AGENDA

- Regulatory Approaches for Bioequivalence (BE)
- Compendial Testing Vs Pharmaceutical Equivalence (PE)
- Inhalation Delivery Systems
  - ANVISA PE Comparison to USP <601> and (905>
  - Additional PE Requirements
- Nasal Sprays
- Statistical Analysis
  - Load & Reload
- Improving BE Outcomes
Global Bioequivalence Regulatory Perspectives

- FDA and Brazil (ANVISA) have issued guidances for bioequivalence (BE) of nasal and pulmonary drug products.
- Europe (EMA) had issued a BE guidance on pulmonary products.
- China releasing updated pharmacopeia.
- Different approaches to bioequivalence:
  - EMA applies step wise approach to BE
  - FDA applies weight of evidence
  - Brazil appears to follow FDA approach
  - Required tests and statistical approaches vary between regions.
Definition of Bioequivalence

- Generally defined as the same rate and extent of absorption as the Reference Drug Product.

- EU, US, Brazil and Canada all require bioequivalence:
  - Common goal: Determine the effectiveness of the proposed generic’s active ingredient[s] at the primary site of action.

- Requirements for chemical “sameness” of the active and non-active ingredients vary among regions:
  - In US, *formulations* are expected to be quantitatively and qualitatively the same (within 5% of reference drug).
FDA Approach for Bioequivalence

- Clinical endpoint
  - Same as a clinical study
  - Measure survival rate
- Pharmacodynamic (PD) endpoint
  - More sensitive than a clinical study
  - Measure lipid lowering
- Pharmacokinetic (PK)
- In Vitro Tests (BE/PE)

Nasal and respiratory drug products place special emphasis on in vitro tests for ANDA applications.
ANVISA Approach

- Generic inhalation or nasal product
  - Contains same active pharmaceutical ingredient (API)
  - Uses similar excipients and polymorphic profile
  - Uses the same dosage form with similar device handling characteristics
  - Demonstrates in vivo equivalence
  - Demonstrates in vitro equivalence
ANVISA

- Technical note explains in vitro requirements
- No final guidelines issued
  - Decisions made on a case by case basis
- Therefore, each company seeking generic approval should submit proposals to Coordination and Therapeutic Equivalence Committee to establish relevant in vitro and in vivo studies
Compendial Testing vs PE

:: Compendial Testing
   - Quality Control (QC) for your Drug Product
   - Routine testing for product quality
   - Specification applies

:: Pharmaceutical Equivalence
   - Is generic equivalent to the brand?
   - Performed once for regulatory approval
   - Primarily a statistical comparison
Inhalation Delivery Platforms

- Metered Dose Inhalers (MDI)
- Soft Mist Inhalers (SMI)
- Nebulizers
- Dry Powder Inhalers (DPI)
DPI Device Metering

- Pre-metered
  - Capsule

- Device metered
  - Blister
  - Reservoir

Advair Diskus  Asthmanex Twisthaler
## Brazil PE Tests: MDIs

<table>
<thead>
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<td>Aerodynamic Particle Size Distribution (APSD)</td>
<td>FPD and FPF MMAD GSD Beginning only</td>
<td>No lifestage requirement</td>
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<tr>
<td>Dose Mass</td>
<td>Mass</td>
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<tr>
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## Brazil PE Tests: DPIs

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</table>
Sample Preparation-Inhalers and Nasal Sprays

Best practices for USP, ANVISA, FDA and more…

For PE

- Brand (RLD) Package Insert

Repriming Sprays

- Number
- Frequency

Shaking (suspensions)
Shaking

- True for nasal sprays AND MDIs

- Shaking technique
  - Duration and frequency

- All analysts must be trained to shake the unit the same way

- Finalize shaking method before starting studies (unless in the method development phase)
Primming

-how many priming sprays are needed to reach target LC?
- For PE, must be same as or better than RLD

What if the number of specified priming sprays are inadequate?

