Case Study 1: Pharmaceutical Development of EXUBERA®

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EXUBERA®

- Insulin human (rDNA origin) Inhalation Powder
- Re-usable Exubera® Inhaler
- 1 mg, 3 mg unit dose blisters
- Indications: Type 1 and Type 2 Diabetes Mellitus
EXUBERA®

Clear chamber: designed to hold aerosolized insulin before inhalation

Base: device provides energy required for dispersion of EXUBERA powder via air pump mechanism in the device base (no batteries required)

Insulin release unit: disperses powder from blister into chamber

Blisters: available in 1-mg (green) and 3-mg (blue) doses

Pharmaceutical Challenges in EXUBERA® Development

... relative to conventional inhalation products

... specific to insulin

Uniqueness presented challenges as well as opportunities!
Challenges Relative to Conventional Inhalation Products

- Systemic Delivery
- Importance of Particle Size
- Standard PK/PD studies are possible
  - BE, Variability, Dose Response, IV / IVc, Interaction Studies, Special Populations, Other Biopharm
- Defining the Relevant Performance Attributes
- Labeling / Label Claim
  - Contained Dose vs Emitted Dose vs Respirable Dose

<table>
<thead>
<tr>
<th>Fill Mass (mg powder)</th>
<th>Nominal Dose (mg insulin)</th>
<th>Emitted Dose (mg insulin)</th>
<th>Fine Particle Dose (mg insulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7</td>
<td>1.0</td>
<td>0.53</td>
<td>0.4</td>
</tr>
<tr>
<td>5.1</td>
<td>3.0</td>
<td>2.03</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Source: EXUBERA® US Package Insert

Challenges Specific to Insulin

- A new, non-invasive route of insulin administration
- Insulin dosing based on mg (not units)
  - Robust Education and Customer Care programs
- Performance benchmark against SC injection
  - Defining the unit doses
  - Performance comparisons in vivo and in vitro
- Biologic
- Stability
  - Opportunity for improvements over current insulin products
  - Refrigeration not required!
Insulin Stabilization Challenge

Insulin Formulation

- Dry powder
- High drug load: 60% insulin in a buffered sugar-based matrix.
- Stabilization approach: Maintain insulin in glassy state
  - Excipients selected to provide a glass transition temperature well above pharmaceutically relevant storage temperatures.
  - Exhibits a single $T_g$ (indicative of a single amorphous phase).
  - The high $T_g$ is maintained over the shelf life of the product and across a range of moisture content.
- Moisture content and its affect on glass transition temperature ($T_g$) was a critical parameter impacting chemical stability.
- Moisture Control challenges throughout the manufacturing process and for packaging design
Glass Transition Temperature

- $T_g$ decreases with increasing water content
- Spray dried powder water content is ~2% (w/w), consistent with a $T_g \approx 80^\circ C$.

Physical Form Stability

- No evidence of crystallization in insulin powder for inhalation upon moisture or thermal challenge

XRPD patterns after up to 88% RH for (A) 22.5, (B) 26, and (C) 28 hours
XRPD patterns before (A) and after (B) exposure to 150°C for 15 minutes
Spray Drying

Solution ⇝ Atomization ⇝ Drying ⇝ Powder Collection

Spray Drying enables production of homogenous particles of controlled size with:
- Low moisture
- High drug purity
- Small particle size (<5 μm)
- Non-critical excipient physical form

Typical Pharm
10 to 20μm

Micro-encapsulation
30 to 40μm

Food
50 to 100μm

Exubera®
<5 μm
Maintenance of Insulin Molecular Structure

- The spray-drying process does not affect the secondary structure of insulin, assuring pharmacological activity
- Techniques included Circular Dichroism, FTIR
- Quaternary/Oligomeric Structure: Insulin Monomer (HP-SEC, SDS-PAGE, DLS)

CD spectra for insulin in the formulation matrix before (blue), and after (green) spray drying, compared with ingoing insulin API (red).

Particle Morphology (SEM)

- Uniform, rugose morphology
- No effect on particle morphology before (left) and after (right) exposure to high humidity (75% RH, 25°C for 36 hours)
Process Scale-Up / Optimization

- DOE on process parameters to map knowledge space
- Design space / control space based on aerosol performance
- Each contour line represents a constant predicted value for FPD

Powder Filling

- Beyond capability of existing technology
- Design Challenges
  - Low density powders
  - Micro fill weights (1.7 mg and 5.1 mg)
  - High speed (>1500 fills/min)
  - Accuracy (~2% RSD)
  - Consistency
Fill Weight Control

![Graph showing fill weight control with sample number on the x-axis and fill mass (% of target weight) on the y-axis. Legend includes individual samples, mean limits, mean of individuals, and individual limits with RSD (%).]

Packaging Design

- Compact Package
  - Patient handling
  - Device interface
- Foil Forming, Filling, Sealing
  - Blister cavity design
  - Tooling and manufacturing scale up
  - Operation in ultra-low humidity environment
- Drug Product Protection
  - High moisture barrier

IPAC-RS Conference November 2006
Particle size: The optimal window for deposition

![Graph showing fractional deposition vs. particle size](image)

- Alveolar region
- Airways
- Mouth and throat


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Powder / Aerosol Particle Size Distribution

![Graph showing cumulative percent less than vs. particle size](image)

- High dispersibility
- Aerosol particle size broadly in line with spray dried powder.

