flutiform® pMDI: Development continues after approval – A global perspective

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Presentation outline

- Global commercial potential for the ICS/LABA class

- *flutiform®*
  - product characteristics
  - development status
  - global roll out

- Development team involvement post approval
  - *flutiform* supply chain
  - manufacturing support
  - quality and change management
  - marketing support & life-cycle management
Global asthma and COPD sales

Overall asthma and COPD sales expected to rise modestly through to 2022

<table>
<thead>
<tr>
<th>Year</th>
<th>Asthma (Billions)</th>
<th>COPD (Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>24.0</td>
<td>13.8</td>
</tr>
<tr>
<td>2017</td>
<td>24.1</td>
<td>14.5</td>
</tr>
<tr>
<td>2022</td>
<td>24.3</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Source: i) Datamonitor COPD report, DMKC0047510, Publication Date: 19/08/2013 ii) Datamonitor Asthma report, DMKC0082148, Publication Date: 07/09/2012 iii) Extrapolation of main market sales to global numbers with a factor of 25%
ICS/LABA forecast to increase share

• ICS/LABA combinations expected to account for 36% of total by 2022 vs. 31% now
• ICS/LABA combination sales in asthma: $8.7B in 2022 vs $7.4B in 2012
• ICS/LABA combination sales in COPD $5.4B in 2022 vs. $4.3B in 2012

Source: i) Datamonitor COPD report, DMKC0047510, Publication Date: 19/08/2013 ii) Datamonitor Asthma report, DMKC0082148, Publication Date: 07/09/2012 iii) Extrapolation of main market sales to global numbers with a factor of 25%
Respiratory market by region

Source: i) Datamonitor COPD report, DMKC0047510, Publication Date: 19/08/2013 ii) *Datamonitor Asthma report, DMKC0082148, Publication Date: 07/09/2012 iii) Extrapolation of main market sales to global numbers with a factor of 25% iv) † LATAM: Company estimates
**flutiform®** - novel fluticasone/formoterol pMDI

- A new fixed combination of two well-known actives delivered via a novel press-and-breath pressurised metered dose inhaler with a dose indicator

- **Fluticasone** (inhaled glucocorticosteroid) (ICS)
  - high local anti-inflammatory activity, low incidence of adverse effects
  - reduces symptoms and exacerbations of asthma

- **Formoterol** (selective long-acting β₂ adrenergic agonist) (LABA)
  - rapid onset of bronchodilatation in approx. 3 minutes
  - bronchodilatation following single dose lasts 12 hours
  - preferential effect on β₂ adrenergic receptors on bronchial smooth muscles to produce relaxation and bronchodilatation
**flutiform**® product characteristics

- Indicated for regular treatment of asthma where use of a combination product (inhaled corticosteroid + long-acting β₂ agonist) is appropriate:
  - for patients not adequately controlled with ICS and ‘as required’ LABA
  - for patients already adequately controlled on both ICS and LABA

- Available in three strengths (EU & ROW):

<table>
<thead>
<tr>
<th>Strength</th>
<th>Dosing schedule</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>50/5 μg</td>
<td>2 puffs b.i.d</td>
</tr>
<tr>
<td>Medium</td>
<td>125/5 μg</td>
<td>2 puffs b.i.d</td>
</tr>
<tr>
<td>High</td>
<td>250/10 μg</td>
<td>2 puffs b.i.d</td>
</tr>
</tbody>
</table>

- Japan: two strengths, adults ≥ 16 years
- Patient facing colour-coded dose indicator
- **Aerochamber Plus**® spacer compatibility

b.i.d: twice daily

1 flutiform UK SmPC.
Global development status

- **Europe (Mundipharma)**
  - first wave DCP: Marketing authorised for asthma in 22 European countries
  - MRP concluded in Spain
  - launched in 14 countries
  - launch in remaining countries once pricing agreed

- **Japan (Kyorin)**
  - approved September 2013; Launched November 2013
  - third ICS/LABA combination onto market
  - NHI price in line with equivalent combination products

- **US & Canada (Available for licensing)**
  - US NDA filed in March 2009; complete response letter received - further clinical work needed

