Development of Inhalation Products for Systemic Applications: Regulatory Challenges

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• I do not have any financial interest or conflict of interest with any pharmaceutical company.
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

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)
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

Regulatory Considerations
Pharmacology/Toxicology

- Characterization of systemic toxicity

- Inhalation toxicology studies
  - Local toxicity

- Leachables

- Extractables

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
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

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

Considerations for Assessment of Pulmonary Safety

- Respiratory adverse events

- Pulmonary function
  - Spirometry
  - Diffusing capacity
  - Lung volumes

- Imaging

- Bronchoscopy with biopsy

- Reversibility

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

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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

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 ≥ 20% from baseline, repeat PFTs
      – If confirmed, discontinue medication

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

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