

Physical and chemical testing method validations in metered dose inhaler production and development (1st part)

Dr. Gyula Körtvélyessy UNIDO Honorary Secretary General of the Hungarian Chemical Society

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New approach in the pharmaceutical developments

- EPA Guidance for Metered Dose Inhalers (and other similar products) in 1998
- ICH Tripartite Guidelines: Quality by Design
- How to apply the new concepts in MDI development?
- International Pharmaceutical Aerosol Consortium on Regulation and Science: 12 member companies
- Product Quality Research Institute: more authority based

Risk assessment for failure Tougas at all. USP presentation, 2010 December Particle Size/morphology MDI New Impurity Stirring speed Water content Stirring time Residual solvents Recirculation time Leachables/Extractables Amorphous content Suspension temperature Drug deposition Physical stability Crimping Moisture ingress Spacer Electrostatics Synthetic route Heat stress Drug Substance Head space Batch size Leak rate Accessories Vessel headspace Piggy backing Vessel size Device-Formulation Impurities Propellant Quarantine time Moisture interactions Damage to valve (pressure Errors in composition API concentration Manufacturing Processes Fill volumes Suspension stability Filling interruptions Cosolvent levels Leakage APSD Surfactants Formulation Packaging integrity Change Shaking Actuation Metering volume Device Valve Testing Impactor assembly Spring tension Airflow Spring sticktion Temperature Stem friction Actuator Can Storage Humidity Process residues Electrostatics Geometric dimensions Actuator cleaning Materials of construction Actuator deposition Can size Orientation Spray orifice diameter Seals, crimps, etc. Temperature Stem block angle Humidity Surface features Flashing in stem Likelihood of Occurrence Spray orifice eccentricity Materials of construction lower probability Electrostatics medium probability IPAC-RS Airflow geometry Similar Analysis done for DPI

higher probability

Physical and Chemical Parameters

- Drug Substance (API) (one or more?)
 - Chemical composition: assay, impurity profile, etc.
 - Particle size distribution: original, delivered by MDI
 - Amorphous content
 - Morphology
 - Solubility (when changing propellant and co-solvents)
- Propellant, co-solvents, additives
 - Chemical composition: assay, impurities
 - Moisture content
- Formulation
 - API concentration

Physical and Chemical Parameters

cont.

- Device
 - Can
 - Surface feature
 - Valve
 - Dose content uniformity
 - Actuator
- Interactions with formulation
 - Leak rate
 - Extractable/Leachable
- Manufacturing process
 - Chemicals
 - Device
 - Filling

Deposition of particles in lung



Measuring the particle size distribution: Cascade impactors



Impactor air flow rate sets the mass of air through the impactor

Large Jet - slow air velocity

Impaction surface

Large particle has higher momentum than small particle at the same velocity – momentum of small particle overcome by drag of air... At the same velocity, momentum of larger particle overcomes drag of air

Small jet - Fast air velocity

Impaction surface

Controlling factor is particle momentum

Impactors and impingers

Andersen Cascade Impactor (8-stages)





Marple-Miller Impactor (5-stages)



Next Generation Impactor (8-stages)





8-stages Andersen impactor





Important questions for the particle size distribution test

- Recovery of API from plates
 - Solvent selection:
 - Good solubility ↔ acceptable for HPLC
 - Volume \leftrightarrow sensitivity of HPLC
 - Recovery technique of API
 - Manual ↔ automatic
- Quantitation lower limit
 - Number of actuation \leftrightarrow sensitivity of HPLC
- Cleaning
 - Nozzle cleaning deformation, corrosion,
 - Frequent stage mensuration
- Pre-separator and back-up filter

Important questions for the particle size distribution test cont.

- Incorrect stage order
- Air leakage
 - − Flow rate ↔ pressure drop

Most relevant validation data for particle size distribution

- Stage mensuration
 - Measuring the nozzle diameters and arrangement dimensions of the cascade
 - Interlaboratory test in 2010: within 0.1%!!
 - Optical measurements of jet diameters: ± 1µm !
- Re-entertainment: particles bounced
 - Plate coating with glycerol or silicone oil deposited from solution by evaporation
- Mass balance: total API collected / avarage delivered dose
 - 75-125%
- Interstage API loss: drug deposited on walls
 ≤ 5%

Documents to be attached for authorities

- Stage mensuration
- Pressure drop measurements (daily basis)
- Conformity to Eur.Pharm and USP
- Leak test
- Flow meter calibration
- Data analysis software validation (if any)
- Process descriptions (inc. Cleaning and drying)
- Installation Qualification and Operation Qualification document according to GxP

New technical solutions

- Detecting with light
 - Quick BUT:
 - Measure the number of particle and not weight
 - Not selective for API
- Raman chemical imaging
 - Quick
 - Number of particle
 - Selective
 - Identify differences in crystallinity and water content

Cost data Mitchell, September 2011

Cascade impactor or multi-stage liquid impinger:

USD 5-10 000/unit

- Time-of-Flight based equipment: USD 35-100 000/unit
- Laser diffractometer:

USD 40-100 000/unit

 Raman chemical imaging: USD 100 000/unit

New approach from 2009 Abbreviated Impactor Measurement



Thank you for your kind attention! Need publications about the topic: k.gyula@chello.hu