2st Medical Valley Inhalation Symposium
The future of inhalation

16 October 2013
09.00–17.00
Medicon Village, Lund, Sweden

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Patents and dry powder inhalation

2nd Medicon Valley Inhalation Symposium
Lund 2013

Jan Trofast
Device → Formulation

Dry powder inhaler
Development of dry powders for inhalation - a complex task

- Micronized particles of low-dosage strength active agents for powder formulations for inhalation, *US 2010/0055192*
Different inventive processes need different approaches to be optimally taken care of

- The problem to be solved has been stated
  Hypothesizing a cause of the problem, designing and performing experiments to test the hypothesis, analyse the data, make conclusions

- The role of serendipity
  Every day work gives more or less unexpected data, which may need coordination in a novel, non-predictive and interdisciplinary way

- Who is defining the unknown questions in an interdisciplinary and scientific manner?
Developing a Patent Strategy for an Invention

- What is the invention? Identification from experimental data!
- Which problem will my invention solve?
- Who is the owner to the problem? – Due diligence.
- What is to be achieved by filing a patent application?
- What additional information is needed for the patent application?
- When must this patent application be filed?
- Who is going to develop the information for the patent application?

Developing a Patent Strategy for an Invention

- Who is going to prepare the technical background and the final application?
- How much information should be disclosed in the application?
- How broadly can/should the invention be claimed? How to find allowable claims that stand up in future litigations when the knowledge today is regarded as general knowledge in the future?
- Where is patent protection wanted?

Intellectual properties

Who is linking an invention in one place in the organisation to a problem in another, e.g. solid state properties, surfactants, particle formation etc?

Who is supporting during examination, opposition, appeal and litigation?

Who is investigating infringement? Due diligence?
Scientists

Scientific Patent Adviser

Inventor

Patent attorneys
Some important features of IP strategy

- Science-based approach to patent work gives high quality protection
- Interdisciplinary thinking stimulates new ideas
- An IP strategy will improve the research process
- Personal visibility and activity create a high awareness of IP questions
- An overall solution - from idea to product
No science – not first
Not first – no patents
No patents – no business
Registration of medicines
with special emphasis on inhalation

Elisabet Joelson
Joelson Regulatory Consulting
16 October 2013
Contents

- What is a registration file?
- What does a registration file contain?
- What governs the contents of a file?
- What processes apply?
Registration file

- **Format**
  - Where the documentation is found. Harmonised between regions.

- **Content**
  - What the documentation should contain

- **Guidelines**
  - ICH, FDA, EU etc
Review process:
“top-down approach”

Review process:
“Bottom-up approach”

(JNDA assessed in a similar way)
What is a CTD?

- Common Technical Document
- A format – an index – same terminology.
- Agreed between the three regions EU, USA och Japan. Is also accepted in other regions.
- Enables industry to compile a global file
- Facilitates exchange of information between authorities.
CTD structure - 5 Modules

- Module 1: Regional administrative information
- Module 2: Summaries
- Module 3: Quality
- Module 4: Nonclinical Study reports
- Module 5: Clinical Study Reports
The CTD structure

Module 1
Regional Administrative Information 1.0
CTD ToC* 2.1
CTD Introduction 2.2

Module 2
Quality Overall Summary 2.3
Nonclinical Overview 2.4
Nonclinical Summary 2.6
Clinical Overview 2.5
Clinical Summary 2.7

Module 3
Quality
Module 4
Nonclinical Study reports
Module 5
Clinical Study reports

Module 1 not part of CTD

*ToC = Table of Contents
Prescribing Information
(claims)

Overview
(Critical assessment)

Summary
(Comprehensive presentation of key elements)

Study Reports
("Raw data")
Registration file

- Quality
- Safety
- Efficacy
Quality

- Active substance
- Raw materials
- Finished product
- Container closure
Safety- Preclinical documentation