- **LATAM (Sanofi) & ROW (Mundipharma)**
  - MAAs are being pursued in a number of countries
  - applications are based on the EU MAA
  - Launched in Hong Kong and Australia
  - Additionally, approved in Switzerland, Israel and South Korea
Global rollout

momentum growing from recent world-wide product approvals

already approved in 28 countries
flutiform® launched in Japan

- special 14-day presentation developed to meet reimbursement requirements
- same presentation and size of can with indicator adjusted to 56 puffs
flutiform® launched in Japan

- an actuation aid is provided to certain patients as is customary for pMDI products on the Japanese market
Development team involvement post approval

- *flutiform*® is manufactured by CMO partner – Sanofi, Holmes Chapel, UK
- key components and ingredients are procured by Skyepharma
- a core multi-disciplinary team continues to manage
  - in-coming goods and finished product supply and quality
  - process improvements
  - matching available capacity with demand
  - reducing risk and managing necessary change
- support to marketing partners
  - generation of further characterisation data
  - life-cycle management
Supply chain management of *flutiform®*

**Active Product Ingredients**
- Fluticasone Propionate
- Formoterol Fumarate

**Excipients**
- DSCG
- Propellant
- Co-solvent

**Components**
- Canisters
- Valves
- Actuators
- Foil wrap
- Cartons
- Patient leaflet
- Packing boxes
- Labels

**Stage 1 Processes**
- Suspension manufacture
- Canister filling
- Post processing
- Quality testing

**Stage 2 Processes**
- Labelling
- Flow wrapping
- Cartoning
- Casing
- Shipping
Logistical support

• a mixture of trains, planes and automobiles .....and boats may be involved in world-wide shipment

• vibrations, temperatures, orientations and pressures can be withstood by the product and its packaging

• product robustness maintained under special excursion conditions outside of normal warehouse and shipment controls
  - elevated temperatures
  - freezing conditions
flutiform® transportation studies

- **Reference** – unshipped control
- **Europe** – shipped to and from Cyprus (road and sea)
- **ROW** – shipped to and from Japan (road and air)

- No change in aerosol performance parameters
- No chemical degradation
- No leakage
Manufacturing support

• pMDI suspension pressure-filling process developed at Skyepharma to pilot scale
• Sanofi selected as CMO
  – inhalation expertise and quality
  – manufacturing, packaging and testing capabilities and capacity
  – accreditation and successful inspection by key regulators
• Post approval development team support and continuous improvement
  – capacity evolution
  – risk and change management
  – continuous analysis of process performance metrics and KPIs
Continuous Improvement

Maximize
- volumes and capacity
- yields
- process capability
- efficiencies
- synergies/economies of scale
- flexibility

Minimize
- risk
- obsolescence
- cycle times
- downtime
- cost
- working capital

Eliminate
- redundancy
- wastage
- excess inventory

using lean and six sigma concepts for process improvement
Commercial batch data trending

• larger dataset available from QC testing
  – in-comming goods
  – finished product

• trending of release and stability data
  – ensures quality of marketed product
  – elucidates step changes & quality drifts
  – confirms correlations between quality and process parameters

• process capability analysed and necessary interventions made
Process capability index: $C_{P_k}$

**Definition:** $C_p K$ - an index which measures how close a process is running to its specification limits, relative to the natural variability of the process.

$$C_{P_k} = \min \left( \frac{USL - \mu}{3\sigma}, \frac{\mu - LSL}{3\sigma} \right)$$

where
- USL: Upper Specification Limit
- LSL: Lower Specification Limit
- $\mu$: Average value of the data
- $\sigma$: Standard deviation of the data

<table>
<thead>
<tr>
<th>$C_{pk}$ value</th>
<th>Failure rate</th>
<th>Sigma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPM</td>
<td>%</td>
</tr>
<tr>
<td>0.33</td>
<td>317311</td>
<td>31.73</td>
</tr>
<tr>
<td>0.67</td>
<td>44431</td>
<td>4.44</td>
</tr>
<tr>
<td>1.00</td>
<td>2699</td>
<td>0.27</td>
</tr>
<tr>
<td>1.33</td>
<td>66</td>
<td>0.01</td>
</tr>
<tr>
<td>1.67</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.00</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
• 6σ quality performance for *flutiform* FPD data
• Process capability usually targets CpK of ≥1.33 (4σ performance)
• A challenging target - mix of input material & components quality, non-continuous processes and quality testing capability
Challenges of targeting and maintaining $\geq 4\sigma$ quality performance

