Analytical Challenges for Orally Inhaled and Nasal Drug Products (OINDPs)
CDER Perspective

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AAPS
Outline

• Complexity of Inhaled Products
• Varied Guidance Documents
• Complex Analytical Methods
  • APSD*
  • DDU*
• QbD for OINDPs

*aerodynamic particle size distribution (APSD), dose content uniformity (DCU)
## Complexity of Inhaled Products

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Press and Breathe MDIs
Breath Actuated MDIs
Premetered DPIs
Capsules/blisters
Device metered DPIs
Formulation/cartridges
Nebulizers
Jet/Ultrasonic/Vibrating Mesh
Low vs High Efficiency
Dose Counters
Complexity of Usage of Inhaled Products

• Varied Patient Population
  Pediatric, Geriatric, Respiration/coordination compromised

• Site of Action
  Systemically acting, (vaccines, hormones, proteins, etc), Locally acting (corticosteroids, bronchodilators, etc)

• Site of delivery
  Lung, nasal passages

• Device operations
Varied Guidance Documents

- PQRI – Safety Thresholds & Best Practices For Extractables & Leachables in OINDP (Extractables/Leachables)
- FDA - MDI/DPI Draft Guidance (Inhalation Product Performance & Characterization)
- FDA – Guidance on Inhalation solution, suspension, spray and nasal spray products
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action
- CDRH - Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators, (Product Characterization including Leachables)
- FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (Packaging Characterization)
- CHMP, CVMP - Guideline for Plastic Immediate Packaging Materials (Packaging Characterization)
- USP <381>, <661> (Physicochemical), USP<87>, USP<88> (Biocompatibility)
Complex Analytical Methods for OINDPs Products

- Particle/droplet Size Distribution
- Dose Content Uniformity
  - Compendial Method
  - Parametric Tolerance Interval Testing (PTIT)
- Aerodynamic Particle Size Distribution
- Extractables/Leachables Testing
- Spray Pattern/Plume Geometry
Aerodynamic Particle Size

Cascade Impaction (aerodynamic)

- ACI*, NGI*, MSLI*, AIM* etc.
  - Flow rate, volume, pressure drop, temperature, humidity, plate coatings
  - Effective Data Analysis (EDA) of Aerodynamic Particle Size Distribution

Laser Diffraction (geometric)

- Sample uniformity, solution vs. suspension,
- in line vs. on line

Parsum Probe

- Spatial filter velocimetry

*Andersen cascade impactor (ACI), next generation impactor (NGI), multistage liquid impinger (MSLI), abbreviated impactor measurement (AIM)
APSD Testing of OINDPs

- APSD is a Critical Quality Attribute (CQA)
- Cascade Impaction (CI) measures the aerodynamic as opposed to the geometric size of particles
- CI measures the mass of the active pharmaceutical ingredient of the drug
- CI measures the mass of the entire emitted dose
Typical APSD Plot from a Cascade Impactor

APSD 100, 200, and 400 mcg Strengths

- Plate 0 (8.6-8.5 mcg/m²)
- Plate 1 (8.5-4.4 mcg/m²)
- Plate 2 (4.4-3.2 mcg/m²)
- Plate 3 (3.2-1.9 mcg/m²)
- Plate 4 (1.9-1.2 mcg/m²)
- Plate 5 (1.2-0.55 mcg/m²)
- Plate 6 (0.55-0.26 mcg/m²)

Wall losses
Limitations for the APSD *in vitro* test for OINDPs

- APSD (CI) - fixed flow-rate vs. variable inhalation flow rate of patients.
- Deposition in the CI (impaction with distinct size cut-offs per stage) vs. lung deposition (impaction, diffusion, and sedimentation over whole lung surface)
- USP throat poor mimic of oropharyngeal path
- Re-entrainment of dry powder particles; plate coating
Dose Content Uniformity

Measures dose variability

– Compendial method (e.g., USP <601>)
  • Zero tolerance
  • USP apparatus
    – Flow rate, volume, pressure drop, temperature, humidity, etc.

– Parametric Tolerance Interval Testing
  • Sample size, goal posts, K values, coverage
Compendial Methods vs. PTIT

• Agency’s method in Draft Guidance* is based on the USP method and based on information provided in applications.

• PTIT approach§ was designed and developed over the years with Walter Hauck at Thomas Jefferson Univ. and with FDA statistical input.

• Recommendations made by FDA at the ACPS Oct. 2005 on the acceptable parameters for PTIT testing for DCU/DDU.

*FDA Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation

§ 1999 AAPS FDA/USP Workshop presentation by Walter Hauck
FDA Proposal

- PTIT applied to DDU testing is in line with FDA current initiatives:
  - QbD and demonstration of product and process knowledge
  - Science and risk-based specification of drug product
- Goalposts are 80% to 120% of label claim
- 87.5% coverage within the goalposts is appropriate
- Sample size and k values are determined a priori and set by the applicant
- Exceptions to proposed criteria could be proposed by the applicant with adequate scientific justification.
Figure 2 The acceptance probability of FDA Draft DDU Method for Multiple Dose (10/10/20/20)

QbD for Analytical Methods

• Identifying the method objective and target operating criteria
• Selection of the analytical principle, development and preliminary validation
• Interaction among analytical parameters should be explored:
• Applying QbD principles to analytical method development will result in better understanding the capacity of the method, reduce measurement variability.

Conclusion

• Analytical testing can confirm compliance to quality specifications of the commercial batches such that the clinical performance can be generally duplicated.

• Testing for OINDPs is challenging due to the complexity of both the drug product/device and testing methods. This requires a well planned, thought out strategy to use the most relevant approaches for assuring quality of OINDPs.

• Applying QbD approaches for analytical methods can increase assurance of testing quality.
Acknowledgements

Prasad Peri
Craig Bertha
Alan Schroeder
Eric Duffy
Rik Losritto
Christine Moore