- Pharmacology
- Pharmacokinetics
- Toxicology
Efficacy- Clinical data

Biopharmacy
- Bioavailability
- Bioequivalence

Clinical Pharmacology
- Pharmacokinetics
- Pharmacodynamics

Efficacy and safety
Guidelines

- ICH guidelines
- EU guidelines
- FDA guidelines
EU Guidelines - Quality

- EMEA/CHMP/QWP/49313/2005
  Guideline on the pharmaceutical quality of inhalation and nasal products
    - Pharmaceutical development
    - Manufacture
    - Specifications
    - Container closure
    - Stability
    - Generic products
FDA guidelines - Quality

Guidance for Industry
Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products
Chemistry, Manufacturing and Controls Documentation

Draft guidance Nov 13, 1998
FDA guidelines -Quality

Guidance for Industry
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation

July 2002
EU Guidelines - Clinical

CPMP/EWP/4151/00

Guideline on the requirements for clinical documentation for orally inhaled products including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and COPD in adults and for the use in the treatment of asthma in children and adolescents

August 2009
EU guidelines - Clinical

EMA/CHMP/483572/2012
Guideline on clinical investigation of medicinal products in the treatment of Chronic Obstructive Pulmonary Disease (COPD)

September 2012
FDA Guidelines - Clinical

Points to consider
Clinical Development programs for MDI and DPI Drug Products

September 1994
FDA Guidelines - Clinical

Guidance for Industry
Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment

Draft Guidance Nov 2007
USA

- NDA- New Drug Application
- ANDA- Abbreviated New Drug Application
MAA- Marketing Authorisation Application

Article 8(3), "full file"
Article 10(1), generic
Article 10(3), hybrid
EU- Procedures

- Centralised procedure
  - Involves all Member States

- Decentralised procedure
  - Chosen Number of Member States

- Mutual recognition procedure
  - When the product is already approved in a Member State

- National procedure
  - Only one country
Purpose of a registration file

- Shall include enough data to support the Quality, Safety and Efficacy of the product
- Shall present both positive and negative findings
- Shall provide an evaluation of the **benefit/risk** of the product
- Shall support the product information
MDI’s – Past, Present and the Future
Phil Cocks 16th October 2013
2012 U.S. sales dropped for the first time in IMS history - generic industry is primarily responsible.

$37bn Inhalation market over 900m devices

For one DPI dose patients can afford 2.5 MDI doses

MDI = 60% of market volume

COPD, world's 3rd biggest killer by 2030

Asthma is the most common chronic childhood disease

2012 U.S. sales dropped for the first time in IMS history - generic industry is primarily responsible.

So what is an MDI…?

<table>
<thead>
<tr>
<th>Pro’s</th>
<th>Con’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portable / Compact</td>
<td>Inhalation technique required</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Patient Co-ordination required</td>
</tr>
<tr>
<td>Formulation in sealed canister</td>
<td>High oral deposition</td>
</tr>
<tr>
<td>Dose reproducibility</td>
<td>Limited maximum dose 1-2 mg</td>
</tr>
<tr>
<td>Multidose (&gt;200 doses)</td>
<td></td>
</tr>
</tbody>
</table>
MDI Evolution Timeline……Past
Same look, new product……Present

- Better Drugs
- Aluminium and SS canisters
- Coating materials
- Cleaner elastomers
- Better valves
- Less environmentally damaging propellants
- More efficient delivery systems!!
1955 - Susie Maison and THE question!

1956 – First pMDI
Medihaler Epi™
Riker Labs

1960 – First systemic
pMDI: Medihaler
Ergotamine™

1970 – First breath
actuated Inhaler
Duohaler™3M

1957 – Span 85,
loss of dose
technology

1959 – O’ring
seals, aluminum
cups

1973 – First DPI
Spinhaler
Fisons

1987 – Montreal
protocol

1989 – Aerolin
Autohaler 3M

1995 – First HFA
pMDI
Airomir – 3M

1998 – FDA MDI/
DPI Guidance
2180

1995 – First HFA
pMDI
Airomir – 3M

1998 – FDA MDI/
DPI Guidance
2180

2003 – FDA
Guidance Dose
counters

2005 – First single
cycle FDA review
for an MDI

2004 – First dose
counter on
GSK own
products only

2008 – FDA
propose
withdrawal CFC
Albuterol

2012 – First
HFA nasal
pMDI - QNasal

2010 – First FDA
approved dose
counter on a new
MDI product
Driving the future of MDI products…as seen by 3M

