Comparison of OIP Experiences in Different Markets

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Any views expressed or implied by the contents of this presentation are based on my own thoughts.

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Developing OIPs In Different Markets: A Worthwhile Goal

- WHO predicts that COPD will become the third leading cause of death worldwide by 2030.
- 24 million adults over the age of 40 in India have COPD. (Source: Datamonitor)
- There are an estimated 350 million smokers in China, smoking a total of 2.0 trillion cigarettes per year. (Zhang H, Cai B. The impact of tobacco on lung health in China. Respirology 2003;8:17–21)
Asthma/COPD Market Overview (G7)

COPD Market is Very Commercially Attractive Market based on Growth

Epidemiology, diagnosis and treated rates for the major markets (US, EU5, Japan)

- Asthma Prevalence, Dx, and Tx Growth in 7 Major Markets
  - 2009: 47.4M
  - 2019: 49.0M
  - 2009: 47.4M
  - 2019: 49.0M

- COPD Prevalence, Dx, and Tx Growth in 7 Major Markets
  - 2009: 66.1M
  - 2019: 77.3M
  - 2009: 66.1M
  - 2019: 77.3M

- Asthma growth is ~3% but represents significant opportunity as ~2/3 of patients are treated

- An aging population yields a ~17% increase in prevalence of COPD by 2019

- New therapies will raise treatment rates in COPD from 25% in 2009 to 29% in 2019, an increase of ~6M treated patients

- Conservative: Still a huge opportunity to further increase diagnosis / treatment rates

© 2010 Decision Resources

G7 Market Size ($ Billions)

- 2009: $22B
  - Asthma $14B
  - COPD $8B
- 2019: $26B
  - Asthma $13B
  - COPD $13B
Development Of OIP's Is Commercially Attractive

- Asthma and COPD represent $36B (88%) of the global respiratory market
- Global respiratory market growth is projected at 2.5% CAGR through 2018
- Products vary by the drug component, formulation, and inhalation delivery device

Global Respiratory Market – 2012
Total = $40.9B, 6.5% of total Rx sales

- $36.0
- $3.6
- $0.6
- $0.8

Source: IMS MIDAS data for period ending 12/12
The Challenge: Many Different Mountains To Climb
Multi-Faceted & Sometimes Conflicting Requirements To Meet Specific Market Needs

**Clinical**
- Regional & National differences in medical practices and preferences
- Complexity & cost of combination product trials
  - Differing requirements for pk & pd endpoints
  - Differing requirements for paediatric approval
  - Differing requirements for maintenance claims

**Market Preferences**
- Effective demonstration of value
- Demonstration of substitutability
- Patient delivery preference
- Pricing & reimbursement

**Regulatory**
- Different philosophies driving different requirements. (e.g. US vs. EU)
- Many ROW requirements still in development and emergent
- Lack of harmonised requirements – regional and national variations
- Drug-device combinations – multiple overlapping requirements

**Delivery Device**
- Device type/market preference/cost of development
- Device improvements: Cost-benefit of additional features
- IP landscape/freedom to operate – national differences in coverage
- Device reg. requirements: generic vs. NCE

**Product Formulation**
- Formulation options – differences in acceptable materials/levels
- IP freedom to operate – national differences in coverage
- Scale up & stability requirements
- Site of manufacture vs. market access

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Global Coverage is & Will Continue To Be Important

Many companies aim to develop a portfolio of brand and/or generic products for the global market

- Ideally using a single world-wide development program for each product
  - More timely access for patients
  - Makes best use of company resources
- Regulators expect global development programs to encompass their individual requirements.

The Global Asthma & COPD Market: Predicted Market Shares (%) by Region, 2017

Source: visiongain 2013
Market Preference For Different Delivery Systems Is Also Important

Inhalation Drug Delivery Market Share by Delivery System Type (2008)

Source: IMS Health

Source : IMS Health

% Sales split per market

% Volume split per market

Source: IMS MIDAS data Jan 14
Emerging Markets Have Very Different Needs

David Howlett (PharmaDelivery Solutions Ltd, UK) presentation at DDL23, Dec 2012, Edinburgh

Typical emerging market split of inhalation products by active

- Salbutamol
- Beclomethasone
- Beclomethasone + Salbutamol
- Budesonide
- Sodium Cromoglycate
- Ipratropium + Salbutamol
- Fluticasone
- Budesonide + Formoterol
- Formoterol
- Ipratropium
- Salmeterol
- Salmeterol + Fluticasone
Choice: How Much Is Driven By Patient Need?

- Patients, Physicians, Payer's & Regulators are faced with a variety of differing drugs & delivery formats.

Off the team
By far the biggest name to lose coverage from Glaxo's product roster is its blockbuster Advair Diskus inhalation device, used by patients suffering from chronic obstructive pulmonary disorder and severe asthma, which is being dropped by Express Scripts on Jan. 1. As part of an unprecedented move, Express Scripts is moving Advair, along with several other major branded medications, to the "Not Covered" category on its preferred drug formulary, citing high costs disproportional to clinical benefit compared to other similar inhalation products.

