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

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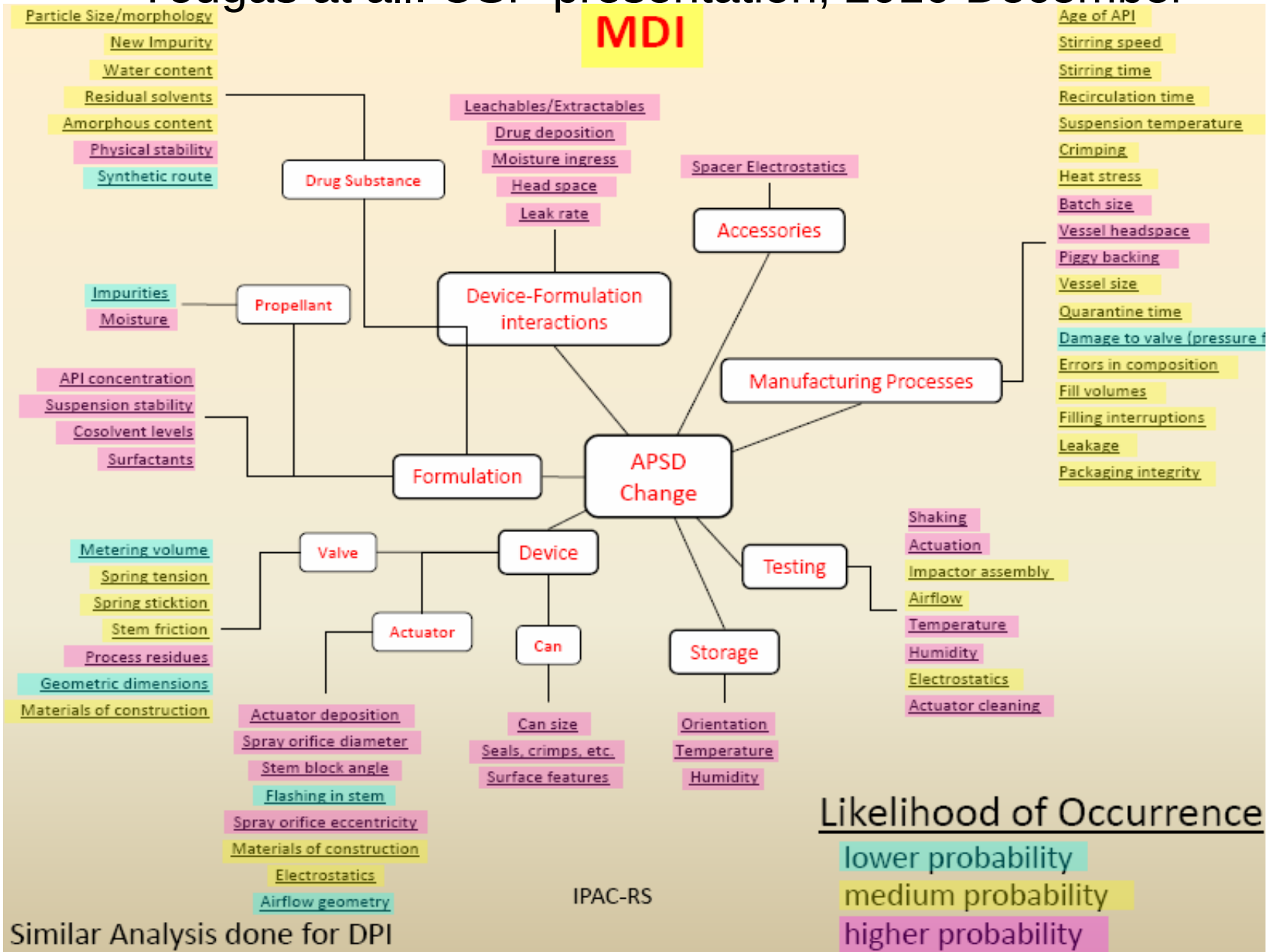
New approach in the pharmaceutical developments