1. Patient Centric
2. Electronic Integration
3. Green Medicine
4. Low Cost
Solutions to address… Patient Centric
Solutions to address....Smarter Devices

- Inbuilt sensors for medication tracking and feedback
- Electronic Training Devices
- e-dose counters
Solutions to address… Green Technology

- Next generation propellant?
- More effective and higher performance MDI’s
- Manufacturing processes designed to improve sustainability
Solutions to address….Low Cost Products

- Components
  - Fewer parts = cheaper
  - Enhanced performance
  - Less costly raw materials
  - Reduced manufacturing costs
  - Smaller & larger doses

- Generic products approved
  - Developed & emerging markets
Solutions to address… Product Differentiation
Take Away Messages............

- **Past...**
  - Evolutionary
  - Low cost
  - Familiar

- **Future...**
  - Evolutionary, remain low cost
  - Growing potential beyond Asthma and COPD
  - Smarter, data driven, patient centric experience
  - Addresses health-economic needs

**MDI Future...EVOLUTION, not revolution....meeting stakeholder needs!**
Precision DPI Filling

Marco Laackmann,
Harro Höfliger Verpackungsmaschinen GmbH
The dry powder inhalation market trends

- Increase of **inhalation as non-invasive application** form:
  - Antiviral: RELENZA (Biota/GSK), Inavir (Daiichi Sankyo)
  - Vaccines: Measles (University of Colorado)
  - Diabetes: AFREZZA (Mannkind)
  - Agitation associated w. schizophrenia: STACCATO loxapine (Alexza)
  - ...

- **Dosing of pure micronized API**
- **Increase of biotech APIs** (proteins, peptides, nucleotides)
- **Asthma / COPD dominates** the market of inhaled drugs
- **Asthma / COPD patent cliff** of 2011 – 2021 timeframe
Powder Formulations for DPI products

- „Ordered mixtures“ with coarse carrier particles, e.g. lactose
  - Example: 4% Beclomethasone-propionate / Lactose Monohydrate

- Spherical aggregates, „soft pellets“
  - Soft Pellets prepared from pure Disodium Cromoglycate

- Spray dried product, (most recently)
  - Proprietary Insulin Formulation
    Source: Neil Canavan, „The Fine Art of Fine-Tuning Drug Formulation“
Powders are more than a heap of particles

- Powders are multiparticulate systems.

- Powder properties are affected by
  - Particle size
  - Particle size distribution
  - Particle shape
  - Particle density
  - Mechanical properties / surface texture
  - Particle porosity
  - Moisture content / hygroscopicity
  - Electrostatic charge
Particle Properties: **Particle Size**

- Particle size and particle size distribution will influence process-ability of powders:
  - Achievable fill weight in fixed volume targets
  - Uniformity of dosed mass
  - Size must fit the dosing range (Limit large particle size)
  - Content uniformity (segregation tendency)
  - Flowability of powders
  - Cohesiveness of powders / Sticking tendency to machine surfaces
  - Long-run process stability (Jamming of moving parts due to fines)
  - Sensitivity to triboelectric charge
Particle Properties: Particle Shape

- Particle shape will also influence the properties of powders, but the effect is rather complex.

- In theory spherical particles should generate minimum interparticulate forces and friction and therefore improve powder flow.

- In many cases angular particles show higher coefficients of friction compared to spherical particles.

- Thus in tableting angular particles lead to increased variation in die fill / tablet weight.

- Influence of shape on filling properties has been investigated in pharmaceutical pellets.

- Influence of particle shape on cohesive forces has been demonstrated (powder blends for inhalation !).

