Understanding Regulatory Global Requirements for Nasal Drug Products

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April 8, 2016
AGENDA

- NDA vs ANDA
- Regulatory Approaches for Bioequivalence (BE)
- FDA Drug Specific Guidances
- FDA, EMA and ANVISA Pharmaceutical Equivalence (PE) Comparison
- Improving BE Outcomes
- Chemistry, Manufacture and Controls (CMC)
Regulatory Pathways-US Perspective

:: NDA: 505(b)(1)
  - Way most new drugs are approved
  - Full pre-clinical and clinical study

:: NDA: 505(b)(2)
  - New formulations of existing drugs
  - Relies on previous studies or references published information

:: ANDA: 505(j)
  - Generic drug submission
  - Same as the Reference Listed Drug (RLD)

:: OTC Switch
  - FDA approval required
  - Treated as an ANDA
  - No OTC monograph issued (yet)
Why 505(b)(2)?

- Faster route to market
- Branded generic—exclusivity
- Sales force needed

<table>
<thead>
<tr>
<th></th>
<th>DISCOVERY</th>
<th>NONCLINICAL RESEARCH</th>
<th>CLINICAL STUDIES</th>
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</thead>
<tbody>
<tr>
<td>505(B)(1)</td>
<td>2-5 YEARS</td>
<td>1-5 YEARS</td>
<td>8-15 YEARS</td>
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<tr>
<td>505(B)(2)</td>
<td>&lt;1-3 YEARS</td>
<td>&lt;1-2 YEARS</td>
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## 505(b)(2) vs. ANDA

<table>
<thead>
<tr>
<th>Test</th>
<th>505 (b) (2)</th>
<th>*ANDA</th>
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<tr>
<td>Scientific Studies</td>
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<td>Bioequivalence</td>
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<td>New Active Moiety</td>
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<td>New Chemical Entity (Ingredient)</td>
<td>Yes/No</td>
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<td>New Indication</td>
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<td>New Formulation</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>New Dosage Form or Strength</td>
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<td>No</td>
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<tr>
<td>Patented</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Market Exclusivity</td>
<td>Yes</td>
<td>No**</td>
</tr>
</tbody>
</table>

** Except against other generics. * Abbreviated New Drug Application (ANDA)
Global Regulatory Perspectives: Generics

- 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 recommends device designs be as close as possible in all critical dimensions to those of the reference product.
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

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

- Generic vs Hybrid
  - Generic establishes bioequivalence by PK
  - Hybrid established by PD, CE or other means
  - Many inhalation products are hybrids

- Prescribable vs Interchangeable
  - Prescribable determined at EU level
  - Interchangeable determined at National level
**EMI Step Wise Approach**

**Applied to Inhalation Products Only**
ANVISA Approach

Generic 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 vitro 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
FDA Nasal Spray BE Requirements

:: Locally Acting Solution
  - In vitro only

:: Systemically Acting Solution
  - New guidances for Sprix, NasalFent and Imitrex
  - In vivo: if not qualitatively (Q1) and quantitatively (Q2) the same
  
  OR

  - In vitro: Q1 and Q2

:: Suspensions
  - In vivo
    - Clinical endpoint to assess local delivery +
    - Clinical endpoint to assess systemic exposure
      OR
    - Clinical endpoint +
    - PK study for systemic exposure

  AND

  - In vitro

  - Particle size removed for mometasone
# In Vitro BE Statistical Analysis Per FDA Guidance

## Nasal Spray Example

<table>
<thead>
<tr>
<th>In Vitro Test</th>
<th>Statistical Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Actuation Content Uniformity</td>
<td>Population Bioequivalence (PBE)</td>
</tr>
<tr>
<td>• Drug mass per actuation</td>
<td></td>
</tr>
<tr>
<td>Droplet Size</td>
<td></td>
</tr>
<tr>
<td>• Dv50</td>
<td>PBE</td>
</tr>
<tr>
<td>• Span</td>
<td></td>
</tr>
<tr>
<td>Spray Pattern</td>
<td></td>
</tr>
<tr>
<td>• Ovality Ratio</td>
<td>PBE</td>
</tr>
<tr>
<td>• Area</td>
<td></td>
</tr>
<tr>
<td>Plume Geometry</td>
<td></td>
</tr>
<tr>
<td>• Width</td>
<td>Point Estimate</td>
</tr>
<tr>
<td>• Angle</td>
<td></td>
</tr>
<tr>
<td>Particle Size by Microscopy</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug in Small Particles by Cascade Impaction (Sprays)</td>
<td>Comparison of means by PBE</td>
</tr>
<tr>
<td>Prime Reprime</td>
<td>Point Estimate</td>
</tr>
</tbody>
</table>
ANDA Expectations (FDA)

- **Q and Q**

- **Q1 – Qualitative Sameness**
  - Active & inactive ingredient the same as Reference Label Drug (RLD)

- **Q2 – Quantitative Sameness**
  - Inactive ingredients ±5% RLD
Statistical Approach for IVBE (FDA)

- Applies to both Nasal and Inhalation!!