Determine if priming is manual or automated

Same number of priming sprays used through entire study

Prime/Reprime
- Three orientations required for repriming (PE)
Electrostatics - Significance

- Electrostatic charging can occur naturally in the absence of electric fields from contact/friction (tribocharging) in solids and spraying in liquids.
- Charged aerosol generation from Dry Powder Inhalers (DPI), Metered Dose Inhalers (MDI), and Spacers affect drug delivery and deposition in lung airways.
- Static effects on devices (DPIs) make it difficult to weigh accurately.
Managing Charge

- Adopt techniques that control electrostatics
  - Gloves
  - Ground system (pads)
  - Dissipator system for balances
  - Maintain lab humidity > 20%
# Delivered Dose Uniformity: MDI

<table>
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<tr>
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<th>PE</th>
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Aptarpharma

PRESCRIPTION DIVISION
Delivered Dose Uniformity: Multidose DPI

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Unit Dose Sampling Apparatus for DPIs

Copley TPK Controller
- Timer
- Pressure sensors
  - P1 absolute sensor → achieves 4 kPa pressure drop
  - P3/P2 flow control → achieves constant flow
DPI Device Resistance

Increasing Resistance

Low
- Aerolizer
- Diskus
- Novolizer

High
- Turbuhaler
- Clickhaler
- Twistrhaler
Device Resistance

Device Resistance and PE

**Disclaimer: My Opinion for Brazil**

- Bioequivalent DPIs should have the similar device resistance
Output Is Dependent On Air Flow Rate?

Effect of Flow Rate

- **Flow rate**: effect on Delivered Dose

Flow Rate has minimal impact on delivered dose values.

- **Flow rate**: effect on Fine Particle Fraction (FPF)

FPF values increase with increased flow rate.
Delivered Dose Method Considerations

- What makes a good method?
  - 100% Label Claim (LC)
    - Test Drug Product LC should be same as RLD for PE

- Good recovery technique
  - Solvent evaporation
  - Drug can adhere to filter or collection apparatus

- Sample prep and device handling consistent between operators

- Use correct tubing (length and diameter)
Aerodynamic Particle Size Distribution (APSD)

Cascade impactors operate on the principle of Inertial Impaction

Each stage has a specific cut-off aerodynamic diameter
- Cut-off diameter or \( D_{50} \)

Stages are assembled in a stack with decreasing cut-off aerodynamic diameter

For PE
- MMAD & GSD
- Fine Particle Dose & Fine Particle Fraction
Choice of Cascade Impactors per USP

- Next Generation Impactor or Andersen Cascade Impactor most common
- Twin stage impinger is not listed in USP
What makes a good cascade impaction method?

- Mass Balance!!! (85-115%LC)
- Mouthpiece inserted correctly into throat
  - Don’t push in too far
  - Tight seals
  - Correct orientation
- Proper flow rate and no leaks
- Assembled correctly
Stage Coating (DPIs)

- Glycerin
- Silicone oil
- Uniform application
- Thin application
- Drug extraction
Critical Points for Method Development

- Good recovery
  - Wash volumes
  - Sonication/shaking of plates
  - Stage coating

- Correct tubing

- Concentrations on stages within linear range of standards

- Determine wall losses (ACI only)
  - Justify washing only plates (not plates + stages)

- Verify that the impactor is not overloaded (dripping/run off/ bounce onto lower stages), especially for nebulizers

- Flow rate for DPIs (based on device resistance)

- Electrostatic charge minimized

- Humidity requirements?
Spray Pattern: MDIs

- Non-compendial
- Characterize plume shape and density
- Impaction plate or laser sheet analysis
- Single actuation preferred
- Beginning lifestage only
- Two distances for PE
Spray Pattern: MDIs

Laser based system (Proveris Scientific)
Spray Pattern Method Optimization

- In order of importance for non-impaction systems
  - Distance(s) to laser sheet
  - Rate of data acquisition
  - Noise threshold
  - Spray duration for analysis
  - Lens aperture

- What makes a good method?
  - Percent area >5% (Proveris platform)
  - Variability on Dmax or Dmin <20-25%
Nasal Delivery Platforms

- Multi-dose Metered Spray
- Unit Dose Spray
- Bi-Dose Spray
- Pressurized Aerosol
- Gels
## Brazil PE Tests: Nasal Sprays

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<td>Dv50, Span B and E Two distances</td>
<td>No lifestage % &lt;10µm No distance requirement</td>
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Automated Actuation Systems