Inhaler Challenges

- Reproducible powder extraction, deagglomeration and dispersion.
- Patient generated compressed air provides energy source
- Capable of aerosolizing relatively cohesive powders
- Suitable for delivering small powder masses (1-10 mg)
- Separate breathing maneuver from aerosol generation
- Chamber allows for patient feedback and dose delivery
- Designed for long-term repeated use

Inhaler Design
Inhaler Design

Device Challenges

- Balancing drug product requirements against device requirements
  - Heavy reliance on risk based approach in Pharm Dev

- Device world embraces continuous improvement
  - Educating device design and manufacturing on type/timing of acceptable changes based on development stage, given regulated as drug product
  - Use of comparability protocol for known changes
  - Building in flexibility as appropriate into submission
Drug + Inhaler System Challenges

- Elaborate performance characterization programs
  - Risk based approach: comprehensive FMEA’s
  - Inhaler Design Verification Testing
  - Testing to failure
  - Clinical experience
  - Use-Life simulations
  - FDA Draft MDI/DPI Guidance (…and beyond)
- Output contributed to:
  - Comprehensive product understanding
  - Assessment of impact on safety/efficacy
  - Instructions in labeling/medication guide; Customer Care

Performance Characterization

- Robust performance (aerosol dose delivery and mechanical integrity) demonstrated over a range of patient usage scenarios
- Environmental (temperature, humidity, altitude)
- Usage reproducibility
  - Independence from inhalation flow rate (10-60 lpm) and volume (400-1400 ml)
  - No priming effect
  - Independence of usage angle
  - Rugged performance with long term use
Inhaler Flow Rate: Little Impact on Aerosol Performance

Characterization Studies (FDA MDI / DPI Draft Guidance)

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<tr>
<th>Section IVB Recommendation</th>
<th>Studies Conducted/ Relevant Data</th>
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<td>Determination of Appropriate Storage</td>
<td>Stability Studies</td>
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<tr>
<td>Condition</td>
<td>DVT studies</td>
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<tr>
<td>Stability of Primary (Unprotected) Package</td>
<td>Stability Studies</td>
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<tr>
<td>Effect of Varying Flow Rates</td>
<td>Square Wave flow rate study</td>
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<td>Pediatric inhalation profile study</td>
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<tr>
<td>Effect of Storage on Particle Size</td>
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<td>Distribution</td>
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<td>Dose Build-Up and Flow Resistance</td>
<td>Use-life studies</td>
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<tr>
<td></td>
<td>Cleaning frequency</td>
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<td>Mass Distribution</td>
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<tr>
<td>Effect of Orientation</td>
<td>Dosing orientation</td>
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<td>Drop and vibration testing</td>
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<tr>
<td>In-Vitro Dose Proportionality</td>
<td>Biopharmaceutics studies</td>
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<tr>
<td>Effect of Patient Use</td>
<td>Planned Returns</td>
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<td>Product Investigation Process</td>
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<tr>
<td>Effect of Moisture</td>
<td>Excursion studies</td>
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<td>Use life studies</td>
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<td>Photostability</td>
<td>Stability study</td>
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<td>Profiling of Doses Near Device Exhaustion</td>
<td>Not applicable since this product is not a DPI</td>
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<td>Fill Weight</td>
<td>reservoir product</td>
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<td>Priming</td>
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<td>Design Verification Testing</td>
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<td>Accelerated Patient Use Simulation</td>
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<td>Cleaning Instructions</td>
<td>Cleaning Frequency</td>
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<td>Cleaning Effectiveness</td>
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<td>Cleaning Detergents</td>
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<td>Microbial Inoculation Study</td>
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Drug + Inhaler System Challenges

- Extended-use inhaler: high bar for durability
  - Unique patient-use simulations
  - Extensive patient-use evaluation

- Findings from clinical experience enabled:
  - Early input for robustness improvements
  - Optimization and “validation” in vitro tests

Inhaler Robustness to Long-Term Use

- Clinical Retrievals (427 Inhalers)
- Accelerated Patient Use Simulation (13 inhalers)
Additional CMC Challenges

• Release Approach
  – Blisters; Inhalers
  – What are the reference standards?
  – (FDA helped to define)

• Controls and Acceptance Criteria
  – Deep Product and Process understanding was critical
  – QbD, Design Space concepts (many variables, interactions)
  – Clinical experience
  – Test methods
  – (FDA helped to define)

EXUBERA® (insulin human [rDNA origin]) Inhalation Powder

• Insulin naturally absorbed by the lungs without enhancers
• Dry powder insulin stable at room temperature
• Ideal particle size for systemic absorption via the lung
• Packaging system protects formulation from moisture
• Robust delivery device enables dosing as reliable as injections
Acknowledgements

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... and many, many more

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