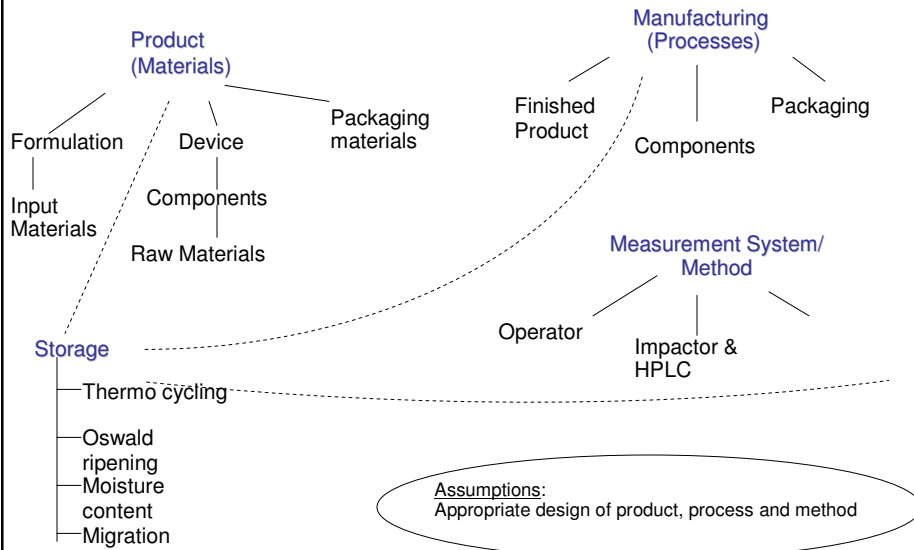
Factors that may change APSD of a Metered Dose Inhaler

- Formulation/Device
- Manufacturing
- Storage
- Measurement System/Method/Testing

Metered Dose Inhaler (MDI)



Elements of Control Strategy Ishikawa-type analysis



Factors That May Change APSD: Formulation/Device

- Water content/storage time (*suspension v/s solution*)
- Moisture in-gress.
- Ethanol (*co-solvent levels*)
- Excipient: suspending agents, propellants,
- API Particle Size/morphology
- Electrostatic (*device, spacers, mouthpieces.....*)
- Change on PSD due to storage (*temperature effect*)
- Leachables: interactions/altering physical property of API.
- Compatibility of formulation with components.
- API deposition on the canister walls

Factors That May Change APSD: Formulation/Device.....

- Valve metering chamber volume.
- Valve stem mechanical strength (*critical dimension*)
- Seals, crimping, leak rates (*container tightness*)
- Spray orifice diameter (SOD) for Mouthpiece: flashing during molding (*all critical diameters*).
- Partial clogging of SOD
- Through-life effects due to wear (*e.g., valve-gasket interface, particulate matter,...*)
- Concentration effect due to canister emptying (*not shaking the canister*)
- Molding equipment for components
- Canister: surface features/inconsistencies, coated surface, canister cleaning
- Component manufacture controls
- Other.....

Factors That May Change APSD: Manufacturing

- Pressure fill (*damage to the valve*)
- Errors in composition
- Problems with crimping units (*height, diameter OOS*).
- Fill volumes of solution/HFA
- Handling of manufactured canisters before packaging
- Filling process interruptions/re-start, e.g., suspension formulations.
- Problems with on-line leakage testers, e.g. FID
- Package integrity (*pouch, packaging of API*)
- Storage of API & milling (*amorphous content*)
- Primary particle size of material prior to milling (*agglomeration, aggregation, oversize particles*)
- *Other.....*

Factors That May Change APSD: Measurement System/Method/Testing

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**Considerations for the Development and Practice of
Cascade Impaction Testing, Including a Mass Balance
Failure Investigation Tree**

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Review Article

**Minimizing Variability of Cascade Impaction Measurements
in Inhalers and Nebulizers**

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Factors That May Change APSD: Measurement System/Method/Testing

- Mix-up in CI stages
- Wall loss effect
- Inaccurate preparation of the impactor (*coating, adaptor-mouthpiece interface-seal alignment, flow rate, wet impactor....*)
- Impactor jets (*deformed, damaged, wear, clogged*)
- Improper assembly (*leakage*)
- Temperature and/or humidity conditions (*outside specified range, evaporation effects*)
- Coating/conditioning plates
- Electrostatic effects
- Stage mensuration/calibration
- Ambient air particle load
- Other....

Factors That May Change APSD: Measurement System/Method/Testing.....

- Analyst technique/handling of equipment
- Firing rate (*chilling effect*)
- Use of in-correct mouthpiece for the test.
- Incorrect preparation of sample (*e.g. wrong solvent, shaking time, dilution step, filling ...*)
- Insufficient number of actuations (*mis-count in number of actuations*)
- Non-standardized handling-shaking, actuation.
- Partially clogged, unclean mouthpiece (*repeated use of mouthpiece*)
- Virgin v/s primed (used) mouthpieces (*MP retention*)]
- Other.....

