Building Efficiencies into Processes
Economies of Scale and Scale-up Technologies

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1 November 2016
Challenges
Industry and Market Trends
Platforms and Process Improvements
Facility Efficiency
Collaboration
Vaccination access & supply shortages

An estimated 19.4 million infants worldwide are still missing out on basic vaccines (3.2 million in humanitarian crisis regions)

Global Vaccine Action Plan is off track, not the least due to supply shortages & affordability

Reduced demand in developed markets
Market failure in markets with high demand
DCVMN members have an opportunity here
Outdated processes with batch failures
Workarounds exist, but big ideas do not

Vaccine Industry Consultation, Unicef, Copenhagen 26-27 October 2015

WHO, updated Sep 2016
Manufacturing of vaccines is inefficient

Patient expectation is 6 sigma

- Low process yield
- Lost batches
- Quality concerns

Efficiency gap

Defects / million opportunities [DPMO]

Sigma Level

Restaurant bills

Airlines baggage check-in

Egypt Air / Air India (5,8)

Lufthansa (6,6)

Qantas, SAS (best in class)

Quality to patients

Source: Motorola, Air Safety Online

Building Efficiencies

Adopted from Alain Pralong, GSK presentation at University College London, May 2014

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Diversification of technology – low efficiency

35-40 vaccines still to be developed

Where would this trend lead?

Production system
- CELL CULTURE
  - Sf9
  - Per.C6
  - CECC
  - WI-38
  - MRC-5
  - MDCK
  - Vero

EGGS
- EGGs
- Sf9
- Per.C6
- CECC
- WI-38
- MRC-5
- MDCK
- Vero

Viral
- Live
- Live-attenuated
- Inactivated
- VLP

Bacterial
- Inactivated
- Live-attenuated
- CPS/PS
- Toxoid

Vaccine type
- Viral
- Bacterial

Infectious agent category
- Viral
- Bacterial

1 November 2016 Building Efficiencies
## What are the Issues?

<table>
<thead>
<tr>
<th>Design of aged processes</th>
<th>Adaptation to changing markets</th>
<th>Access to new vaccine technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Many “weak steps”, low yield, low robustness</td>
<td>• Markets for classic vaccines shrink in developed markets with high prices</td>
<td>• Virus-like particles</td>
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<tr>
<td>• Lack of use of technology improvements</td>
<td>• Need to remove hurdles for investment and improvement, including regulatory hurdles</td>
<td>• High safety</td>
</tr>
<tr>
<td>• Lack of platforms, re-use of technology modules</td>
<td>• Reduce cost for highest standard production technology</td>
<td>• Low immunogenicity</td>
</tr>
<tr>
<td>• Open handling and regulatory concerns</td>
<td>• Scale down without losing economic advantages</td>
<td>• Complex processes</td>
</tr>
<tr>
<td>• Regulatory practice does not support new technology implementation</td>
<td>• Use any technology option to remove non-productive, costly activities</td>
<td>• rec Antigens &amp; adjuvants</td>
</tr>
<tr>
<td>• CapEx demand very high due to weak processes</td>
<td>• Overcome lack of flexibility in production infrastructure</td>
<td>• Easy processing</td>
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**Access to new vaccine technology**
- Virus-like particles
- High safety
- Low immunogenicity
- Complex processes
- rec Antigens & adjuvants
- Easy processing
- Good safety
- Immunogenicity dependent on adjuvant
- Messenger RNA
- High safety
- Simplified processing, no cold-chain
- Unproven in clinic
- ...and more
- Plasmids, cells, viral vectors
- Technology in its infancy
Industry and Market Trends
Important Industry Trends

Part 1

Vaccine-Sparing Technologies

• Adjuvant technologies improve the immunogenicity of vaccine components, reduce dose – safety of adjuvants in focus

Cell Culture-Based Vaccine Production

• Cell culture the next generation large scale whole virus vaccine production technology – hurdles against process changes

‘Universal’ Vaccine Technologies

• Developing vaccines that can target multiple or drifted strains of the same pathogen

• Focus on highly conserved antigens, anticipate drift or target all known strains of a specific pathogen.
Important Industry Trends (2)

Part 2

**Needle Free Vaccine Delivery Technologies**

- Needle-based delivery of vaccines an impediment to broader vaccine use – efficiency of delivery

**Pursuit of Rapidly Adaptable, Scalable Production Technologies**

- Lead times for conventional vaccine manufacturing exceed lifespan of some outbreaks – *infrastructure is “frozen in the past”* of market demands

- High fixed cost structure of production capacity to serve inherently volatile markets

- Move toward modular, disposable, mobile manufacturing systems as a source of surge capacity and rapid vaccine production and delivery.
The improvement history of Polio vaccines

Time limited market opportunity for IPV until successful eradication

- 1955: inactivated Polio vaccine (IPV) launched (Salk type)
- 1960: attenuated Polio vaccine launched (Sabin type)
- 1960s: collaboration between Prof. Van Wezel (RIVM/NVI NL) and Pharmacia Biotech around microcarrier cultures of primary monkey cells (unsafe)
- 1970s: new IPV purification method using GE’s chromatography resins
- **1980s: switch to Vero cell (safe) production using GE’s Cytodex 1 microcarriers in large bioreactors (Salk type)**
- **Global certification of eradication of Polio**
Virus-like Particles Technology: The Bet

Successes and Failures, complex processing and long implementation time

- Hepatitis B and HPV vaccines, (Gardasil and Cervarix)
  - successful in clinic and market
- The vaccines of tomorrow? Many VLPs in early and clinical development
- Recent failure of Novavax RSV phase III trial,
- High safety but limited immunogenicity - Adjuvants needed?
- Complex processing, expression in yeast or insect cells, purification challenging
  - high production costs
What are the Options?