- Registered Specifications
  - may need to account for regional requirements
  - mainly release & shelf-life therefore slight off-centering required
  - justified on performance of development & clinical batches - step changes avoided at full scale
  - a subset based on guidance or pharmacopoeial limits not actual process capability
  - aerosol parameters are in “exquisite balance”
  - maintained on continuous improvement - increases of scale and 2nd sourcing of materials
Manufacturing scale-up

Early Development
- Lab scale: 100 - 1,000 units

Process Development & Clinical Supplies
- Pilot scale: 3,000 – 4,500 units
- Pilot scale: 12,000 – 20,000 units
- Industrial scale: 50,000 units

Formulation Definition

Process Development
- Clinical trial supply: Phase II
- Clinical trial supply: Phase III

Validation

Initial Commercial Production

scale-up

Validation

Scaled Commercial Production: millions of units per year

Capacity evolution plans in place in anticipation of continued global roll-out and successful *flutiform* product growth.
Supplier Risk Mapping

• with key (N-1) suppliers, critical components are identified and their composition and processes mapped to at least the N-3 level.

• an example of materials used in typical MDI valves (adapted from Extractables and Leachables Handbook).

<table>
<thead>
<tr>
<th>N-2</th>
<th>N-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastomers</td>
<td>base polymer, anti-oxidant, curing agent, stearic acid, colorant</td>
</tr>
<tr>
<td>Polymers</td>
<td>Monomers, catalysts, chain transfer agent, release wax, lubricant, stabiliser, anti-oxidant</td>
</tr>
<tr>
<td>Steel spring</td>
<td>Steel wire, drawing oil, degreasing agent, polishing agent, detergent, pickling agents</td>
</tr>
<tr>
<td>Aluminium Ferrule</td>
<td>Mostly as for spring</td>
</tr>
<tr>
<td>Silicone lubricant</td>
<td>Siloxane, chain transfer agent, catalyst, deodorant</td>
</tr>
</tbody>
</table>

• tools used by pharmaceutical companies (level N) to manage risk
  − quality agreements
  − change control procedures
  − in-coming goods quality trending
  − risk assessment (FMEA)
  − stockpiling and 2nd sourcing
Variations

- as the product evolves and commercial risk is managed, changes to the registered product will be notified to the regulators

- Where necessary regulatory submissions are made – e.g., «variations» (EU) or «partial/major changes» (Japan)

- The lead times for review and approval varies significantly and timely phasing and prioritisation needs to be considered

- Certain significant changes may require *in-vitro* or *in-vivo* data bridging or even «bioequivalence» to be demonstrated
Marketing Support

• different marketing and branding between territories but consistency in messages and data for patients and prescribers

• support of partners in design, review, data generation and publications further characterising and differentiating the benefits of flutiform

• To date there have been > 17 published articles and >160 abstracts & posters in all areas
**flutiform® aerosol efficiency**

- High and consistent fine particle fraction (in-vitro) of approximately 40% across 2 flow rates\(^1\)

![Bar chart showing fine particle fraction for different medications](chart.png)

**LABA component**

- Dark bars with solid border were measured at 28.3 L/min and pale bars with dashed border at 60.0 L/min

- Flutiform (125/5 µg)
- Fluticasone/salmeterol (250/50 µg)
- Budesonide/formoterol (200/6 µg)
- Beclometasone/formoterol (100/6 µg)

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\(^{a}\)Dry powder inhaler; \(^{b}\)pressurized metered-dose inhaler; fine particle (particle diameter < 5 µm) fraction was calculated as a percentage of the metered dose; similar results were obtained for the ICS component; doses in brackets are strengths tested; comparable treatment doses are: flutiform, 250/10 µg; fluticasone/salmeterol, 250/50 µg; budesonide/formoterol, 400/12 µg; beclometasone/formoterol, 200/6 µg; all twice daily

