Applying concepts of mAbs and Vaccines manufacturing to Cellular Immune Therapy

Alain Pralong

05th September 2016
Agenda

- mAbs and Vaccines - where do we stand
- Approaches proven for mAbs and Vaccines
- Challenges in cellular immune therapy
- Summary and conclusion
Where do we stand

- Biopharmaceuticals have a long history
- History started with Vaccines
- Recombinant DNA technology transformed biopharmaceutical industry
- Cellular immune therapy offers major promises for the future

Variolation described in *The Golden Mirror of Medicine*, 1742

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Where do we stand

- First biopharmaceutical: Humulin in 1982
- Recombinant human insulin produced in *E. coli*
- Developed by Arthur Riggs in 1978
- Launched by Genentech
- Later acquired by Eli Lilly
- Replaced by follow on products
Where do we stand

Sales forecast 2010: 5 out of top ten

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Sales Forecast 2010 (Billion US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lipitor (cholesterol)</td>
<td>Pfizer</td>
<td>11.7</td>
</tr>
<tr>
<td>2</td>
<td>Plavix (anticlotting)</td>
<td>Sanofi / Bristol</td>
<td>9.6</td>
</tr>
<tr>
<td>3</td>
<td>Advair (asthma / COPD)</td>
<td>GlaxoSmithKline</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>Remicade (arthritis)</td>
<td>Merck / J&amp;J</td>
<td>7.4</td>
</tr>
<tr>
<td>5</td>
<td>Enbrel (arthritis)</td>
<td>Pfizer / Amgen</td>
<td>7.1</td>
</tr>
<tr>
<td>6</td>
<td>Humira (arthritis)</td>
<td>Abbott</td>
<td>6.8</td>
</tr>
<tr>
<td>7</td>
<td>Avastin (cancer)</td>
<td>Roche</td>
<td>6.7</td>
</tr>
<tr>
<td>8</td>
<td>Rituxan (cancer)</td>
<td>Roche</td>
<td>6.1</td>
</tr>
<tr>
<td>9</td>
<td>Diovan (hypertension)</td>
<td>Novartis</td>
<td>6.0</td>
</tr>
<tr>
<td>10</td>
<td>Crestor (cholesterol)</td>
<td>AstraZeneca</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Source: http://www.reuters.com/article/2010/04/13/roche-avastin-drugs-idUSLDE63C0BC20100413
Where do we stand

Sales forecast 2014: 8 out of top ten

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<td>Humira (arthritis)</td>
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<td>Roche</td>
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<td>7</td>
<td>Lantus (diabetes)</td>
<td>Sanofi-Aventis</td>
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<td>Advair (asthma / COPD)</td>
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<tr>
<td>9</td>
<td>Herceptin (cancer)</td>
<td>Roche</td>
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<tr>
<td>10</td>
<td>NovoLog (diabetes)</td>
<td>Novo Nordisk</td>
<td>5.7</td>
</tr>
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</table>

Source: http://www.reuters.com/article/2010/04/13/roche-avastin-drugs-idUSLDE63C0BC20100413
Where do we stand

Sales forecast 2016 for biopharmaceuticals: 167 bUS$

Emerging markets are the key drivers of total spending

Source: IMS market prognosis for pharmaceuticals, KPMG 2011
Where do we stand

- Significant product portfolio’s
- Significant global manufacturing infrastructure
- Significant disease control and therapeutic successes
- Significant commercial successes
Where do we stand

- Adoption and embedding of new technologies
- Massive evolution of single-use technologies
- Cost reduction, simplification, safety
- Closing of manufacturing process

20 years
La perfection est atteinte, non pas lorsqu'il n'y a plus rien à ajouter, mais lorsqu'il n'y a plus rien à retirer.

Antoine de Saint-Exupéry
Where do we stand

- New facility layouts enabled by new technologies

Source: picture courtesy of Parrish Galliher
Where do we stand

- Facility design based on modular construction
Where do we stand

- Most of current vaccine portfolio is at stage of commercial maturity
Where do we stand

- Patent cliff for mAbs materializes

Massively increasing R&D costs since 25 years

**PHARMACEUTICAL R&D EXPENDITURE IN EUROPE, USA AND JAPAN (MILLION OF NATIONAL CURRENCY UNITS*), 1990-2012**

* Note: Europe: € million; USA: $ million; Japan: ¥ million x 100
(e): estimate
Source: EFPIA member associations, PhRMA, JPMA
Where do we stand

- Increasing failure rates in R&D

Source: IFPMA: The pharmaceutical industry and global health: Facts and Figures 2012
# Where do we stand