UK - NICE: “No device should be excluded on grounds of cost effectiveness; however, when more than one device is felt to satisfy the considerations...the device with the lowest overall cost should be chosen.”

Market Preference & Payer Pressures

• Symbicort – **Different** devices by market
  – US: pMDI sales of $1.5Billion
  – EU: Turbohaler DPI sales of $1.4Billion
    - IMS : Nov13

• Advair – **Choice of devices in each markets**
  - US: pMDI sales of $393Million
  - US: Diskus DPI sales of $4.9Billion
    - IMS : Nov13
Meeting Regulatory Expectations

• **What is in the guidelines & which one applies?**
  – >20 regulatory guidelines on inhaled products including US, EU, Canada, Australia, Turkey, Brazil.
  – NCEs and generics, monotherapies and combinations, devices, clinical and CMC requirements.
  – Draft and final versions

• **What is required by other countries?**
  – Will they align with US or EU approach?
  – Uncertain timelines hampers development

• **Can I conduct one development programme that fits all territories?**
  - Regional clinical, CMC, device development requirements.
  - Regional safety issues.
  - Individual member state preferences…..

• **What Registration strategy?**
  – US: 505b(2) or 505(j); EU: NCE, Generic or Hybrid.
  – How do I file my generic when the approved indications differ across EU states?
  – Who has respiratory expertise?
<table>
<thead>
<tr>
<th>Region</th>
<th>Study Duration</th>
<th>Placebo Controlled</th>
<th>Active Comparator</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>3 months minimum for bronchodilator indication</td>
<td>Not mandated Case-by-case decision.</td>
<td>May not be required</td>
<td>FEV1 (to improve airflow obstruction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dose response studies to be conducted in the most relevant sensitive population.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CHMP Guideline: Required for assay sensitivity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>But... some countries will not permit inclusion of placebo on ethical grounds.</td>
</tr>
<tr>
<td></td>
<td>6 months minimum for bronchodilator Indication</td>
<td>CHMP Guideline: Required for assay sensitivity.</td>
<td>Required by some countries</td>
<td>Co-primary endpoints of FEV1 + outcomes endpoints such as SGRQ or exacerbations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>But....some countries have individual primary endpoint requirements......</td>
</tr>
<tr>
<td>Country/Region</td>
<td>In Vitro Data Only Acceptable</td>
<td>PK Equivalence Acceptable</td>
<td>Weight of Evidence Required: In Vitro + PK + Clinical Safety &amp; Efficacy</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
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<td>-------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>US*</td>
<td>No</td>
<td>No</td>
<td>Required</td>
<td>Clinical Equivalence Study required. Dose response does not need to be demonstrated.</td>
</tr>
<tr>
<td>EU</td>
<td>Yes</td>
<td>Yes</td>
<td>Only required if PK not equivalent</td>
<td>No consensus on design of clinical studies should PK equivalence fail. Charcoal block required in PK studies</td>
</tr>
<tr>
<td>Canada</td>
<td>No</td>
<td>No</td>
<td>Required</td>
<td>Is Dose Response still required?</td>
</tr>
<tr>
<td>Australia</td>
<td>Yes</td>
<td>Yes</td>
<td>Only required if PK not equivalent</td>
<td>Have adopted EU CHMP guideline. Requires demonstration that local product = EU marketed product.</td>
</tr>
<tr>
<td>Brazil</td>
<td>No</td>
<td>Yes</td>
<td>Only required if PK not equivalent</td>
<td>Guidelines in preparation.</td>
</tr>
<tr>
<td>Turkey</td>
<td>No?</td>
<td>TBD</td>
<td>TBD</td>
<td>Guideline recently released requires clarification.</td>
</tr>
</tbody>
</table>

* Fluticasone/Salmeterol combination guidance used for comparison
Regulatory Requirements

Different approaches for generic approval in different regions

**US:** Device Switchability is required for ANDA
- Same energy source, comparable basic external operating procedure(s), Same metering principle, Dose counter, Comparable device resistance, Same number of doses, Similar size and shape, “Closed” device if RLD is a “closed” device.

**EU:** Device Switchability is NOT required for “generic”
- Determined by separate body after regulatory approval (majority of countries)

Respiratory Generic in the EU are treated as hybrid applications even if same device & in vitro only equivalent!

