Recent advances in drug delivery and how they affect Life Cycle Management in Pharmaceutical Industry

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**Agenda**

- Brief introduction to Novartis
- Pharmaceutical industry trends
- Life Cycle Management (LCM) and Drug Delivery Technologies (DDT):
  - Definition
  - LCM & DDT at Novartis
  - LCM & DDT: what do drug delivery systems offer? Examples
  - Solubilisation through nanonisation: Examples
  - Bypassing First pass liver effect: Examples
  - Convenience and compliance: Examples
  - Patient convenience and compliance expressed in sales
- Conclusions
Novartis Organisation

**Pharmaceuticals**
- Cardiovascular & Metabolism
- Oncology & Hematology
- Neuroscience
- Respiratory & Dermatology
- Infectious Diseases, Transplantation & Immunology (IDTI)
- Ophthalmics
- Arthritis/Bone/Gastrointestinal/Urology (ABGU)

**Sandoz**
- Generics

**Consumer Health**
- OTC
- Animal Health
- Medical Nutrition
- Gerber
- CIBA Vision

**NOVAD**
- Former Chiron
- Novel/conventional vaccines
- Blood testing
Novartis achievements

- 8 significant approvals in 2005, including 2 high priority reviews
- 73 projects in development
- 4 new compounds to be filed in 2006 for approval
- Ranked as one of the fastest and most productive in development
- Leading Partner of the FDA in Critical Path Initiative
Global Technical Research & Development

Industry Trends: R&D Productivity is Declining

Global Pharma R&D expenditures (in $ bn)

# NMEs approved by FDA

Source: FDA CDER & CBER; Evaluate
Safety related withdrawals of oral products in the US: Number of patients exposed in the 12 months prior to withdrawal (‘000s)
The cost to develop a drug product ascends to $900 M and 10-15 years before launch.

Possible Solutions

- Research
  - Proteonomics
  - Genomics
  - etc

- Development
  - Accelerate development timelines
  - Liase with regulatory authorities over development paths
  - Life Cycle Management

License-in
Obvious in some industries.

What does it mean in Novartis?

All measures/projects initiated in addition to mainstream development –

throughout its life cycle to enhance the value of a brand to the benefit of the patients.

What does it mean in Novartis?

Life-Cycle Management (LCM)
Novartis LCM&DDT organisation

11 pharmacists /chemists with

- At least several years of experience in
  - drug product development
  - application of DDT to projects
  - LCM strategies
- Individual areas of expertise (oral/parenteral/transmucosal)
- Experience in patent strategies and patent life extensions
- Experts in competitive environment
Global Technical Research & Development

Truly Global Pharmaceutical & Analytical Development

- East Hanover
- Orleans
- Basel
- Tsukuba
- Mumbai
- Singapore

Novartis
Novartis LCM&DDT Tasks

- Initiation of proactive LCM
- Contribution to late-phase LCM
- Information on competitors
- Lead feasibility studies both internally and with external partners
- Assessment of external technologies
LCM – why is it so important?

• Mainstream development focuses on bringing therapeutic benefits to patients as rapidly as possible
  (Glivec: development < 1000 days)

• LCM focuses on tailoring drug product to patient’s needs and preferences and on optimising the therapeutic value of drug products

  Ideally LCM leads to a higher market share for the brand → increased sales
LCM – how is it achieved in general?

Through…….

- New indications
- Alternative drug delivery systems, packaging and devices
- Alternative drug substance properties
- Improved manufacturing processes
Novartis LCM&DDT: The DDT Part

– Search for innovative Drug Delivery Technologies

– Assessment of external technology
  » Fit to Novartis development portfolio?
  » Fit to Novartis technology portfolio?

– Evaluation of (technical) feasibility
  » Paper assessment
  » Feasibility trial up to (and including) clinical trial (stepwise approach, final proof of feasibility)

– Coordinate evaluation of external DDT alliance proposals
LCM – what do DDTs offer?

Patient benefits such as:

– Improvement of therapeutic index (efficacy/safety)

– Improvement of convenience for patient

– Improvement of patient compliance
LCM – what do DDTs offer?

**Improvement of efficacy/safety**

- Reduced side effects
- Increased bioavailability & reduced variability
- Optimized based on PK-PD correlation
LCM – what do DDTs offer?

Improvement of patient convenience

• Reduced dosing frequency
• Reduced injection volume
• Preferred administration route
• Improvement of swallow-ability
• Combination products
LCM – what do DDTs offer?

Improvement of patient compliance

• Administration without water
• Optimal dosage forms for patient populations (children / elderly)
• Optimized dosage form for disease (e.g. acute treatment)
LCM – the first example 1898

2 years after the foundation of Hoffmann-La Roche

The 3rd launched product is a LCM product:

- A cough syrup containing Roche's Thiocol
- The syrup's orange flavour makes it a success
<table>
<thead>
<tr>
<th>Issue</th>
<th>Techniques/Methods</th>
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<tr>
<td>Solubility/permeability</td>
<td>Nano/micronisation, Cyclodextrins, Hot melt extrusion, Lipid formulations</td>
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<td>1st pass metabolism</td>
<td>Transmucosal delivery, e.g. buccal, nasal delivery, transdermal, parenteral delivery</td>
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<tr>
<td>Controlled release (sustained)</td>
<td>Matrix tablets, coated multiparticulate Osmotic systems, Gastric retention systems, depo formulations</td>
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<tr>
<td>Patient convenience/compliance</td>
<td>ODT, thin films, patches etc, Alternative delivery route</td>
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LCM & DDT examples on how to address solubility problems
Solubility problems

- 40% of the selected drug molecules for development are lipophilic.
- From the NCEs approved in 2002, > 50% were poorly soluble in water.
Nanosising: Why do we need nanoparticles in drug delivery?

