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

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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

Several dosage forms:	Several Devices
Aerosols Solutions/Suspensions Dry Powder Inhalers Neat/Carriers Nasal Sprays Solutions/Suspensions Nebulized Products Solutions/Suspensions Inhalation Sprays Solutions	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- FDA - MDI/DPI Draft Guidance (Inhalation Product Performance & Characterization)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

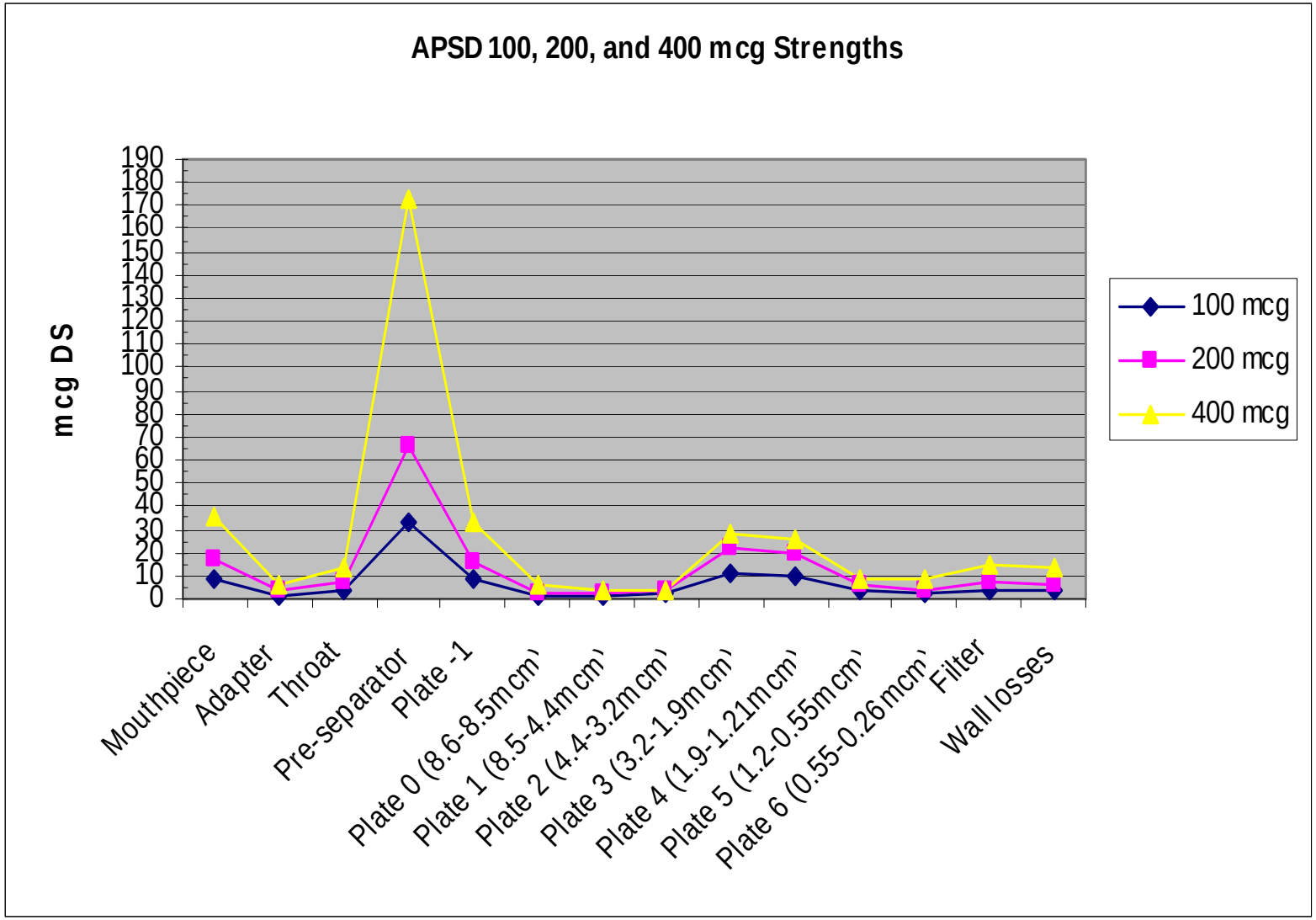
- Spatial filter velocimetry

*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



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.

