Need for updated vaccine processing and process optimization for global access
Process development and optimization training workshop—DCVMN Taipei

Speakers

Dr. Mats Lundgren  
Customer Applications Director, Life Sciences  
GE Healthcare, Sweden

Mia Bennemo  
Senior Research Engineer, Life Sciences  
GE Healthcare, Sweden
Preliminary agenda

• Introduction to process development for vaccine production
• Process economy
• Group discussion exercise—how to overcome technical and economical challenges in DCVMN companies
• Analytics
• Lunch break
• Upstream process development
• Downstream process development
• Quality by design (QbD) in process development
• Practical exercise: QbD
• Future scenarios, wrap up discussion and test
Introduction to process development for vaccine production
Outline

• Vaccine process history
• Why is process development for vaccines important?
• Vaccine processing
• Single-use technologies for vaccine manufacturing
• Conclusions
1796: Edward Jenner develops smallpox vaccine

1885: Pasteur develops rabies vaccine

1943: Egg-based influenza vaccine

1955: Injectable polio vaccine introduced

1962: Oral polio vaccine introduced

1967: Smallpox eradication program started

1979: Smallpox eradicated from the world

1986: First recombinant human vaccine

1994: Last case of polio in the Americas

2006: First cancer vaccine HPV vaccine

2010: First therapeutic cancer vaccine approved
The evolution of vaccine processes

- First generation processes:
  - Focus on upstream, optional inactivation

- Second generation processes:
  - Separation based on centrifugation, filtration

- Currently developed processes:
  - Quality based approach: QbD
  - Focus on entire process including purification and virus safety
Historic vaccine timeline: propagation

- **1796**: Edward Jenner develops smallpox vaccine
- **1885**: Pasteur develops rabies vaccine
- **1943**: Egg-based influenza vaccine introduced
- **1955**: Injectable polio vaccine introduced
- **1962**: Oral polio vaccine introduced
- **1967**: Smallpox eradication program started
- **1986**: First recombinant human vaccine
- **1979**: Smallpox eradicated from the world
- **1994**: Last case of polio in the Americas
- **2006**: First cancer vaccine (HPV) approved
- **2010**: First therapeutic cancer vaccine approved

In vivo

In ovo

Primary cell line

Diploid cell line

Continuous cell line
Historic vaccine timeline: purification

1796: Edward Jenner develops smallpox vaccine

1885: Pasteur develops rabies vaccine

1943: Egg-based influenza vaccine introduced

1955: Injectable polio vaccine introduced

1962: Oral polio vaccine introduced

1967: Smallpox eradication program started

1979: Smallpox eradicated from the world

1986: First recombinant human vaccine approved

1994: Last case of polio in the Americas

2006: First cancer vaccine HPV vaccine approved

2010: First therapeutic cancer vaccine approved

1943: Egg-based influenza vaccine introduced

Non-purified

Filtration

Filtration/centrifugation

Chromatography

Quality by design
The history of polio vaccines and GE

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1955</td>
<td>Inactivated polio vaccine (IPV) launched (Salk Type)</td>
</tr>
<tr>
<td>1960</td>
<td>Attenuated polio vaccine launched (Sabin type)</td>
</tr>
<tr>
<td>1960s</td>
<td>Collaboration between Prof. Van Wezel (RIVM/NVI Netherlands) and GE (former Pharmacia) around microcarrier cultures of primary monkey cells</td>
</tr>
<tr>
<td>1970s</td>
<td>New IPV purification method using GE’s chromatography resins</td>
</tr>
<tr>
<td>1980s</td>
<td>Switch to Vero cell production using Cytodex™ 1 microcarriers</td>
</tr>
<tr>
<td>2010s</td>
<td>Updating the IPV processes using modern technology from GE</td>
</tr>
</tbody>
</table>
Polio vaccine process

<table>
<thead>
<tr>
<th>Production system</th>
<th>Vaccine type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vero cell line</td>
<td>Polio vaccine (IPV). Naked virus (~30 nm). Type 1, 2, and 3 subtypes in the</td>
<td>Netherlands Vaccine Institute (NVI) - Vaccine 29, p.7188–7196, 2011</td>
</tr>
<tr>
<td></td>
<td>vaccine. (Sabine–OPV, Sabine-IPV, Salk-IPV)</td>
<td>- <a href="http://www.plosone.org">www.plosone.org</a>, 1 December 2013, Vol. 8, Issue 12</td>
</tr>
</tbody>
</table>