EWP comment: Orally inhaled products are definitely not “generics” but “hybrids”. Therapeutic equivalence testing in OIPs is a stepwise approach. The simple bridging to the bioequivalence model is mostly not sufficient. Due to the specialities of this administration route all influencing factors have to be considered and addressed in the development plan.
Guidance Is Evolving

Committee for Medicinal Products for Human Use (CHMP)

Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents

London, 22 January 2009
Doc. Ref. CPMP/EWP/4151/00 Rev. 1
Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

Active ingredient: Fluticasone Propionate; Salmeterol Xinafoate

Form/Route: Powder/Inhalation

Recommended studies: In Vitro and In Vivo Studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing fluticasone propionate and salmeterol xinafoate.
**In Vitro Equivalence requirements**

<table>
<thead>
<tr>
<th><strong>Single Actuation Content</strong></th>
<th>fundamental measure of product similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impactor Size Mass</strong></td>
<td>a reproducible measure of a product attribute broadly representing the dose delivered to the lung.</td>
</tr>
<tr>
<td><strong>APSD data</strong></td>
<td>an opportunity for identifying gross differences between Test and Reference product.</td>
</tr>
</tbody>
</table>

**In Vivo Equivalence requirements**

- **Systemic bioequivalence based on PK**
  - Highly sensitive indicator of any difference between Test and RLD
  - Best examined in healthy subjects as this population most sensitive in who to detect formulation differences
  - Good literature supporting extrapolation to populations in which RLD is approved
  - Exacting acceptance criteria proposed may also be indicative of equivalent local delivery of test and RLD at the site.

- **Local equivalence based on a Clinical End Point Study**
  - Proposed design strikes a good balance between confirming local equivalence at the site of action within the lung and the challenge in determination of dosage-response for both ICS and LABA classes
The Way Forward

Is Global Harmonisation of Regulatory Guidance likely?

Place your bets!
Regulatory Requirements

Different approaches for generic approval in different regions

US

Weight of Evidence

In vitro Similarity → Bioequivalence (BE) → Therapeutic Equivalence (TE) → Device Equivalence → ANDA

EU

Stepwise

In vitro Equivalence → BE → TE

ROW

under development

If BE not achieved
• Closer alignment of US and EU guidelines would be a significant step forward
  – Guidance in other regions tends to align with one or the other

GDUFA Regulatory Research Priorities 2014: “The lack of efficient bioequivalence methods for locally acting drugs has limited the availability of generic drugs in this category. Equivalence of Locally Acting Products includes research into new bioequivalence (BE) methods and pathways for local acting drugs. Product categories in priority order are inhalation….
Encouraging Signs!

GDUFA OIDP Dissolution Grant

- **Phase 1:** Development/modification of existing dissolution methods for OIDPs, by accounting for mass of drug deposited per unit surface lung area, limited lung lining fluid and other factors that may impact drug dissolution in vivo.

- **Phase 2:** Selection of OIDPs for dissolution study. OIDPs should be selected to represent a range of physicochemical properties of the API (e.g., solubility, particle size, crystallinity, lipophilicity, adhesive/cohesive properties). The selected OIDPs should represent solution and suspension-based metered dose inhalers, and DPIs. OGD’s research fluticasone propionate formulations will be provided for the study.

- **Phase 3:** Development of a mathematical model to describe a relationship between the in vitro dissolution data and PK.
GDUFA OIDP Dissolution Grant

Three grants awarded in 2013:

- In vitro fluid capacity-limited dissolution testing and its kinetic relation to in vivo clinical pharmacokinetics for orally inhaled drug products
  Masahiro Sakagami, Ph.D.
  Virginia Commonwealth University

- Development of an in vitro dissolution technique to understand the clinical based outcomes of orally inhaled drug particles
  Robert Price, Ph.D.
  University of Bath

- An optimized dissolution test system for orally inhaled drugs:
  Development and validation
  Guenther Hochhaus, Ph.D.
  University of Florida
Developing Products For Different Markets

Mylan Generic Advair DPI and pMDI Programs

Respiratory: U.S. generic Advair®

- Expected launch: 2H 2016
- U.S. market: ~$4.7 billion

2013 Mylan Investor Day Presentation
Aug 01, 2013

Respiratory: EU generic Seretide® DPI and generic Seretide® pMDI

- Generic Seretide DPI expected launch: 2H 2015
- EU market: $1.4 billion

- Generic Seretide pMDI expected launch: 1H 2015
- EU market: $800 million

Suite of branded combinations to follow in same device platform and including NMEs
Enabled By A Science Based Understanding Of Critical Product Performance Attributes

- Determine critical characteristics that control performance
- Design product around these attributes
  - Predictable scale up and process transfer
  - Through development and post-approval
- **Ensure** robust product performance attributes
  - Correct understanding of the biorelevant deposited fraction of the emitted dose *in vitro* and *in vivo*
- Integrate understanding from Clinical and Pharmaceutical Sciences
Global R&D Respiratory Platform - Strategy

Build a Global Respiratory Franchise supported by strong science:

- Focus on **Complex Device and Product Combinations.**
  - Asthma
  - COPD (Chronic Obstructive Pulmonary Disease)

- Support **Emerging Market** needs for Cost Competitive Products through Device / Product Innovations and Business Development.

- Leverage **Internal Science** to Engage and Support **Product and Technology Acquisitions.**
THANK YOU