Particle Properties: Particle Density

- Particle density will influence powder flow, which normally is caused by gravitational forces acting on the powder particles:

\[ F = m \times g \]

\[ (m = \rho \times V) \]

- Influence of density on flow can be observed with some powders for inhalation having very low density of < 0.1 g/ml: They show poor flowability, despite having a spherical particle shape.
# Filling Technology at a Glance

<table>
<thead>
<tr>
<th>Filling Technology</th>
<th>Device Technology</th>
</tr>
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<tbody>
<tr>
<td><strong>Dosator</strong></td>
<td><img src="image" alt="Dosator" /></td>
</tr>
<tr>
<td><strong>Vacuum Drum</strong></td>
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<tr>
<td><strong>Membrane</strong></td>
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</table>

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Filling Technology: **Dosator**

- Dose range of ~ 15 - 2000 mg, typically for filling of (gelatin) capsules
- Control of fill weight by adjustment of height of powder bed and position of dosator pin
- For powders showing Carr’s Index of approx. 15% – 30%
Filling Technology: **Dosator**

Customized dosator unit:
- 20-up dosator head to dose 5mg DPI drug

1. **Dosator unit:**
2. Rotating powder bowl
3. DPI disk carrier
Filling Technology: **Dosator**

Smallest standard dosator

1 mm Ø
Advantages of Dosator Filling

- Flexible and well established dosing technology
- Dosators can be build in different form and sizes
- Dosed mass can be easily adjusted

- Easy up-scaling from lab to large scale
- Transfer of process settings from lab to commercial manufacturing
- Shortest time to market due to minimal process development

Available technology

- Filling technology is open to originator or generic business
- No limitations to commercial volume (niche market vs. mass market)
Filling Technology: Vacuum Drum

- The Spiriva inhalation powder is delivered from a hard gelatin capsule by using the HandiHaler device

- Each capsule is filled with 5 mg powder blend (containing 18 µg API)
  - Dosator limitation occurs for < 10 mg dosage
  - IPC - Checkweighing of dosed mass impossible due to mass fluctuation of hard gelatin capsules.
  - IPC - Brutto / Tara checkweighing concepts complex and equipment intensive.

- Individual capsules placed in a blister with high water vapor barrier
Filling Technology: Vacuum Drum

- Vacuum Drum technology

Diagram:
- Stirrer
- Powder bed
- Dosing bore
- Filter membrane
- Vacuum/air channel
- Exhaust
- Scraper blade
- Drum sleeve
- Drum core
- Blister transport system
- Blister
Filling Technology: **Vacuum Drum**

- Vacuum Drum Filling technology can be customized to any individual fill weight.
- Dosed mass is determined by the volume of the dosing bore.
Filling Technology: Vacuum Drum
Filling Technology: Vacuum Drum Filling

- Vacuum Drum technology: 1.2 mg rice starch; 1–10 µm particle size
Advantages of Vacuum Drum Filling

- Exact dosing of very low amounts starting from 0.5 mg
- Low impact forces leave inhalation powder properties unaffected
- Dosing accuracy is regardless from powder cohesion and flow-ability
- Easy combination with 100% mass control
  - 100% weight verification with “Advanced Mass Verification”
  - Automatic rejection of overweight or underweight capsules
- Easy up-scaling from lab to large scale
  - Transfer of process settings from lab to commercial manufacturing
  - Shortest time to market due to minimal process development
- Available technology
  - Filling technology is open to originator or generic business
  - No limitations to commercial volume (niche market vs. mass market)
Verification of dosed mass: VisioAMV Sensor

Dosing powder into blister pockets

Dosing powder into any other target receptacle

Regarding the critical powder properties a 100% verification of the dosed mass is a highly desirable feature!
Verification of dosed mass: VisioAMV Sensor

Functional principle: Capacitive sensor in high frequency mode with high data acquisition rate
Verification of dosed mass: VisioAMV Sensor

VisioAMV-Sensor

Powder dose

Change of capacitance over time

Signal x mass factor = recorded mass

Calculation of dosed mass

13.456 mg

Send mass data to PLC

PLC

Process control
Verification of dosed mass: **VisioAMV Sensor**

**Determination of accuracy and linearity of VisioAMV – sensor using a triple-row drum (target volume / 90% of target / 110% of target)**
Verification of dosed mass: VisioAMV Sensor