## Evolving business environment

<table>
<thead>
<tr>
<th>Bases of competitive advantage today</th>
<th>Bases of competitive advantage in 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development resources, sales and marketing scale</td>
<td>Value of products and services, distribution strength</td>
</tr>
<tr>
<td>Global high prices, restricting access</td>
<td>Pricing based on ability to pay driving volume uplift</td>
</tr>
<tr>
<td>Multiple competitors in major therapeutic areas, scale permitting success</td>
<td>Fewer competitors in a broader range of diseases</td>
</tr>
<tr>
<td>Multi-billion dollar drug revenues covering high fixed costs</td>
<td>More products with lower revenues and lower costs</td>
</tr>
<tr>
<td>End to end operational capabilities for “self-sufficiency” strategy</td>
<td>Significant outsourcing of operations such as manufacturing and support functions</td>
</tr>
<tr>
<td>Acquisitions of technologies and products to augment product pipeline</td>
<td>Greater collaboration with academia, biotech and peers</td>
</tr>
<tr>
<td>Focus on mature Western Markets</td>
<td>Focus on Emerging Markets</td>
</tr>
</tbody>
</table>
Where do we stand

- Still growing world population – today 7.4 billion people

Where do we stand

Changing demographics

Sources: https://www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html
http://www.indexmundi.com/world/demographics_profile.html
http://theenergycollective.com/robertwilson190/281991/population-growth-addressing-real-problem
Where do we stand

- Access to drugs is not ensured to all

Source: http://www.msfaccess.org/content/medicines-shouldnt-be-luxury
Where do we stand

- How mature is the biopharmaceutical industry
## Where do we stand

### Current biological product shortages

<table>
<thead>
<tr>
<th>Product</th>
<th>Start</th>
<th>Reason</th>
<th>Resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow Fever Vaccine YF-VAX®</td>
<td>Apr 2016</td>
<td>Limited supply of Yellow Fever Vaccine YF-VAX®.</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed,</td>
<td>May 2012</td>
<td>Manufacturing delay for Pentacel®</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugate) Vaccine Pentacel®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG Live (Intravesical) TheraCys®</td>
<td>May 2012</td>
<td>TheraCys® BCG is currently unavailable.</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Where do we stand

Consequences of product shortages

Press Statement

24 March 2008

STOCK-OUTS OF TB MEDICATION ON WORLD TB DAY 2009

As people around the globe mark the World Tuberculosis (TB) Day, we the partners1 of the Stop Stock-Outs Campaign in Uganda are extremely concerned that even at this very moment there is a stock-out of anti-TB drugs at Mulago Hospital, Uganda’s national referral hospital.

For the last seven months, since October 2008, Mulago Hospital has been experiencing shortages of anti-TB drugs. These shortages have been affecting not only Mulago Hospital, but also the sub-district health centres. This is disastrous to Uganda’s efforts to prevent and eliminate TB cases in the country. According to the World Health Organization (WHO), Uganda ranks 15th in the world for TB burden. Mulago Hospital receives about 20% of all the country’s TB cases, attending to 250 or more patients every month. Mulago is not the only public health facility affected; TB medication stock-outs are also being experienced at sub-district health centres across the country.

This ongoing situation is totally unacceptable. Children with TB have not been able to get TB treatment at Mulago Hospital because there have been no pediatric TB medicines at the hospital since December 2008. Even more alarming, are the reports that Mulago Hospital’s stocks of ethambutol/INH combination (a TB medicine used in the continuation phase of TB treatment) expired in January 2009 and some patients are currently receiving expired medication.

Ironically, while the slogan for this year’s World TB Day states “I am stopping TB”, the Ugandan Government, by allowing this situation to prevail, is doing the opposite, and instead is promoting the spread of the disease because:

1. Patients identified with TB have to delay starting treatment because of the stock-outs. This delay means that these TB patients can potentially infect more people. It is important for someone infected with TB to start medication as quickly as possible, because the chance of infecting another person is drastically reduced after even one week of treatment.

2. The stock-outs mean that patients who are already on treatment will have to interrupt the course of treatment because the medicines they need are not in stock. Patients who interrupt their treatment are at increased risk of developing multi-drug resistance (MDR) TB. This exacerbates the crisis as MDR TB is more expensive and more difficult to treat.

"Stock outs have led to resistance among patients, most especially the TB patients. They start the course of the treatment and somewhere in the course of treatment, the drugs run out of stock causing resistance in the body."2

1 The partner organisations in Uganda involved in the Stop Stock-Outs Campaign include: MTPC, Uganda, Action Group for Health Human Rights and AIDS (AGHAH), National Forum of PLHIV Networks Uganda (PFOPNAU).