- Reduce operator induced subjectivity
- Actuation parameters relevant to patient use
- Expectation by FDA to utilize automated actuation (also mentioned in ANVISA Guidance)

- Bottle Booster from WM-Consulting
- SprayVIEW NSx from Proveris Scientific
- NSP VA from InnovaSystems
- NSP UA from InnovaSystems
- MightyRunt from InnovaSystems
<table>
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<th>Force (Kg)</th>
<th>Droplet Size as Measured by Laser Diffraction</th>
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<tr>
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<td>Dv50 (um)</td>
</tr>
<tr>
<td>3</td>
<td>50.12</td>
</tr>
<tr>
<td>4</td>
<td>43.90</td>
</tr>
<tr>
<td>5</td>
<td>40.86</td>
</tr>
<tr>
<td>6</td>
<td>39.31</td>
</tr>
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<td>7</td>
<td>37.37</td>
</tr>
<tr>
<td>8</td>
<td>36.66</td>
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Automated Actuation Systems

- Insertion of nasal spray or MDI is critical
  - Secure, no slippage
  - Maintain vertical orientation
  - Syringe based systems—stroke length doesn’t break flange

- Waste sprays (spray down)
  - Must use automated actuator
  - Account for the number of waste sprays in the protocol
Delivered Dose Uniformity: Nasal Spray

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Sample Preparation

:: Shaking

:: For PE
  - Follow RLD Package Insert

:: Establish consistent procedure

From Flonase OTC Instructions for Use
Sample Preparation

:: Repriming Sprays

- Number
- Frequency

**How to prime your VERAMYST Nasal Spray**

Priming helps to make sure you always get the same full dose of medicine. You need to prime VERAMYST Nasal Spray:

- before you use a new bottle for the first time.
- if you have not used your VERAMYST Nasal Spray for 30 days or longer.
- if the cap has been left off the bottle for 5 days or longer.
- if the device does not seem to be working right.

To prime VERAMYST Nasal Spray:

**Figure 1**

**Figure 2**

**Figure 3**
Delivered Dose Considerations

What makes a good method?

- 100% Label Claim (LC)
  - Need to verify assay value (determine in house or from client)
- Good recovery technique

For Release

- Acceptance criterion defined by Regulatory Guideline or Pharmacopeia

For Bioequivalence

- Population BE
Delivered Dose Uniformity

- For PE—single actuation, even though dose may be 2 sprays
- For USP—collect the dose, may use up to two sprays per collection

- For PE studies, delivered dose target is 100% label claim
- For PE, do not use the USP acceptance criteria
Droplet Size Distribution by Laser Diffraction

USP <601>

Light Diffraction Measurements USP <429>

PE

- 2 distances between spray tip and laser beam

97 Malvern Spraytec

Malvern Spraytec STP 2000
• Time history defined by the % transmission values using the Spraytec

• Data selected from stable phase
Droplet Size Distribution (DSD) By Laser Diffraction

- Volume diameter

Report

- $D_{v10}$, $D_{v50}$, $D_{v90}$
- Span
- % <10 um (USP)
- For PE: $Dv50$ and Span

Malvern 97 Spraytec with Proveris Scientific NSx-MS
DSD Method Optimization & Development

- In order of importance
  - Distance(s) to the laser beam
  - Stable phase selection
  - Filter and trigger
  - Rate of data acquisition—most data collected to date indicate that there is no real difference

- What makes a good method?
  - Dv50 with less than 10%CV (other parameters may vary more)
  - Well defined stable phase
Spray Pattern

- Characterize plume shape and density
- Impaction plate or laser sheet analysis
- Single actuation preferred
- Beginning lifestage only
- Distance to laser sheet
  - PE/BE: 2 distances
Spray Pattern Analysis

- \( D_{\text{max}} \)
- \( D_{\text{min}} \)
- Ovality Ratio
- Area (BE Studies)

Images captured with SprayVIEW NSP
Spray Pattern Method Optimization and Development

- In order of importance
  - Distance(s) to laser sheet
  - Rate of data acquisition
  - Noise threshold
  - Spray duration for analysis
  - Lens aperture

- What makes a good method?
  - Percent area >5%
  - Variability on Dmax or Dmin <20-25%
Approaches for Increasing Success for In Vitro BE

- Evaluate RLD and Test during method development
- Perform pre-screening studies
- Avoid the temptation to compare averages and standard deviations to judge equivalence
- Sample variance is factored into the PBE equation
Population Bioequivalence

- The comparison is made on average and variances at the same time.