- 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



Physical and Chemical Parameters

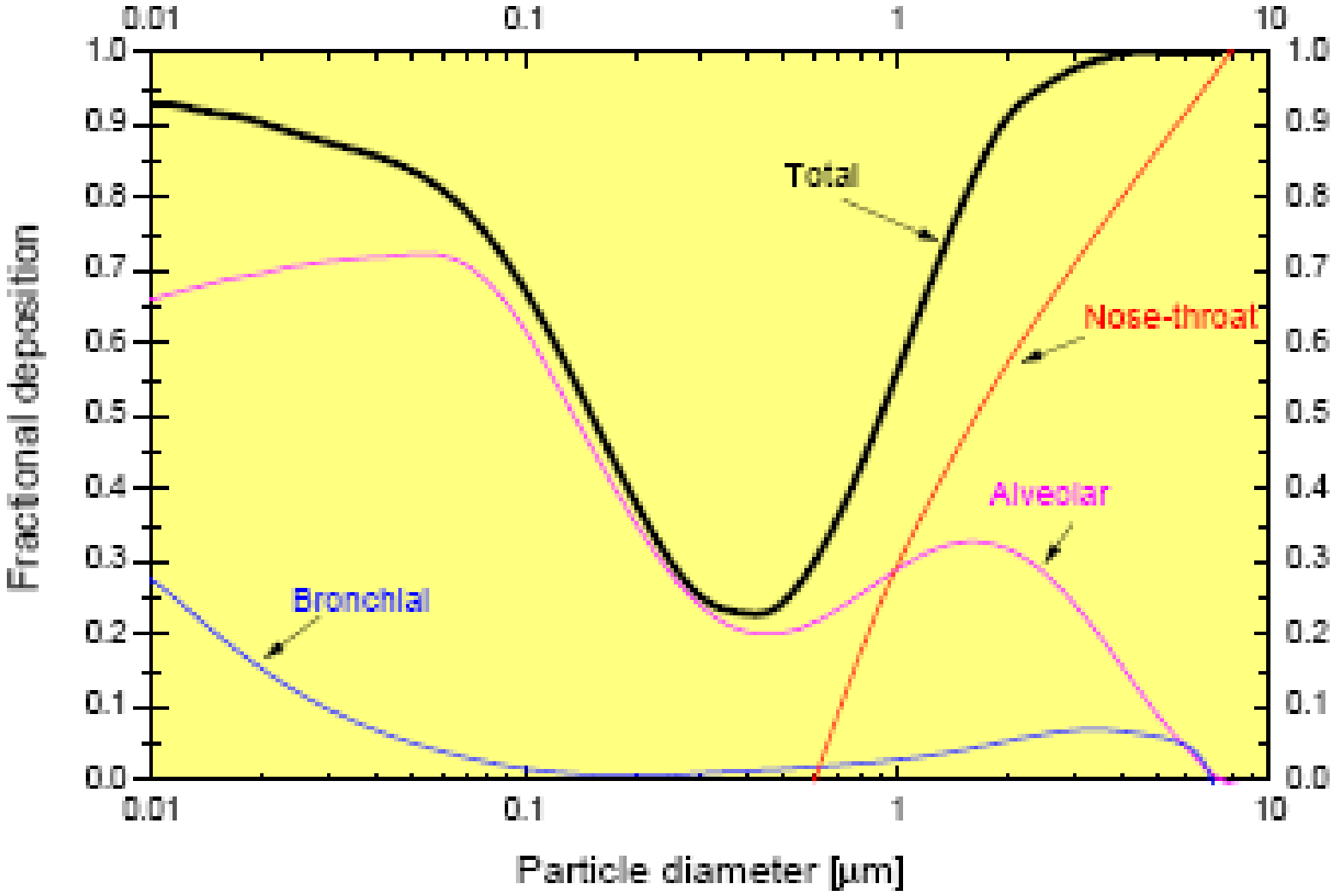
- Drug Substance (API) (one or more?)
  - Chemical composition: assay, impurity profile, etc.
  - Particle size distribution: original, delivered by MDI
  - Amorphous content
  - Morphology
  - Solubility (when changing propellant and co-solvents)
- Propellant, co-solvents, additives
  - Chemical composition: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