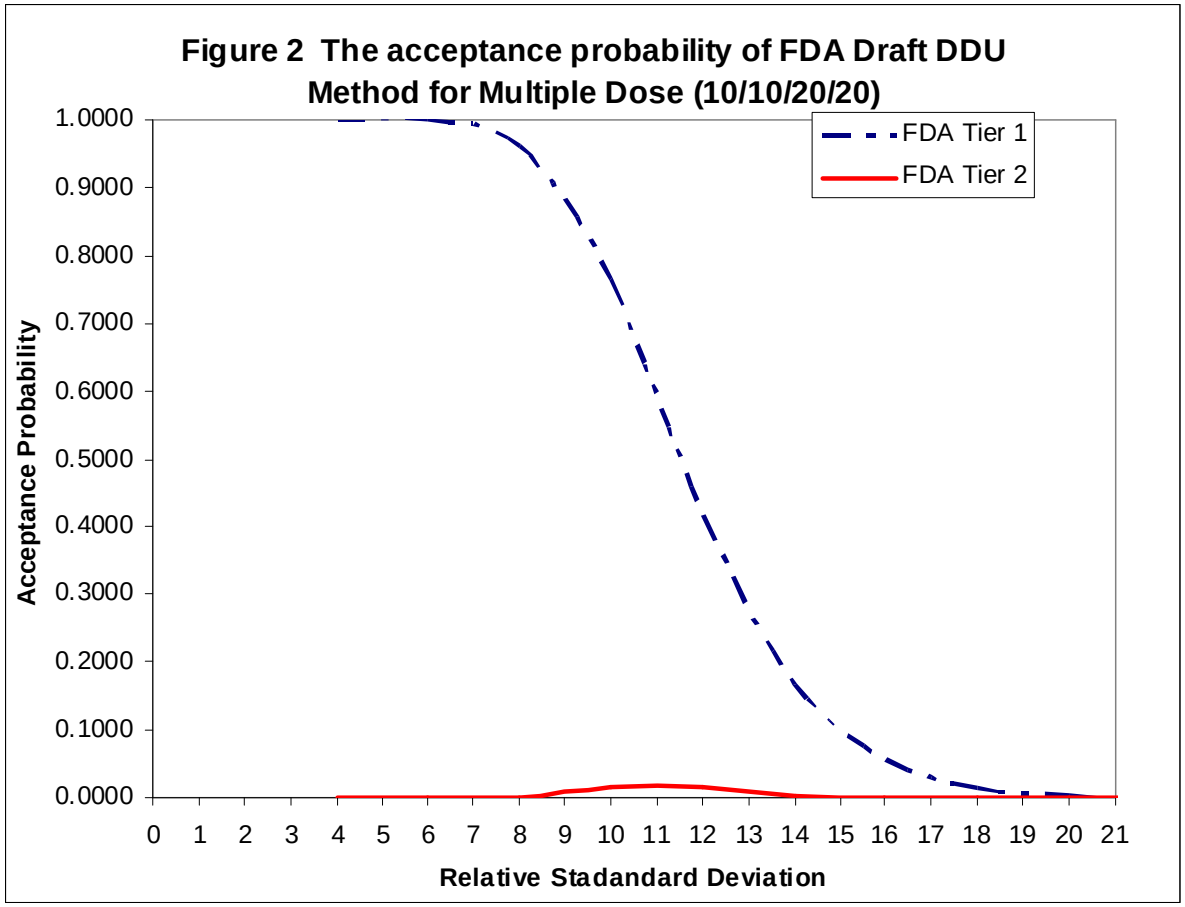
*FDA Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation

§ 1999 AAPS FDA/USP Workshop presentation by Walter Hauck

FDA Proposal

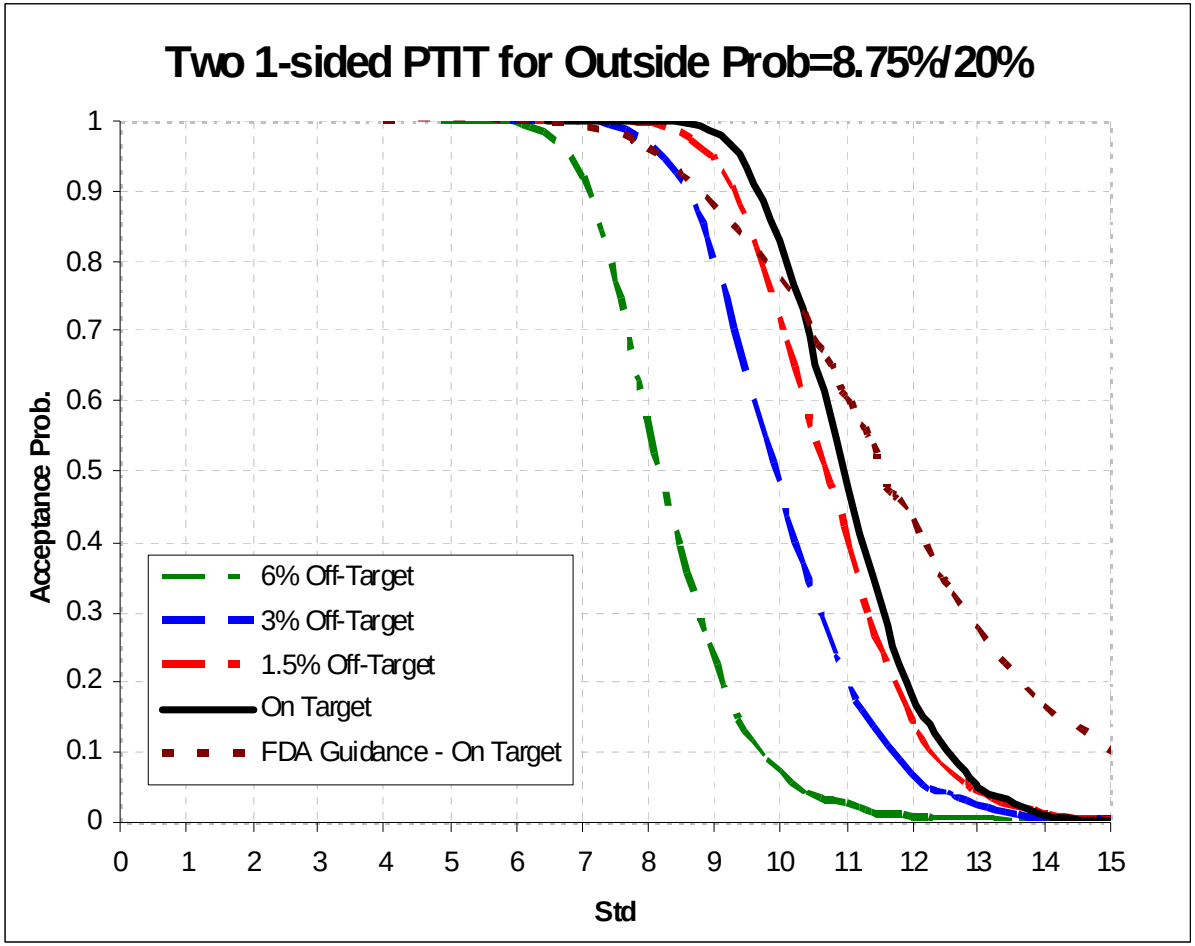
- PTIT applied to DDU testing is in line with FDA current initiatives:
  - QbD and demonstration of product and process knowledge
  - Science and risk-based specification of drug product
- Goalposts are 80% to 120% of label claim
- 87.5% coverage within the goalposts is appropriate
- Sample size and 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.

Draft DDU method



Tsong, Yi, Shen, Meiyu, Lostritto, Richard T. and Poochikian, Guiragos K.(2008) Journal of Biopharmaceutical Statistics,18:5,976 — 984

DDU Test PTIT Approach



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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.

Rignal et al., Pharmaceutical technology Oct. 2008

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.

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