ICS, inhaled corticosteroid; LABA, long-acting β2-agonist

Johal, B; Howald, M; Fischer, M; and Marshall, J. ERS poster. Vienna, Austria. 2012
**flutiform**® plume characteristics

- Gentle plume allows more time for patients to inhale drug, reduces drug deposition at back of throat

**Spray velocity**

<table>
<thead>
<tr>
<th>Interval distance from actuator (cm)</th>
<th>flutiform 125/5 µg</th>
<th>Fluticasone propionate/salmeterol 125/50 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>20.3</td>
<td>15.2</td>
</tr>
<tr>
<td>6.0</td>
<td>26.5</td>
<td>14.8</td>
</tr>
<tr>
<td>9.5</td>
<td>14.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>

**Spray duration**

<table>
<thead>
<tr>
<th>Plume duration over 9.5 cm (ms)</th>
<th>flutiform 125/5 µg</th>
<th>Fluticasone propionate/salmeterol 125/50 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>168.3</td>
<td>114.0</td>
</tr>
</tbody>
</table>

Johal, B; Murphy, S; and Marshall, J. ERS poster P3079. Barcelona, Spain. 2013
**flutiform®**: life-cycle management

- **Paediatric indication**
  - For asthmatic patients 5-11 years of age: post-approval commitment in Europe
  - Clinical trial comparing *flutiform®* with Seretide and Flixotide on-going
  - Study sponsored by Mundipharma

- **COPD**
  - Global market $13.8B in 2012 with annual expected growth c.1%*
  - Worldwide prevalence c. 210M people*, with only 18-33% currently treated**
  - 1,530 patient international study initiated by Mundipharma September 2013

- **Additional confidential projects**

Source: *WHO 2007, **Data Monitor COPD report, DMKC0047510, Publication Date: 19/08/2013;*
**flutiform® post approval - a single quality delivered to multiple markets**

<table>
<thead>
<tr>
<th>Attribute/Requirement</th>
<th>EU</th>
<th>JAPAN</th>
<th>ROW (incl. LATAM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentations</td>
<td>3 strengths One month presentation</td>
<td>2 strengths One month &amp; Two week presentations</td>
<td>2-3 strengths One month presentation</td>
</tr>
<tr>
<td>Specifications</td>
<td>Release &amp; Shelf-Life ref. EP</td>
<td>Shelf-life ref. JP</td>
<td>Mixed requirements ref. EU MAA ref. Local pharmacopoeia</td>
</tr>
<tr>
<td>Shelf-life/ climatic zone</td>
<td>Zone II (Sub-tropical/mediterranean)</td>
<td>Zone II (Sub-tropical/mediterranean)</td>
<td>Zone II to IVB (Hot and very humid)</td>
</tr>
<tr>
<td>Change management</td>
<td>Variations (3-6 month+ approval times depending on type)</td>
<td>Partial or Major Change notifications (long lead times for approval)</td>
<td>Variations (long lead times for approval)</td>
</tr>
<tr>
<td>GMP inspection</td>
<td>Covered by scheduled GMP inspections except when outside EEA</td>
<td>Mutual Recognition (Accreditation), GMP compliance inspection (may be document-based)</td>
<td>Mainly covered by scheduled GMP inspections. Importation testing</td>
</tr>
</tbody>
</table>
Summary

- the development team continues to support **flutiform** post approval
  - additional registrations, continuous improvements, capacity evolution and LCM
- products designed according to QbD principals
  - robust manufacturability - easier to maintain/improve and maximise profitability
- a single high quality product for all markets with harmonized specifications
  - leverage economies of scale
  - commercial viability in ROW can be challenging due to low pricing
- a multi-disciplinary team of «product stewards» working alongside supply chain, manufacturing, quality assurance & marketing groups help maintain and grow a successful **flutiform** product
- key learnings from commercialization feed back into new product developments
Acknowledgements

- Skyepharma multi-disciplinary *flutiform* team
- Mundipharma
- Kyorin Corporation
- Sanofi (Holmes Chapel, UK and LATAM Team)