- Defined in the Budesonide Inhalation Suspension Draft Guidance (September 2012)
  - All FDA applications will be evaluated using this guidance
  - Ignore the examples in the 1999/2003 Nasal BE Drafts

- ANVISA requires PBE

- EMA PBE and/or ABE
# In Vitro BE Across Regulatory Bodies for Nasal Sprays

<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>Brazil (ANVISA)</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Droplet Size</td>
<td>Droplet Size</td>
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<tr>
<td>Single Actuation Content Uniformity</td>
<td>Single Actuation Content Uniformity</td>
<td>Other in vitro tests appear to be used</td>
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<tr>
<td>Spray Pattern</td>
<td>Spray Pattern</td>
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<tr>
<td>Prime Reprime</td>
<td>Prime Reprime</td>
<td></td>
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<tr>
<td>Particle Size</td>
<td>Number of Metered Doses</td>
<td></td>
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</tr>
<tr>
<td>Plume Geometry</td>
<td>Pump Delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particles &lt; 10µm</td>
<td></td>
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</tbody>
</table>
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
Pre-BE Studies—Nasal Spray Study

- Investigate likelihood 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>3 cm</th>
<th>6 cm</th>
<th>3 cm</th>
<th>6 cm</th>
<th>3 cm</th>
<th>6 cm</th>
<th>3 cm</th>
<th>6 cm</th>
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<tbody>
<tr>
<td><strong>Dmax (mm)</strong></td>
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<tr>
<td>Innovator</td>
<td>21.2</td>
<td>34.6</td>
<td>25.4</td>
<td>47.1</td>
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<td>1.364</td>
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<tr>
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<td>21.1</td>
<td>35.9</td>
<td>24.8</td>
<td>43.5</td>
<td>1.181</td>
<td>1.200</td>
<td>418.4</td>
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<td><strong>Dmin (mm)</strong></td>
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<tr>
<td>Innovator</td>
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<tr>
<td><strong>Area (mm²)</strong></td>
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</tbody>
</table>

### Droplet Size Distribution

- **DSD - 3 cm**
  - Innovator
  - Generic

- **DSD - 6 cm**
  - Innovator
  - Generic

### 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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<tr>
<td><strong>Dv50 (µm)</strong></td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td><strong>Span</strong></td>
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<td><strong>Plume Angle</strong></td>
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<td>Yes</td>
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</tbody>
</table>

Outcome of Population Bioequivalence (PBE) Statistics reported for Beginning of Life (BOL) and End of Life (EOL)
FDA Chemistry Manufacturing and Controls
Stability Studies

- Three registration batches required for both NDA and ANDA applications

- 24 to 36 month stability program

- Stability storage of drug product in multiple orientations, e.g. upright and inverted
  - Expands the scope of stability significantly

- Additional stability studies to assess foil overwrap, pouching or specialty packaging
FDA CMC Specifications for Nasal Sprays

- Appearance
- Identification
- Assay
- Impurities and degradation products
- Particulate matter
- Microbial limits
- Net content
- Leachables
- Weight loss on stability
- pH, osmolality, viscosity

- Pump delivery
- Spray content uniformity
- Spray pattern
- Plume geometry
- Droplet size distribution
- Particle size distribution

Release Testing

Stability

Support IND or NDA

Refer to CMC guidance—not all tests required on stability
One Time CMC Studies

- Cascade Impaction
  - If for BE, not a CMC study

- Robustness
  - Drop & Vibration Testing
  - Cleaning

- Temperature Cycling

- Photostability

- Prime/Reprime Studies
  - Two orientations required
  - If for BE, one orientation for BE, second for CMC purposes

Short stack Andersen Cascade Impactor
Amount of Small Particles by Cascade Impaction

- Not a measure of aerodynamic diameter
- Mass of “small droplets”
- FDA BE requirement
Lung Penetration Via the Nose?

No lung deposition was demonstrated following administration of radiolabeled saline by spray pumps.

Ventilation scan showing radioactive gas penetrating the lungs and nasal cavity.

Nasal spray scintigraph from a typical volunteer.
One Time CMC Studies

- Tail-off (Profiling)
- Effect of Dosing Orientation

Studies may include:
- Pump delivery
- Spray content uniformity
- Droplet size by laser diffraction

Example Tail-off Study Graph with Droplet Size Component
## Release Tests: Regulatory Differences

<table>
<thead>
<tr>
<th>Study</th>
<th>FDA</th>
<th>EMA/HC</th>
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<tbody>
<tr>
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<td>X</td>
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<tr>
<td>Plume Geometry</td>
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<td></td>
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<tr>
<td>Droplet Size</td>
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</tr>
</tbody>
</table>

Thank you for your attention

Questions????

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