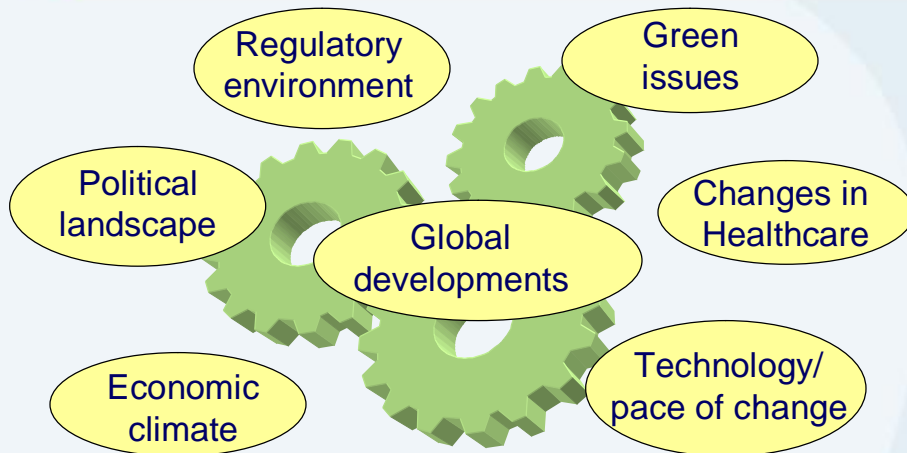




Future Opportunities in Orally Inhaled and Nasal Drug Product Development

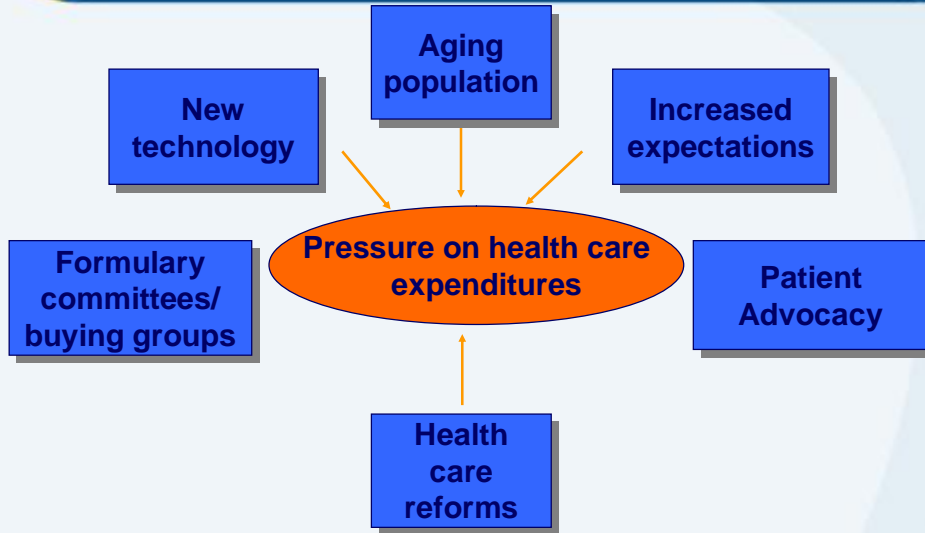
Paul Huckle, Ph.D.,
Senior Vice-President, Global Regulatory Affairs,
GlaxoSmithKline
September 24, 2008

Challenges for Development of Orally Inhaled and Nasal Drug Products



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A Changing Healthcare Environment

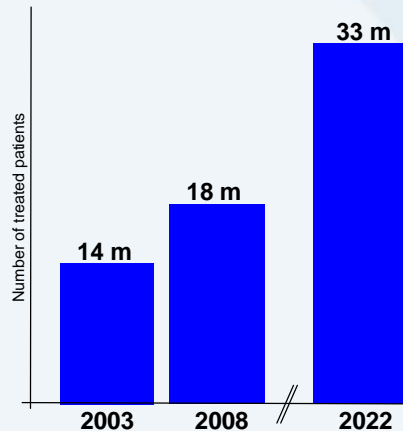


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An Increasing Need for COPD Treatments

- Number of treated patients set to nearly double by 2022
 - Increased Government focus globally
 - Prevalence increasing and physician diagnosis and management improving
- COPD will become the third leading cause of death worldwide by 2030 (WHO)
- Unmet need continues to be high across all major parameters
 - Lung Function, Quality of Life, Symptom control, Exacerbations management and Disease progression / Survival
 - Compliance
- Inhaled therapies expected to dominate until at least 2015
 - 2-3 oral therapies expected 2015 onwards