To decrease the particle size and increase drug particle surface area, which leads to:

**Parenteral route:**
- i.v. injectability of nanosuspensions without risk of thrombosis
- Solubilization of poorly soluble drugs without a risk of precipitation
- Entrapment of irritating drugs, prevention of phlebitis at injection site

**Oral route:**
- Enhanced in-vivo dissolution
- Enhanced absorption
- Reduced variability
Commerially available “nano-scale” therapeutics

• Liposomes (Doxil, DaunoXome, Myocet, AmBiome, Visudyne)

• Albumin-bound nanoparticles (Abraxane, APP)

• Gadolinium chelate for MRI imaging (Magnevist, Gd-DTPA Dimeglumine, Berlex)

• Iron oxide particles for MRI imaging (Feridex, Berlex)

• Microemulsions (Neoral® Cyclosporine, Novartis)

• Products using Élan’s NanoCrystal technology (Rapamune®, Wyeth, Emend®, Merck)
Novartis Improved Bioavailability and reduced Variability through Neoral microemulsion formulation
Micro/nanonisation alternatives: > 10 DD companies

Top-down technologies:
- Nano-Milling
- Homogenization

Bottom-Up technologies:
- Precipitation
- SCF

Combinations:
- Elan
- Baxter
- Skyepharma
- Pharmasol
- Dow
- Soliqs
- SoluBest
- Nektar
- Eiffel
- Ferro
- Activery
How do the nanosizing technologies differ?

- Technology principle (bottom up vs. top down)
- Established scale and maturity (GMP, dev. stage)
- Creation of amorphous or crystalline nanoparticles
- Choice of stabilizers: polymers and/or surfactants
- Coating efficiency
- Use or omittance of a solvent
- IP protection
Nanonisation: NanoCrystal tech. in 4 marketed drugs

• Wyeth’s immunosuppressant Rapamune® (sirolimus)
  • Formulated in a tablet
  • Previously available only as an oral solution in bottles or sachets which required:
    ➢ Refrigeration storage
    ➢ Must be mixed with water or orange juice prior to administration

• Merck’s Emend® (Aprepitant) formulated in a capsule
  ➢ Emend was developed as an NCE

Convenience & Compliance

Bioavailability improvement
Nanonisation: NanoCrystal technology in 4 marketed drug products (Cont)

• Abbott’s TriCor® (fenofibrate)
  • Formulated in a tablet
  • Can be administered with or without food
    ➢ In the original formulation administration with a meal was needed

• Megace® ES (megestrol) formulated as oral solution
  • Improved dissolution rate and bioavailability
    ➢ Patients are able to take one-fourth of the volume of the original product

Convenience & Compliance

Bioavailability improvement
Nanonisation- Skyepharma: IDD-P™: one marketed product

First Horizon **Triglide™** (Fenofibrate):

- Formulated in a tablet
- Can be administered with or without food
  - In the original formulation administration with a meal was needed
Nanotechnology Development: a few concluding remarks

- The nano-based biomedical technology candidates are expanding*
  - 68% increase in the clinical pipeline from 2005
  - 130 nanotech-based drugs and delivery systems
  - 125 devices or diagnostic tests

- Demand for nanotechnology health care products in the US is projected to increase nearly 50 percent per year to $6.5 billion in 2009.

* Source: 2006 Nanomedicine, Device & Diagnostic Report, National Health Information, LLC.
LCM & DDT examples on how to address 1st pass metabolism
Example of a Dosage Form with Increased Bioavailability and Reduced First-Pass Metabolism

10 mg Zydis tablet delivers nearly **eight times** the concentration of selegiline than an ordinary 10 mg tablet

Source: http://www.cardinal.com/pts/content/aboutus/whoweare/broch/CH-PTS-DLV-Zydis.pdf
LCM & DDT- Examples of patient convenience and compliance improvement
Example of Inhalation replacing Injectable dosage form

Exubera: Pulmonary INSULIN

Approved by the FDA in January 2006

1st new administration route since it was discovered in 1921!!
Example of Inhalation replacing Injectable dosage form

Hepatic sinusoidal plasma insulin levels for Exubera inhalation and Humulin IVC-infused insulin

Hepatic glucose load for Exubera inhalation and Humulin IVC-infused insulin

Lungs provide an attractive target for both systemic and local drug delivery

Source:  http://diabetes.diabetesjournals.org/cgi/content/full/54/4/1164
Example of Oral replacing Injectable dosage form

Zydis apomorphine tablet delivers comparable bioavailability to injectable apomorphine

Source: http://www.cardinal.com/pts/content/aboutus/whoweare/broch/CH-PTS-DLV-Zydis.pdf
Example of convenience and compliance improvement

Zolmitriptan – a migraine drug

Fast melt tablets:
Can be taken without water any time and anywhere, even when patient feels nauseous

Nasal spray:
Shorter $t_{\text{max}}$
Earlier symptom relief
Patient convenience and compliance expressed in sales

Source: S. Milojevic, Drug delivery Partnership Conference, Europe, 2004
Life-Cycle Management – value of patent protection

It’s commercial reward for innovation!
Conclusions

LCM through technical line extensions provides the following benefits:

» Improvement of therapeutic value of drug products through improved therapeutic index (efficacy/safety)

» Improvement of convenience for patient

» Improvement of patient compliance

» Enriches Novartis portfolio

» Increases the business value of a brand

» Prolongs the life cycle of a brand
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