Physical and Chemical Parameters

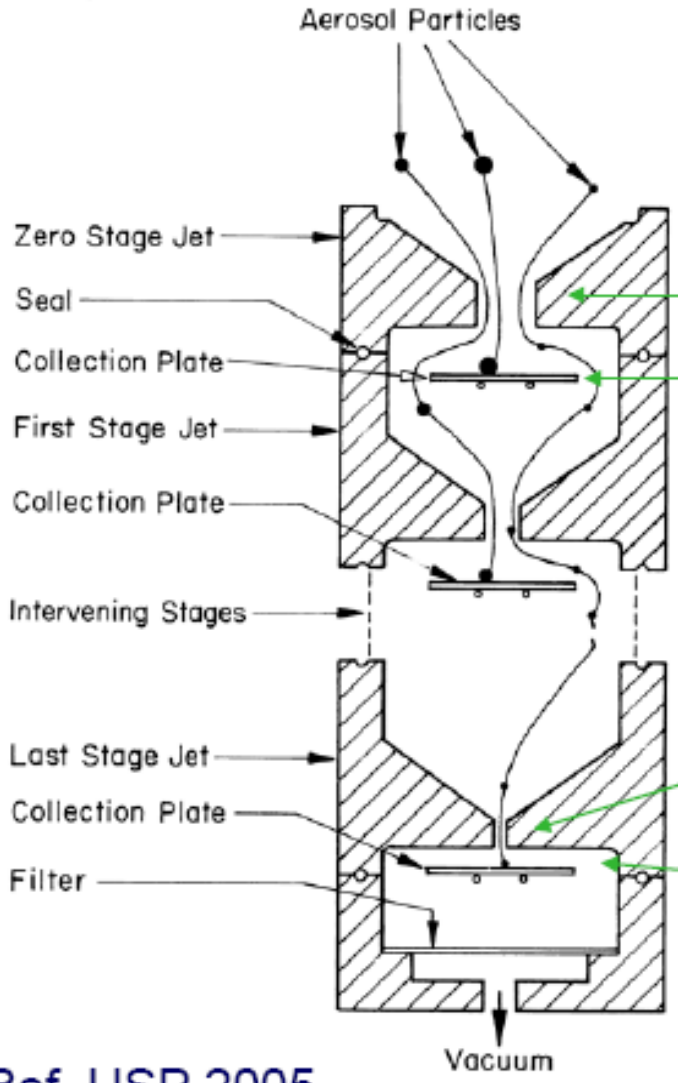
cont.

- 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



Ref. USP 2005

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

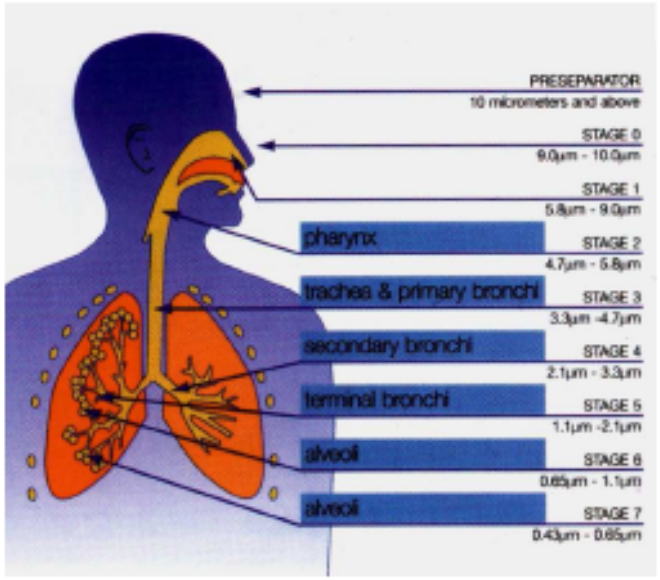
Small jet – Fast air velocity

Impaction surface

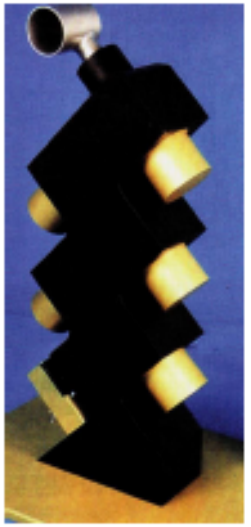
Controlling factor is particle momentum

Impactors and impingers

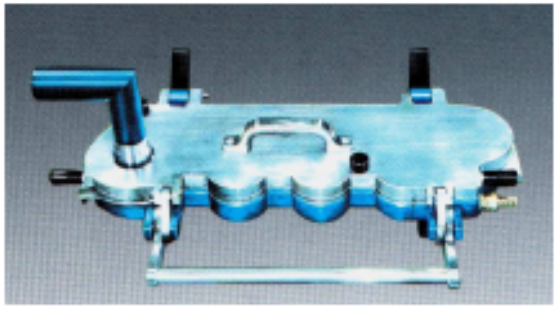
Andersen Cascade Impactor (8-stages)