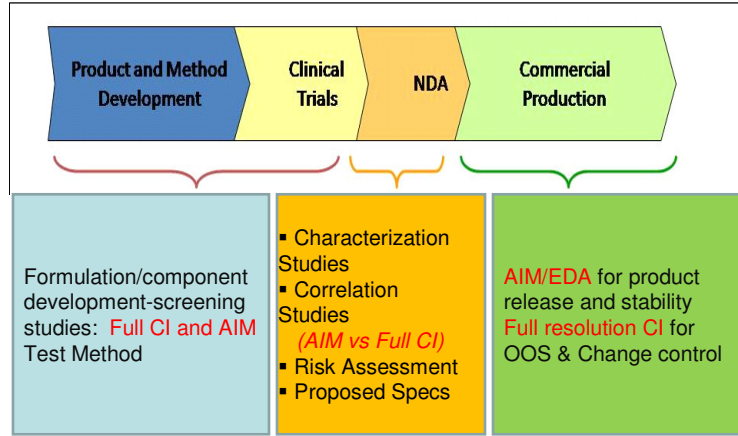
Factors That May Change APSD: Measurement System/Method /Testing.....

- HPLC System & Chromatographic errors (*buffers, mobile-phase composition, column, flow rate, temperature, injection volume, wavelength, sampling rate, wrong order of vials, ...*)
- Non validated method (*linearity ?*)
- Purity & integrity of reference standard.
- Errors in preparation of standard solution (*e.g. balance failure, reference substance, calculation mistake, dilution incorrect, wrong solvent,..*)
- Sample recovery solvents & recovery problems.
- Impurities from the system.
- Evaluation (*data input, integration, processing method, calibration,..*)
- Other.....

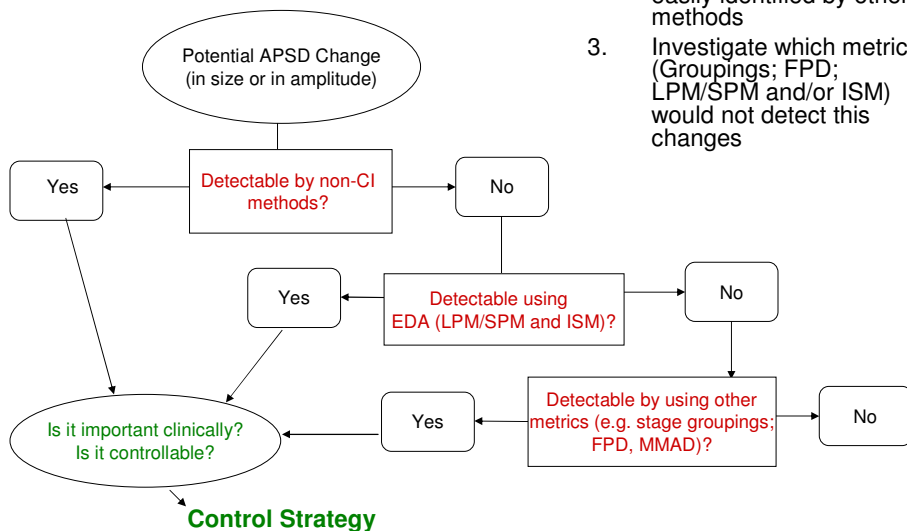
Factors That May Change APSD: Storage/Shipping

- Extreme conditions (*uncontrolled storage & shipping, altering chemical / physical properties of the product, vibrations*).
- Storage/shipping orientation.
- Other....

Control Strategy: Measurement Method



APSD Risk Assessment



1. Identify possible source of APSD change
2. Clarify if these changes can be prevented, very unlikely to happen or easily identified by other methods
3. Investigate which metrics (Groupings; FPD; LPM/SPM and/or ISM) would not detect this changes

Control Strategy for APSD

- Control Strategy Development: A structured and iterative activity involving multidisciplinary team!
- Product characterization and “knowing your product” for development of control strategy.
- AIM-EDA as part of ‘control strategy’
 - *Reliable, discriminating test.*
 - Release of clinical supplies.
 - Stability Studies.

Control Strategy for Drug Product

- Standard Control Strategy: Drug product quality is controlled primarily by intermediate and end product testing.
- Enhanced Control Strategy: Drug product quality ensured by risk-based control strategy for well understood product and process, and quality controls are shifted upstream, with the possibility of real-time release or reduced end-product testing.
- → *A Design Space is established, and the Control Strategy will ensure that the product is manufactured within the Design Space.*

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Thank you