2 A health worker in South Sudan recently receivedurban TB patients with multi-drug resistance.

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Where do we stand

FDA has issues 787 a 483 for drugs in 2012

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cite Id</th>
<th>Ref No</th>
<th>Frequency</th>
<th>Short Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1105</td>
<td>21 CFR 211.22(d)</td>
<td>169</td>
<td>Procedures not in writing, fully followed</td>
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<tr>
<td>3</td>
<td>1361</td>
<td>21 CFR 211.100(a)</td>
<td>116</td>
<td>Absence of Written Procedures</td>
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<tr>
<td>6</td>
<td>1215</td>
<td>21 CFR 211.67(b)</td>
<td>73</td>
<td>Written procedures not established / followed</td>
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<tr>
<td>8</td>
<td>1112</td>
<td>21 CFR 211.25(a)</td>
<td>65</td>
<td>Training-operations, GMPs, written procedures</td>
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<tr>
<td>10</td>
<td>1358</td>
<td>21 CFR 211.100(b)</td>
<td>64</td>
<td>SOPs not followed / documented</td>
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<tr>
<td>13</td>
<td>1133</td>
<td>21 CFR 211.25(a)</td>
<td>54</td>
<td>GMP Training Frequency</td>
</tr>
</tbody>
</table>

Source: http://EnforcementActions/www.fda.gov/ICECI/
Where do we stand

- Primarily reactive way of working
Where do we stand

- Resource intensive
- Time consuming
- Major risk exposure for company
Proven approaches

“A complex system designed from scratch never works and cannot be patched up to make it work. You have to start over, beginning with a working simple system."

Jason Fried
Co-founder and CEO of 37signals
Proven approaches

- Product development is a bumpy journey
Proven approaches

- Adapt and embed from other industries

**Toyota Production System**

- Results for a sample year:
  - More than 700,000 improvement suggestions.
  - That is an average of over 10 improvement suggestions per employee per year.
  - Over 99% of suggestions were implemented.
Proven approaches

- Embed Operation Excellence as:
  - Multiple actors: QA, RA, QC, Operations, R&D
  - Multiple activities executed in parallel
  - Activities need to converged at specific moments in the development process
Proven approaches

Objective is clarity and alignment

- How can we get a better view from Discovery to Launch?
- Where are my raw materials suppliers?
- What are the constraints of Manufacturing?
- What is the impact of my job on the launch?
- How can we get more collaborative relationships?
- Are we aligned internally?
- Do we have the right talent?
- How to ensure that we understand what brings value?
Proven approaches

- Ambition is “Efficient process for efficient products”

1. Standardize and optimize the existing product development process

2. Create more continuity to ensure efficient knowledge management

3. Provide structure and limit risks in the decision making process
Proven approaches

Development pathway structured through stage gates

Product Development Value Stream: PDVS
Proven approaches

Possible organizational structure for product development
Proven approaches

- Preparing and understanding technical life cycle management

Technical Life Cycle Management

Product Lifecycle Management

- Design

Supply Chain Management

- Source
- Plan
- Produce
- Fulfill
- Service

Product Development

Partners

Suppliers

Consumers

Customers
Proven approaches

- Purpose and scope of life cycle management is modulation the product life cycle.
Proven approaches

- Two types of life cycle management:
  - Commercial life cycle management
  - Technical life cycle management
- Commercial life cycle management:
  - Marketing & sales strategy
  - Line extension
- Technical life cycle management:
  - Manufacturing processes
  - Analytical assays
Proven approaches

- All contributors have to be integrated
Proven approaches

Integration permits gathering a holistic understanding
Proven approaches

- Holistic understanding enable pro-active risk management: Technical Life Cycle Value Stream - TLCVS
Proven approaches

- Holistic understanding enable pro-active risk management
Proven approaches

- PDVS and TLCVS complement each other

1. Quality is “Built-in”
2. Lifecycle approach from Development to Product Discontinuation
3. Understand the complex supply chain and CMO networks
4. Robust process measurements & analytical tools
5. Real-time assessment of product & process capability
6. Maintaining “state of control” throughout commercial lifecycle
7. Ensuring an effective and timely change management system for continuous improvement and optimization
Proven approaches

- Training and Ways of Working adapted to personnel
Challenges in immune therapy

- Cellular immune therapies are personalized medicines
  - New class of products – experience of RA
  - High inter-patient variability
  - No stockpiling possible
- Significant risk in supply chain:
  - Complex manufacturing protocols
  - Semi-open aseptic processes
  - Manual, operator dependent handling
  - Currently limited automation
  - Transport from and to patient
- Manufacturing cost per dose - accessibility
Summary

- mAbs are very well established
- Vaccines exhibit issues with technical life cycle management
- Main focus for mAbs and Vaccines is accessibility
- mAbs and Vaccines have extensive experience with RA
- Structured approaches exist for product development and product life cycle
- Cellular immune therapy offers massive promise
- Young field in manufacturing - requires steep learning process
Conclusion

- Build on experience from mAbs and Vaccines
- Embed structured product development process
  - Control (pipeline development, cost, risk)
  - Time to market
  - Reduce regulatory hurdles
  - Enable life cycle management in the future
- Holistic approach
  - Humans
  - Products (processes & analytical methods)
  - Technology & facilities
  - Timelines
Thank you

Transforming patients’ lives through cellular immunotherapy

alain.pralong@cellmedica.co.uk

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