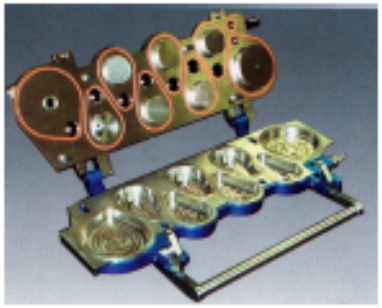


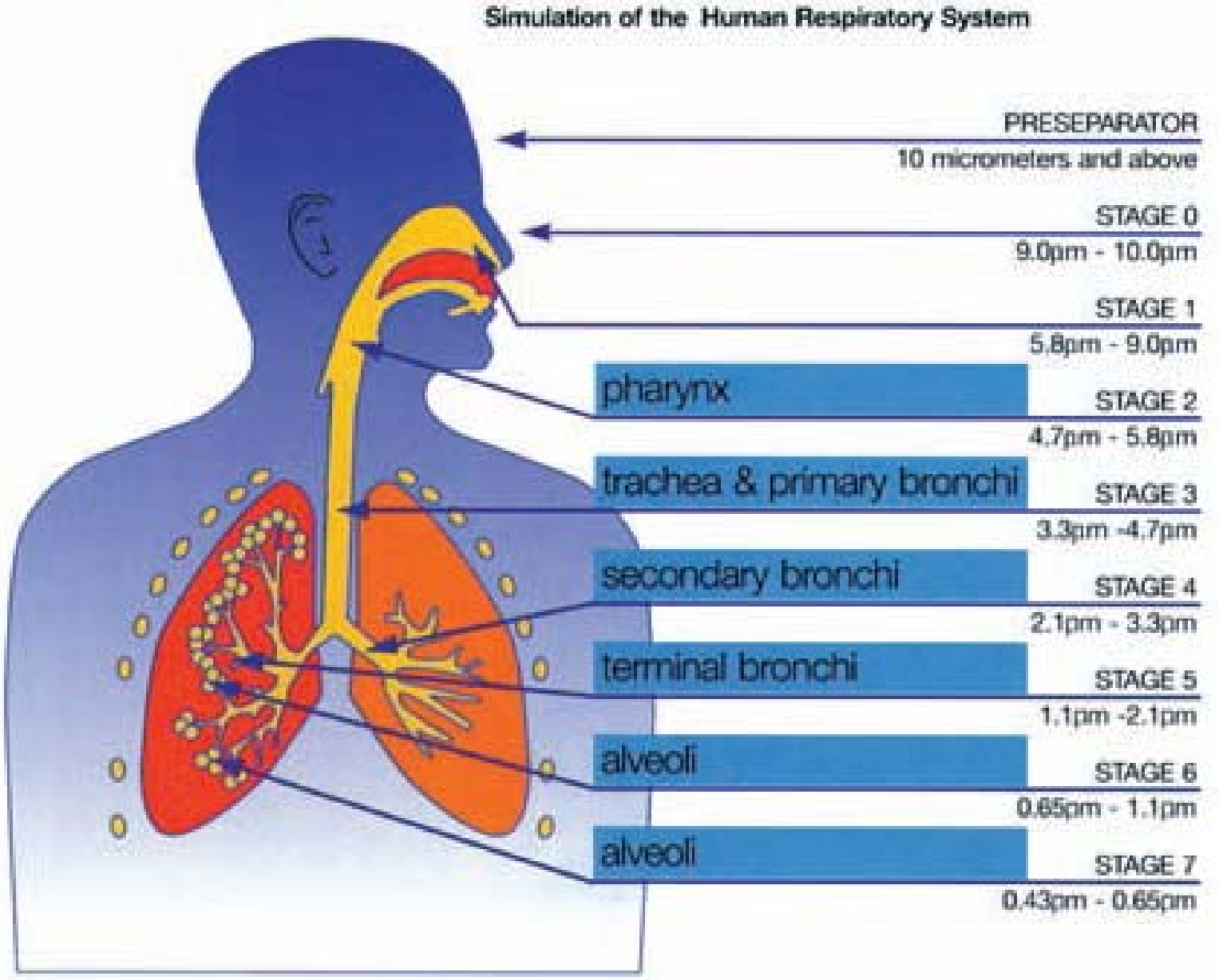
Marple-Miller Impactor (5-stages)



Next Generation Impactor (8-stages)