1. Cell expansion 1
2. Cell expansion 2
3. Production & filtration
4. Concentration
5. Chromatography 1
6. Chromatography 2
7. Virus inactivation & sterile filtration

**UPSTREAM**

1. **Cytodex™ 1 (3g/L, 15 L)**
   - serum containing media, trypsination
cell transfer

2. **Cytodex 1 (3 g/L, 40 L)**
   - recirculation grow cells to $5 \times 10^6$ cells/mL
tripsination, cell transfer

3. Lower reactor temperature at infection
   - wash cells to change to serum-free media

**DOWNSTREAM**

3. 0.45/0.22 µm removal of cell debris on depth filters
4. Tangential flow filtration (TFF), 100 kD flat sheet
   - Virus concentration
5. **Sepharose™ CL 6B resin**
   - cell debris and host cell protein (HCP) removal
6. **DEAE Sephadex™ A50 resin**
   - purification, DNA, and HCP removal
7. 0.025 % formaldehyd, 13 days, 37°C
8. 0.2 µm
Why is process development for vaccines important?
What are the challenges for vaccine producers?

**Design of aged processes**
- Many “weak steps”, low yield, low robustness
- Lack of platforms, re-use of technology modules
- Open handling and regulatory concerns
- Regulatory practice does not support new technology implementation
- CAPEX demand very high due to weak processes
- Economy very dependent on scale

**Adaptation to changing markets**
- Markets for classic vaccines shrink in developed markets with high prices
- Need to remove hurdles for investment and improvement, including regulatory hurdles
- Reduce cost for highest standard production technology
- Overcome lack of flexibility in production infrastructure

**Access to new vaccine technology**
- Virus-like particles (VLP)
  - High safety
  - Low immunogenicity
  - Complex processes
- Rec Antigens and adjuvants
  - Easy processing
  - Good safety
  - Immunogenicity dependent on adjuvant
- ...and more
  - Viral vectors
  - Plasmids, mRNA
  - Cells
  - Technologies in its infancy

CAPEX = capital expenditure
What are the challenges for vaccine producers?

**Design of aged processes**
- Many “weak steps”, low yield, low robustness
- Complex processes, re-use of modules
- Open handling and regulatory concerns
- Regulatory practice does not support new technology implementation
- High CAPEX demand due to weak processes
- Economy very dependent on scale

**Adaptation to changing markets**
- Markets for classic vaccines shrink in developed markets
- Needs for new capabilities for innovation and growth
- Re-engineering existing equipment and processes
- Regulatory issues to be overcome
- High immunogenicity depending on adjuvant

**Access to new vaccine technology**
- Virus-like particles
- High safety
- Low immunogenicity
- Complex processes
- Rec Antigens and adjuvants
- Easy processing
- Good safety
- Immunogenicity dependent on adjuvant
- ...and more
- Viral vectors
- Plasmids, mRNA
- Cells
- Technologies in its infancy

**Flexible, right-scaled production infrastructure and facilities**
- Improved scalability, yield and process robustness with modern technology

Implement platform technologies upstream and downstream
Process development—trends and solutions

- Quality must never be compromised
- You always need to spend enough time and money to understand what the process does to the product
- Your process will be most efficient in terms of time and cost, if you build its performance on solid understanding
## Vaccines are difficult to characterize

<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
<th>Vaccines</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often well-characterized</td>
<td>Often difficult to characterize</td>
<td>Less definitive analytical comparability pathways Less ability to monitor product quality in mid-process</td>
</tr>
<tr>
<td>Clear link to mechanism of action (MoA) and/or biomarker surrogate for clinical performance</td>
<td>Difficult to establish clinical potency surrogates</td>
<td>Challenging to improve process post-licensure</td>
</tr>
<tr>
<td>Consistent process and product</td>
<td>Sometimes more complex, less predictable process/product</td>
<td>Variability over product/process life cycle</td>
</tr>
<tr>
<td>Therapeutic patient population</td>
<td>Prophylactic patient population</td>
<td>“Process is product” philosophy to assure quality</td>
</tr>
<tr>
<td>Well-understood process; good detectability for test methods</td>
<td>Less understood process; difficult to measure attribute changes</td>
<td>Empirical process models for linking parameter inputs to quality outputs More stringent threshold for reporting manufacturing changes</td>
</tr>
</tbody>
</table>
A-VAX case study objectives I

Substantial changes in quality systems and regulatory approaches might be needed

• Apply QbD to develop a robust vaccine manufacturing process. This includes:
  • Risk-based approaches to vaccine development
  • Leveraging of science to gain process and product understanding
  • Continuous improvement
  • Merging of process and analytical controls for vaccine manufacturing
  • Make the rationale for development more transparent in regulatory submissions
A-VAX case study objectives II

