

Development of Inhalation Products for Systemic Applications: Regulatory Challenges

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Outline of Presentation

- Introduction
- Regulatory Considerations
- Pulmonary Safety
 - Exubera (insulin human) Inhalation Powder example
- Additional Clinical Considerations
 - Exubera (insulin human) Inhalation Powder example
- Remaining Questions

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Introduction

- Pulmonary route used for systemic delivery for years
 - Anesthesia
 - Nicotine
- Pulmonary route of administration for systemic therapy is undergoing intense research and development
- Various indications and stages of development
 - Diabetes
 - Insulin
 - Migraine headaches
 - DHE (www.mappharma.com/News/Press/090506.asp)
 - Erectile dysfunction
 - VR004 (www.vectura.com/productPipeline/sexualdysfunction.asp)
 - Osteoporosis
 - PTH (www.zelostherapeutics.com/httpdocs/media/09212006.html)

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Introduction

Rationale for Pulmonary Route of Administration

- **Extensive surface area available for absorption**
 - **Dense capillary network**
 - **Minimal barrier between alveoli and bloodstream**
 - **Large capacity for solute exchange**
- **Potential for rapid onset of action**
- **Avoids issues related to**
 - **Gastric enzymes, pH, emptying time**
 - **First pass metabolism**
- **Non-invasive**

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Regulatory Considerations

- **Drug-device combination**
 - Office of Combination Products
 - Center for Drug Evaluation and Research (CDER)
 - Center for Devices and Radiological Health (CDRH)
 - Complicated device
 - Electronic components
 - Nebulizer
- **Specific considerations related to each discipline**
 - Pharmacology/Toxicology
 - CMC
 - Clinical
- **Potential dual division review**
 - Primary division
 - Pulmonary and Allergy Division



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Regulatory Considerations Pharmacology/Toxicology

- **Characterization of systemic toxicity**
- **Inhalation toxicology studies**
 - Local toxicity
- **Leachables**
- **Extractables**



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Regulatory Toxicology and Pharmacology 1997 (25): 189-193

Regulatory Considerations CMC

- Dose content uniformity
- Particle size distribution
- Foreign particulates
 - Plastic
 - Device components
 - Manufacturing
- Leachables
- Extractables

Guidance for Industry: MDI and DPI Drug Products

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Regulatory Considerations CMC

- Durability
 - In use
 - Drop testing
 - Shipping effects
- Specifications
- Dose indicator

Guidance for Industry: MDI and DPI Drug Products

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Regulatory Considerations Clinical

- **Pulmonary safety**
- **Unique issues related to particular drug substance**
 - **Hemodynamic alterations**
 - **Growth factor**
- **Immunogenicity**
 - **Proteins and large molecules**
- **Therapeutic index**
- **Patient use – device performance**



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Regulatory Considerations Clinical

- **Coexisting lung disease**
- **Smoking**
- **Upper respiratory infection**
- **Other inhaled medications**



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Challenges of Assessing Pulmonary Safety


- **Novel concept**
 - **Monitoring**
 - **Number of subjects**
 - **Length of follow up**
 - **Need for control group**
- **Effect of underlying disease on pulmonary function**
 - **e.g. diabetes and pulmonary microangiopathy ***
- **Reversibility**

*Am J Med. 2005 Mar; 118(3): 205-211

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Considerations for Assessment of Pulmonary Safety

- **Respiratory adverse events**
- **Pulmonary function**
 - **Spirometry**
 - **Diffusing capacity**
 - **Lung volumes**
- **Imaging**
- **Bronchoscopy with biopsy**
- **Reversibility**

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Example of Pulmonary Safety Program

- **Exubera (insulin human [rDNA origin])
Inhalation Powder**
 - **Blisters containing human insulin inhalation powder**
- **Approved January 27, 2006**
- **Treatment of adult patients with diabetes for control of hyperglycemia**
- **Endocrine Metabolic Drugs Advisory Committee**
 - **September 2005**
 - **Pulmonary safety discussion**

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Example of Pulmonary Safety Program Exubera Inhalation Powder

- Two year controlled pulmonary safety data
 - Spirometry, lung volumes, diffusing capacity
 - Type 1 and type 2 diabetics
 - Reversibility