Simulation of the Human Respiratory System
PRESEPARATOR
10 micrometers and above
STAGE 0
9.0μm - 10.0μm
STAGE 1
5.8μm - 9.0μm
pharynx
STAGE 2
4.7μm - 5.8μm
trachea & primary bronchi
STAGE 3
3.3μm -4.7μm
secondary bronchi
STAGE 4
2.1μm - 3.3μm
terminal bronchi
STAGE 5
1.1μm -2.1μm
alveoli
STAGE 6
0.65μm - 1.1μm
alveoli
STAGE 7
0.43μm - 0.65μm

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 ↔ sensitivity of HPLC
  - Recovery technique of API
    - Manual ↔ automatic
- Quantitation lower limit
  - Number of actuation ↔ 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:**

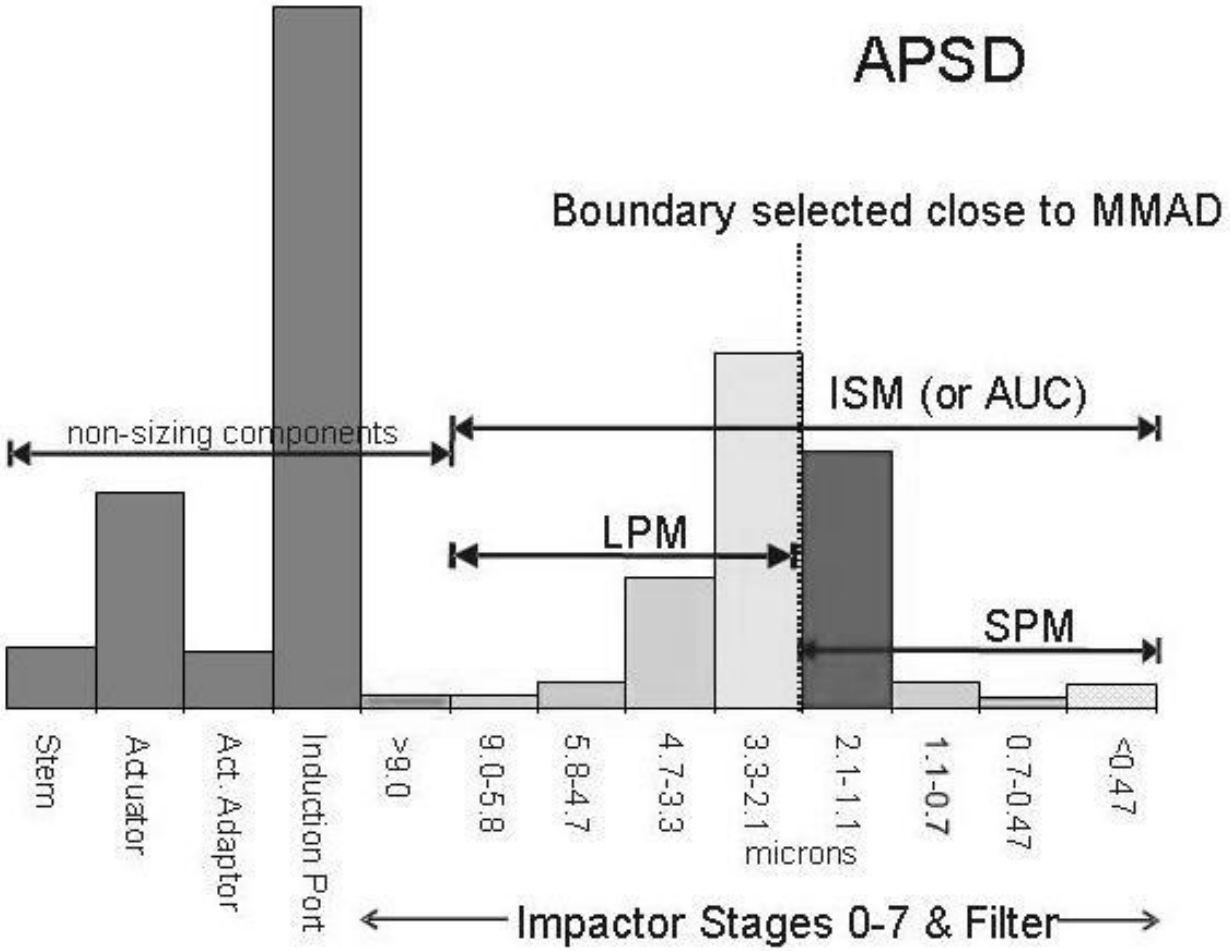
  USD 5-10 000/unit
- **Time-of-Flight based equipment:**

  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:
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