- Sensor detects products „in flight“ in a non-destructive process, starting from 1mg
- Detects monolithic or dispersed objects (integration of signals over time period)
- Triggered by filling system Independent of target (blister, capsule, cartridge,...)
- Independent of dosing system (vacuum drum, dosator, ..)
- System can be calibrated on mass („weight“) basis
- Easy to install, to maintain and to clean
- Suited to determine mass of other uniform solids (tablets, capsules), too
The Accuhaler / Diskus device contains a blister strip with 60 cavities.

During manufacturing the powder is filled into a preformed aluminum strip.

Each cavity is 100% filled up to the rim.

- Double strips cut apart
- Individual strips coiled for placement inside Diskus / Accuhaler.

- Final device assembly
Filing Technology: Membrane Filling

- Membrane filling technology

1  powder reservoir  
2  powder feeder  
3  vacuum chamber  
4  gasket  
5  membrane  
6  filled blister cavity
Filing Technology: Membrane Filling

- Membrane filling technology
Advantages of Membrane Filling technology

- No powder spillage on the sealing area
- Functionality of peelable lid foil remains unaffected
- Sealing integrity remains unaffected

- No powder dust generation during filling
- Work place requirements easily achieved
- Contamination control (corticosteroids)

- Easy up-scaling from lab to large scale
- Transfer of process settings from lab to commercial manufacturing
- Shortest time to market due to minimal process development

Available technology

- Filling technology is open to originator or generic business
- No limitations to commercial volume (niche market vs. mass market)
Inhalation Product Development

Proof of Concept

Excipient selection

API particle size reduction and conditioning

Powder Formulation

Testing drug product performance
(PSD, ED, FPF, CU)

DPI Prototype

Moulded Device (Pilot / Commercial)

Filling Technology / Packaging Process

Assembly Technology

Primary Packaging

DPI concept

Stability Industrialization Validation
Summary

- Excipient selection
- API particle size reduction and conditioning
- Powder Formulation
- Testing drug product performance (PSD, ED, FPF, CU)
- DPI Prototype (Pilot / Commercial)
- Moulded Device
- Assembly Technology
- Primary Packaging
- Filling Technology / Packaging Process

DPI concept
### Summary: Filling Technology at a Glance

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<tr>
<td><strong>Filling Technology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing volume</td>
<td>20mm³ - 1.000mm³</td>
<td>1mm³ - 100mm³</td>
<td>20mm³ - 1.000mm³</td>
</tr>
<tr>
<td>Dosing mass</td>
<td>~10 - 500mg</td>
<td>0,5 - 50mg</td>
<td>10 - 500mg</td>
</tr>
<tr>
<td>Advantages</td>
<td>Flexible</td>
<td>Very small quantities</td>
<td>100% filling up to the rim</td>
</tr>
<tr>
<td></td>
<td>Easy dose adjustment.</td>
<td>Cohesive Powder</td>
<td>No spilleage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very low compaction</td>
<td>No dust generation</td>
</tr>
<tr>
<td>Residual Vol.</td>
<td>appr. 150ml</td>
<td>appr. 50ml</td>
<td>appr. 50ml</td>
</tr>
<tr>
<td>RSD*</td>
<td>~2%</td>
<td>~1%</td>
<td>~3%</td>
</tr>
</tbody>
</table>

*depending on powder characteristics

**Dosator**

- Flexible
- Easy dose adjustment.

**Vacuum Drum**

- Very small quantities
- Cohesive Powder
- Very low compaction

**Membrane**

- 100% filling up to the rim
- No spilleage
- No dust generation

***Residual Vol.***

- Dosator: appr. 150ml
- Vacuum Drum: appr. 50ml
- Membrane: appr. 50ml

**RSD***

- Dosator: ~2%
- Vacuum Drum: ~1%
- Membrane: ~3%
Thank’s for your attention
2nd Medical Valley Inhalation Symposium
The future of inhalation

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inhalationsymposium.com