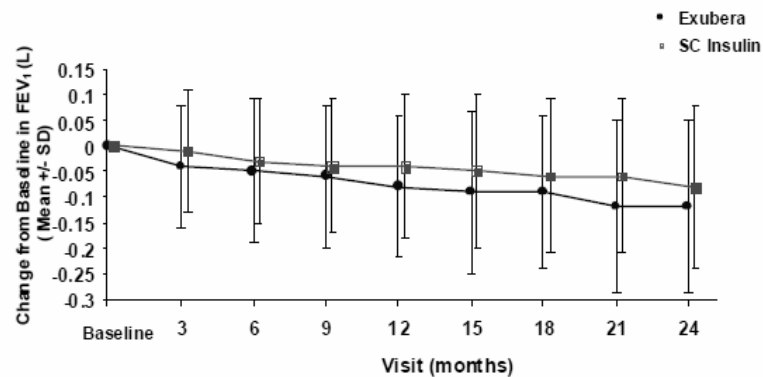
- High resolution computed tomography
 - Two year data in subset of patients

- Respiratory adverse events

http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4169S1_00_Slide-Index.htm

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Pulmonary Safety - Exubera Inhalation Powder Change from Baseline FEV₁ (L) in Type 1 Diabetes (Mean +/- SD)

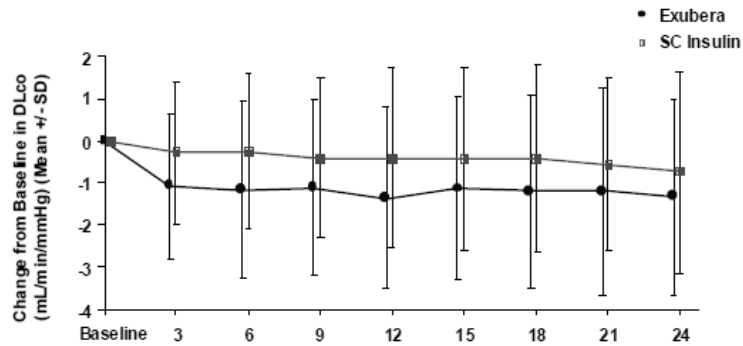


Exubera N:	282	277	260	247	240	235	226	217	208
SC N:	280	263	273	264	259	250	230	224	216


Exubera (insulin human [rDNA origin]) Inhalation Powder Package Insert

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Pulmonary Safety - Exubera Inhalation Powder Change from Baseline DL_{CO} in Type 1 Diabetes (Mean +/- SD)



	Baseline	3	6	9	12	15	18	21	24
Exubera N:	280	276	260	246	239	234	226	216	206
SC N:	282	264	273	266	257	249	230	224	216


Exubera (insulin human [rDNA origin]) Inhalation Powder Package Insert
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Additional Clinical Considerations Exubera Inhalation Powder

- **Effect of smoking**
 - PK/PD studies
 - Increased insulin absorption and exposure

- **Coexisting lung disease**
 - Dedicated 1 year studies in patients with COPD and asthma

- **Immunogenicity**
 - Insulin antibodies monitored
 - Relationship to pulmonary function, efficacy, AEs

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Additional Clinical Considerations - Labeling Exubera Inhalation Powder

- **Contraindications**
 - Patients who smoke
 - Patients with unstable or poorly controlled lung disease

- **Warnings**
 - All patients should have pulmonary function assessed prior to initiating therapy
 - Use in patients with underlying lung disease not recommended

- **Precautions**
 - Assess spirometry prior to initiation and consider DLCO
 - Assess spirometry after the 1st 6 months, annually thereafter
 - If FEV₁ decline \geq 20% from baseline, repeat PFTs
 - If confirmed, discontinue medication

Exubera (insulin human [rDNA origin]) Inhalation Powder Package Insert

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Additional Clinical Considerations Exubera Inhalation Powder

- **All pulmonary safety questions not answered**
- **Post-marketing commitments to further assess safety**
 - **5 year controlled trial in 5000 patients with diabetes**
 - **Pulmonary function**
 - **Completion of two ongoing studies in type 1 and type 2 diabetics to obtain PFT data over 5-7 years cumulative exposure**
 - **Completion of two ongoing studies in diabetics with COPD and asthma**

<http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>



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Remaining Questions

- Has the approval of Exubera made the regulatory pathway for other inhaled medications for systemic therapy easier?
 - Has the approval of Exubera changed the amount of pulmonary safety data needed for other inhaled insulins or other inhaled medications for systemic therapy?
- How much pulmonary safety data is needed for medications with intermittent use?
- Will the effects of smoking, coexisting lung disease, upper respiratory infection need to be investigated for each new product?

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Sources of Information

- *Regulatory Toxicology and Pharmacology* 1997 (25): 189-193
- **Guidance for Industry: Metered Dose Inhaler and Dry Powder Inhaler Drug Products**
- **Transcript from Endocrine-Metabolic Drugs Advisory Committee Meeting on September 8, 2005**
 - www.fda.gov/ohrms/dockets/ac/cder05.html#EndocrinologicMetabolic

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