- Why not use a T-test? A t-test demonstrates that there is a difference between two samples. If there is difference which is significant, the assumption for equivalence could be accepted but wrong.

- Here, we want to demonstrate equivalence. A small difference $\Theta$ is defined. If samples differ by less than $\Theta$, samples will be considered equivalent.
Population BE test

$$H1: \frac{(\mu_T - \mu_R)^2 + (\sigma_{TT}^2 - \sigma_{TR}^2)}{\max(\sigma_{TR}^2, \sigma_{T0}^2)} \leq \Theta_{BE}$$

$$\mu_T = \text{average of measurements on Test product}$$
$$\mu_P = \text{average of measurements on Reference product}$$
$$\sigma_{TT} = \text{total variance on Test product}$$
$$\sigma_{TR} = \text{total variance on Reference product}$$

$$\sigma_{T0} = \text{standard variance defined by FDA for spray tests}$$
$$\Theta_{BE} = \text{Limit of bioequivalence defined by FDA according to each test}$$

ANVISA follows Shao approach and also defines a value for $$\Theta_{BE}$$
Load and Reload

For PE: The *geometric averages* of the 30 results of the load test and 30 results of the reload test should be in the range of 95% - 105% of the labeled value.

How can range of 95-105% for load and reload be tighter than delivered dose criteria?

- Calculate a point estimate
- Based on geometric mean of all 30 results
Pre-BE Studies—Nasal Spray Study

- Investigate likely hood of a successful outcome

**KEY TEST METRICS**

- Innovator and Generic Pumps tested with Innovator formulation
- Hand study determined actuation parameters
- All units actuated using Proveris Scientific platform
- Droplet size (DSD) measured at beginning and end of unit life using a Malvern Spraytec
- Spray pattern (SP) measured using SprayVIEW
- Plume geometry (PG) measured using SprayVIEW
- Statistical analysis by population bioequivalence (PBE) and point estimates
IN VITRO BIOEQUIVALENCE: INNOVATOR VS GENERIC

RESULTS

- All results show as average of 15 bottles

### Average Spray Pattern Results

<table>
<thead>
<tr>
<th></th>
<th>Dmax (mm)</th>
<th>Dmin (mm)</th>
<th>Ovality Ratio</th>
<th>Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 cm</td>
<td>6 cm</td>
<td>3 cm</td>
<td>6 cm</td>
</tr>
<tr>
<td>Innovator</td>
<td>21.2</td>
<td>34.6</td>
<td>25.4</td>
<td>47.1</td>
</tr>
<tr>
<td>Generic</td>
<td>21.1</td>
<td>35.9</td>
<td>24.8</td>
<td>43.5</td>
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### Droplet Size Distribution - 3 cm

<table>
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<tr>
<th>Microns</th>
<th>Dv10</th>
<th>Dv50</th>
<th>Dv90</th>
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<tbody>
<tr>
<td>Innovator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td></td>
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### Droplet Size Distribution - 6 cm

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<th>Dv50</th>
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<tr>
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</tr>
<tr>
<td>Generic</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

### Spray Angle (°)

- Innovator: 51.0
- Generic: 52.0

### Plume Width (mm)

- Innovator: 28.9
- Generic: 29.3

### IN VITRO BIOEQUIVALENCE SUMMARY

<table>
<thead>
<tr>
<th></th>
<th>DSD - 3 cm</th>
<th>DSD - 6 cm</th>
<th>SP - 3 cm</th>
<th>SP - 6 cm</th>
<th>PG</th>
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<tbody>
<tr>
<td></td>
<td>Dv50 (µm)</td>
<td>Span</td>
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<td>Span</td>
<td>Ovality Ratio</td>
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<tr>
<td>Innovator</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Generic</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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Outcome of Population Bioequivalence (PBE) Statistics reported for Beginning of Life (BOL) and End of Life (EOL)
Thank you for your attention

Questions????