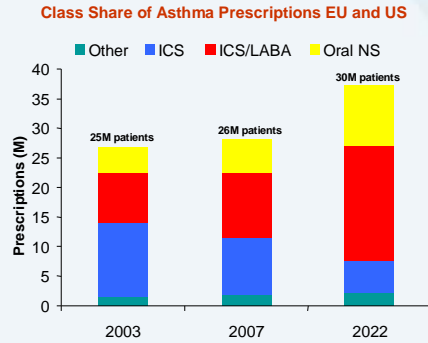
Treated COPD patients US & EU



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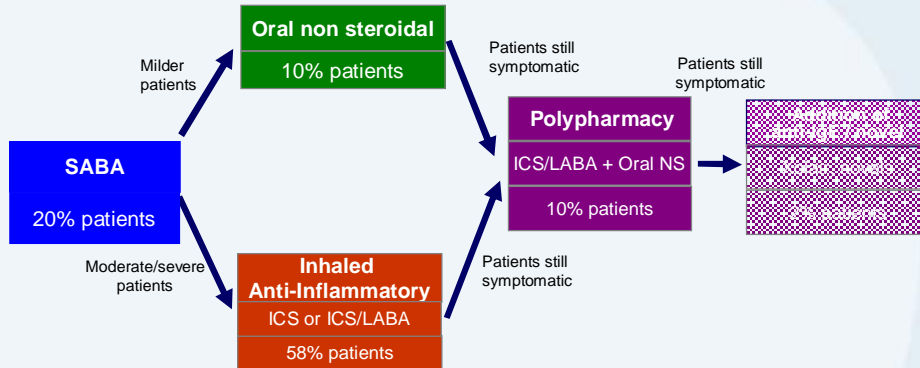
An Increasing Need for Asthma Treatments

- Asthma is under-diagnosed and under-treated, and is the most common chronic disease among children.
- Estimated 300 million people suffer from asthma and 255 000 people died of asthma in 2005 (WHO).
- There remains a significant unmet need.
- Current treatment pathway for Asthma still dominated by inhaled therapies



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Current treatment pathways for Asthma are dominated by inhaled therapies



Patients numbers are US and EU

Source: Adelphi DSP 7, 2007

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Developments in Cystic Fibrosis Treatment

Class	Developments
Anti-infectives	<ul style="list-style-type: none"> ■ Improvements in time to take medication (e.g. Tobramycin formulated as inhaled medication (Tobi), 2 min.) ■ New drugs in the class (e.g. Aztreonam, nebulized)
Mucolytic agents	<ul style="list-style-type: none"> ■ New drugs in the class, e.g.: <ul style="list-style-type: none"> – Bronchitol (hyperosmolar agent, inhaled) – Aerolytic (trypsin inhibitor, nebulized); – VR496 (heparin, inhaled)
Pancreatic enzyme supplements	<ul style="list-style-type: none"> ■ Potential new products
New anti-inflammatory agents	<ul style="list-style-type: none"> ■ New drugs launched ■ Benefits - reduction in exacerbations, improved lung function and Quality of Life
Therapies addressing CFTR malfunction	<ul style="list-style-type: none"> ■ New drugs, e.g.: <ul style="list-style-type: none"> – VX-770 (CFTR potentiator, oral) – VX-809 (CFTR corrector, oral) ■ Therapies addressing the basic defect in cystic fibrosis

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Endpoints key to successful drug development

- Traditional
 - FEV1; PEF; microbiological; Other non-respiratory
- Novel Endpoints
 - Objective assessment: e.g. imaging
 - Biomarkers e.g. sputum eosinophils, exhaled nitric oxide, DNA
 - Improved, validated PROs applicable for paediatrics
 - GSK ECLIPSE study (COPD) – designed to define the parameters that predict disease progression
- Can novel clinical endpoints be linked to critical quality attributes?
- Payers Demanding Outcome Studies (i.e., Reduction Exacerbation, Hospitalizations, Survival)
 - Large – Thousands of Subjects
 - Lengthy – Years

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Patient Factors

- Annex to ICH Q8: “In all cases, the product should be designed to meet patients’ needs and the intended product performance.”
- Factors to be considered in new OINDP development:
 - Provide safe and effective treatment
 - Easy to use and unobtrusive vs complex
 - Incorporate patient and physician feedback
 - Robust and reliable through patient use and miss-use
 - Add-ons: Breath actuated, Dose indicator (counter), etc.
 - Inexpensive
 - Ease of access by patient
 - Environmentally responsible, etc

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Regulatory Focus - Quality

- OINDP are being developed in an evolving regulatory environment:
 - ICH Q8, Q9, Q10 ‘Quality should be built in by design.’
 - FDA initiative for cGMPs for the 21st Century, etc
- Focus on product knowledge, good science and enhanced process understanding.
 - Knowledge rich submissions
 - Prior knowledge
 - Risk based approaches
 - Multivariate analyses
 - Increased understanding of what matters for quality, efficacy and safety
- Lifecycle approach to maintaining product is understanding.
- Appropriate regulatory relief based on understanding and control.