**Design of aged processes**
- Many “weak steps”, low yield, low robustness
- Technology can drift over time
- Platforms, re-use of technology
- Economy very dependent on scale
- Limited value post-eradication or in shrinking markets?

**Adaptation to changing markets**
- Markets for classic vaccines shrink in developed markets with high prices
- Need to find new markets for investment, including emerging, developing, and non-pharmaceutical purposes
- Economy very dependent on scale
- Overcome lack of flexibility in production infrastructure

**Access to new vaccine technology**
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**Scalability and yield, process robustness with current technology**
- Limited value with pressing short-term challenges

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Building Efficiencies
Platforms and process improvements
Vaccine technology shift – cell culture platform

- Evolution of production techniques has created the option to use cell culture as a platform for viral vaccine manufacturing
- Egg-based vaccines transferred to cell culture using adherent cells on microcarriers
  - Vero cells
  - MDCK
- Production in roller bottles or cell factories transferred to easily scalable bioreactors
  - Polio vaccine (implemented)
  - Rotavirus vaccine (development)
  - More than 20 other virus vaccines can be produced using microcarriers
Technology evolution – more robust workflow

Classic microcarrier:

Dry Cytodex → Weigh in → Swell in buffer → Sterilise Autoclave (small scale) / Fermenter (large scale) → Drain buffer → Wash with cell culture media → Swell in cell culture media

NEW Cytodex™ gamma:
Ready-to-use (enabling single-use reactors)

Gamma-Irradiated Cytodex packages for 10, 100 and 1000 L cultures → Add directly into Bioreactor
Capto Core, towards a chromatography platform for vaccine purification

Combination of two chromatographic steps

1. Size exclusion properties (base matrix cut-off vs target size)
2. Bind /elute properties (ligand-impurity interaction)

The performance of Capto Core based resins is based on two events:

1. Does the target or the impurities penetrate the bead (SEC)?
2. Does the target or the impurities bind in the functionalized core (B/E)?
Buffer preparation – deal with other inefficiencies

In-line conditioning (IC)

- Single component stock solutions adjusted to buffer needs
- Offline production of buffers into bags
- Direct feed to unit operation
- Can be fully integrated into the unit operation (no separate skids)

Hold-up tanks and bags
Quality features in an Inline Conditioning system

Watch commands and alarm levels verify that incoming stock solutions meet specifications.

Dedicated monitoring and control sensors.

Buffer data is electronically stored.

Feedback loops adjust recipe if slight variations in incoming stock concentrates occur.

Any produced buffer that does not meet specifications will be diverted to drain.
pH control in a salt gradient situation: IC vs ID

20 mM citrate pH 3.5, 0 to 1 M NaCl 400 L/h flow feedback

A four-pump solution allows constant pH along the gradient

A two-pump solution leads to pH variations along the gradient
Facility related efficiencies
Reduce facility investment cost

Construction costs are adjusted to 2009 level using 3% constant inflation rate.

\[ y = 2,9251x + 37,813 \]

\[ R^2 = 0,9631 \]

Legacy facilities bear a huge fixed cost burden.

CAPEX can be 30% lower for single-use facility.

### Bioreactors [L] Configuration Cost [$ M]

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<th>Configuration</th>
<th>Cost [$ M]</th>
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<tbody>
<tr>
<td>2.000</td>
<td>2x 1.000</td>
<td>43.7</td>
</tr>
<tr>
<td>6.000</td>
<td>6x 1.000</td>
<td>55.4</td>
</tr>
<tr>
<td>12.000</td>
<td>6x 2.000</td>
<td>72.9</td>
</tr>
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Confirmed in bottom-up analysis by M+W authors ($42.6M).
Simplified path to pre-qualification

- Right sized facility built to highest standards of GMP requirements
  - Engineering design
  - Off-site construction
  - Transport, logistics
  - Insurance, local labor
  - Final construction, qualification

Current offering for mAbs
18 months to completion
Single-use FlexFactory™

Platform for vaccines ???
Collaboration opportunities
How can suppliers like GE support ... ?

Cell culture media & supplements | Develop a robust media and feed formulation strategy

Upstream PD | Convert from stainless to single-use processes with robust scale up

Downstream PD | Purity of your product with process robustness, minimize the number of units operations for maximum economy

Clinical manufacturing | Produce material for tox-batches or for phase I & II clinical trials

Analytical development / Quality control | Develop robust analytics and stability testing

Process transfer | Managing your process for delivery on time

Training & education | Training for managers, PD and Manufacturing teams
Conclusions

• Significant efficiency gains possible from process design
• Cell culture promising as platform for viral vaccines
• Chromatography platform increases yield and purity
• Manufacturing infrastructure smaller and more flexible
• Efficient processes and infrastructure attract funding and procurement partners
• Changing market landscape suggests collaboration