Drug/Device Combination Products: Bioequivalence

• Three stories:
  – 1. The story of Nasal and Inhalation Product BE
  – 2. The story of the “Generic” Auto-Injector
  – 3. The story of User Interface Considerations
Bioequivalence of Locally Acting Orally Inhaled and Nasal Drug Products: Regulatory Histories and Milestones

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Approved Combination Product ANDAs (by Year)
Approved Combination Product ANDAs

Nasal

Inhalation

Transdermal Patch

Transdermal Metered

Injection, Prefilled
Orally Inhaled and Nasal Drug Products (OINDPs)

Nasal

• Nasal Spray (example)

Inhalation

• Metered Dose Inhalers (MDI)
• Dry Powder Inhalers (DPI)
• Nebulized Inhalation Products
Outline

• Introduce FDA’s rigorous regulatory standards for BE of OINDPs
  – Why do we recommend such a rigorous program for generic OINDPs?
  – What are elements included in FDA’s recommendation?
  – How does such recommendation support a generic product equally efficacious and equally safe as reference listed product?

• Updates about FDA’s recent nasal and inhalation product recommendation and approvals
Definition of a Generic Drug

A drug product that is **THERAPEUTICALLY EQUIVALENT** to reference listed drug product.
• Drug products are considered to be therapeutic equivalents when they are

   – PHARMACEUTICALLY EQUIVALENT

   – BIOEQUIVALENT
Pharmaceutical Equivalence

• Same active ingredient(s)
• Same dosage form
• Same route of administration
• Identical in strength or concentration
• Meet applicable quality standards
What is Bioequivalence (BE)?

- “The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study...” [21 Code of Federal Regulation (CFR) §320.1]

- No significant difference in the rate and extent when the drug becomes available at the site of drug action
Locally Acting Drugs

- Dose (e.g., Nasal & inhalation)
- Site of Activity
- Therapeutic Effect
- Clinical/PD Measurement
- Systemic Circulation
- Pharmacokinetic Measurement
Approaches to Determining BE (21 CFR 320.24)

- In vivo PK study comparison
- In vivo PD study comparison
- In vivo clinical study comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA
Orally Inhaled and Nasal Drug Products (OINDPs)

• OINDPs differ from the systemically acting traditional dosage forms in:

  – Most OINDPs are locally acting drugs exerting their therapeutic effects through reaching the sites of action, and their drug delivery does not directly rely on the systemic circulation
  
  – OINDPs are complex dosage forms which include a formulation integrated with a device, therefore performance depends on the interaction between the formulation and the delivery device

BE evaluation of OINDPs has been considered as one of the most challenging tasks
FDA’s Considerations for Generic Locally Acting Inhalation Products to Demonstrate Therapeutic Equivalence

- Equivalent In Vitro Performance
- Equivalent Systemic Exposure
- Equivalent Local Delivery

Device and Formulation Similarity
Scientific Rationale for Weight-of-Evidence Approach

Equivalent in vitro Performance → Device Similarity

Equivalent Efficacy

Systemic Toxicity

Equivalent Safety

Local Toxicity

Equivalent Local Delivery: Clinical Endpoint

Equivalent Systemic Exposure

Formulation Q1/Q2 Sameness

(confirmatory)
FDA BE recommendations for Locally Acting Nasal Suspension: Weight-of-evidence Approach

**Equivalent In Vitro Performance**
- Single Actuation Contents Through Container Life (SAC)
- Droplet Size Distribution by Laser Diffraction
- Drug in Small Particles/Droplet Size Distribution by Cascade Impactor
- Spray Pattern
- Plume Geometry
- Priming and Repriming

**Equivalent Systemic Exposure**
- Based on PK (AUC and Cmax) data (For nasal suspensions)

**Equivalent Local Delivery**
- Based on clinical endpoint study (For nasal suspensions)

**Device Similarity**
- Valve, pump, and actuator designs be as close as possible in all critical dimensions
- Metering chamber volumes and actuator orifice diameters be the same

**Formulation Sameness**
- Q1/Q2 the same
Could clinical endpoint study be waived?
Why clinical endpoint study is needed for most of the locally acting nasal suspensions?

• “In vivo (clinical endpoint) studies are recommended because of an inability at the present time to adequately characterize drug particles distribution (PSD) in aerosols and sprays”. ---General BA/BE Guidance for Locally Acting Nasal Drugs, 2003

• For most of the locally acting nasal spray suspensions, both API and inactive ingredients are suspending particles in drug products. The conventional method for particle size distribution measurement cannot differentiate API and excipient
If the API particle size distribution can be reliably measured in the drug product, the *in vivo* clinical endpoint studies are not necessary.

Comparable drug particle size distribution + Comparable solubility of drug substance → Comparable local dissolution → Comparable local availability → Comparable clinical effect
Advancement of technology

• Morphology Directed Raman Spectroscopy (MDRS) for particle size characterization:
  – Separate inactive ingredient particles from API through morphology filter
  – API Identification by Raman spectra

• FDA has approved a generic drug product utilizing this technology
## Generic NS ANDAs Approved by FDA

<table>
<thead>
<tr>
<th>Drug Product Name</th>
<th># of Applications Approved</th>
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<tbody>
<tr>
<td>Azelastine hydrochloride Nasal Spray</td>
<td>6</td>
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<tr>
<td>Budesonide Nasal Spray</td>
<td>1</td>
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<tr>
<td>Butorphanol tartrate Nasal Spray</td>
<td>3</td>
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<tr>
<td>Calcitonin salmon Nasal Spray</td>
<td>2</td>
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<tr>
<td>Cromolyn Nasal Spray</td>
<td>4 (2 discontinued)</td>
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<tr>
<td>Desmopressin Nasal Spray</td>
<td>4</td>
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<tr>
<td>Flunisolide Nasal Spray</td>
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</tr>
<tr>
<td>Fluticasone propionate Nasal Spray</td>
<td>4</td>
</tr>
<tr>
<td>Fluticasone propionate Nasal Spray - OTC</td>
<td>2</td>
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<tr>
<td>Ipratropium bromide Nasal Spray</td>
<td>8</td>
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<tr>
<td>Mometasone furoate Nasal Spray</td>
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<td>Olopatadine hydrochloride Nasal Spray</td>
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<tr>
<td>Sumatriptan Nasal Spray</td>
<td>1</td>
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<tr>
<td>Triamcinolone acetonide Nasal Spray</td>
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<tr>
<td>Tetrahydrozoline Nasal Spray</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>46</strong></td>
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* Data collected per Orange Book, Jan 2017
Conclusions

• Establishing bioequivalence (BE) of locally acting OINDPs is considered as one of the great challenges
• FDA has approved a number of generic OINDP combination products over the recent years
• FDA utilizes a weight-of-evidence approach to evaluate BE of locally acting OINDPs, taking into account:
  – Device and formulation
  – In vitro drug product performance
  – in vivo studies of local delivery and systemic exposure
• FDA embraces emerging technologies in approving OINDP combination products
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