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Quality links to Safety and Efficacy

- Inhaled route of administration eliminates the potential for poor absorption and/or high metabolism in the gastrointestinal tract and it eliminates first-pass losses in the liver.
- What is the link between in vivo and in vitro performance?
- What are appropriate markers for topically acting drugs? FEV1?
- What is the appropriate particle size distribution of the delivered dose? Asthma? COPD? Systemic?

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Dry Powder Inhaler Innovation



Single dose
Pre-filled capsules
e.g. Rotahaler,
Spinhaler



Multi-dose
Pre-filled blisters
e.g. Diskhaler



Multi-dose
Pre-filled blisters
e.g. Diskus

Multi-dose
Reservoir
e.g. Turbuhaler

?

What next?

1960s to now – growing complexity and innovation

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Innovation – Pfizer's Exubera®

- Exubera (Inhalation Powder)
 - Novel inhaler device
 - Alternative to injecting insulin.
 - Reusable, manually operated, pneumatically powered, dried powder delivery system for unit dose blisters containing insulin spray dried powder.
- Regulatory approval 2006 (EU & US 2006) - a non-invasive treatment of diabetes.
- Product was not a commercial success.
- Withdrawal from market announced in October 2007.
- However, successful technical approach to a pulmonary delivery system for insulin.



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Innovation – MDI Dose Counter

- 1995 University of Michigan Study:
 - > 50% patients unaware of number of actuations in their canister
 - 92% of patients did not track the number of actuations used.
 - patients may extend the use of their meter-dose inhalers beyond the specified maximum number of actuations
 - Hence need for a dose counter
- Guidance for Industry 'Integration of Dose-Counting Mechanisms into MDI Drug Products', March 2003.
- Ventolin® HFA (albuterol sulfate HFA inhalation aerosol) - the first US MDI with built-in dose counter technology – FDA approved 2006
- Alvesco® (ciclesonide) Inhalation Aerosol including integral Trudell AEROCOUNT® Dose Indicator - FDA approved 2008

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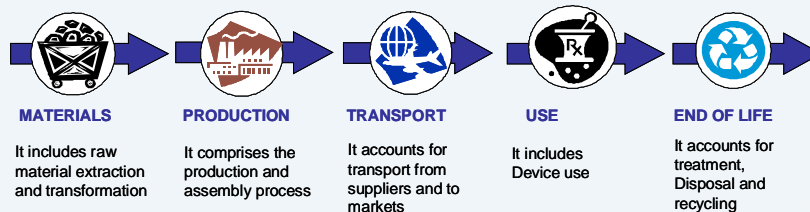
Innovation for OINDP

- PowderHale® (Vectura)
 - DPI in development, e.g. VR776 Aspirair® for premature ejaculation and VR004 Aspirair® for erectile dysfunction (systemic)
 - Using PowderHale® technology, designed to allow aerosolised drug particles to achieve high lung penetration with low dose variability
- Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim)
 - Solution for Inhalation, e.g. Berodual® Respimat®
 - High lung deposition and low mouth/throat deposition independent of inspiratory flow, together with ease and convenience of use
- Conix One Inhaler (Cambridge Consultants)
 - based on a novel 'reverse flow cyclone' and contains no moving parts or propellants designed specifically for vaccines and certain medications

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Environmental Impact of Delivery Devices

- GSK Pilot Program for Delivery Device Recycling
- Develop the tools and experience to assess the environmental life cycle impacts of products.
- Evaluate devices for opportunities to reduce their environmental footprint



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Conclusions

- COPD, asthma and CF are examples of diseases with an unmet medical need for which OINDP are at forefront of treatment.
- Other disease areas have been shown to be treatable by OINDP, e.g. migraine.
- Greater understanding of the links between control strategy and in vivo markers may allow development of control strategies appropriate to the route of administration and the disease being treated.
- Encouragement by regulators of innovation and continuous improvement by manufacturers is essential.