Substantial changes in quality systems and regulatory approaches might be needed

• Document techniques for safe and effective vaccines to reach market more quickly

• Strive to make reviews more efficient; decrease the number of post-approval supplements needed

• Develop realistic examples to better illustrate how QbD can be applied within the development space and overall product quality system

• Highlight and/or develop tools, frameworks, etc., to enable ICH Q8, Q9, Q10, and Q11 implementation strategies

• Tie key benefits with the strategies illustrated in the case study
Note of caution on A-VAX

It should be understood that this document does not represent new regulatory policy, nor does it define a new “gold” standard for future regulatory submissions. However, it is aligned with the available guidance from ICH and other sources. Individual companies will interpret and apply the principles differently. The extent of applicability will vary for each development effort. There are simplifying assumptions, e.g., the effect of multiple changes across unit operations is not considered. There are aspects left out due to differences in opinion between participating companies. By no means should this case study be turned into regulatory expectations or standard.
Impact of process economy

Typical vaccine business

• Legacy processes: manufacturing cost represents more than 50% of the revenue.

• Impact of process optimization on process economy (cost per dose reduction).
Vaccine processing
Vaccines and production

Vaccines

- Bacteria based
- Virus based
- Protein based
- Polysaccharide based

The manufacturing process

- Cell culture/fermentation
- Purification
- Fill and finish
- Analysis (QA/QC)
Diversification of technology—low efficiency

Production system
- CELL CULTURE
  - Sf9
  - Per.C6
  - MDCK
  - Vero
  - MRC-5
- EGGs
- MICROBIAL
- CELL CULTURE

Vaccine type
- Live
- Live-attenuated
- Inactivated
- VLP
- Inactivated
- CPS/PS
- Live-attenuated
- Toxoid

Infectious agent
- Viral
- Bacterial

Infectious agents:
- H. influenzae
- B. anthracis
- S. typhi
- B. pertussis
- S. pneumoniae
- N. meningitidis
- V. cholerae
- C. tetani
- C. diphtheriae
- S. cerevisiae
## Vaccine production today

<table>
<thead>
<tr>
<th>Processes developed decades ago</th>
<th>Processes difficult to scale up</th>
<th>Unfavorable process economy</th>
<th>Increased regulatory requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old cell substrates or eggs</td>
<td>Centrifugation</td>
<td>Low yields</td>
<td>Open handling</td>
</tr>
<tr>
<td>Limited purification</td>
<td>Fixed installations</td>
<td>Long process times</td>
<td>Batch variability</td>
</tr>
<tr>
<td>Significant expertise required</td>
<td>Roller bottles</td>
<td>Labor-intense processes</td>
<td>Serum supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dedicated facilities</td>
<td></td>
</tr>
</tbody>
</table>
## Vaccine production tomorrow

<table>
<thead>
<tr>
<th>Processes developed decades ago</th>
<th>Processes difficult to scale up</th>
<th>Unfavorable process economy</th>
<th>Increased regulatory requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platform cell lines</td>
<td>Scalable technologies enabled by, e.g., single-use technologies</td>
<td>Efficient and rational process design</td>
<td>Closed handling</td>
</tr>
<tr>
<td>Efficient purification</td>
<td></td>
<td></td>
<td>QbD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexible facilities</td>
<td>Chemically defined cell culture media</td>
</tr>
</tbody>
</table>
Vaccine manufacturing

Major challenges

- Product titer
- Regulatory
- Old substrates
- Yield
- Scale-up
- Consistency
- Open handling
- Yield
- Aggregation
- Yield
- Aggregation
- DNA and HCP reduction
- Potency
- Stability
- Analytical precision
- Number of methods

Potential solutions

- Vaccine technologies
- Cell lines
- Expression systems
- Disposable bioreactors
- Cell culture media
- Microcarriers vs suspension
- Filters
- Novel capture formats
- Chromatography resins
- Novel purification formats
- Analytical methods
- Bioassays

Single-use technologies, FlexFactory™ platform and facility solutions
Single-use systems suitable in vaccine production

- Vaccines often manufactured in relatively small batch sizes makes single-use technology appropriate.
- Campaign manufacturing is common, single-use allows multi-product manufacturing.
- Pandemic preparedness requires faster development and manufacturing times.
- Higher cost constraints on vaccine manufacturing call for improved process economics.
- Safety concerns makes closed systems suitable.
Single-use processing

Closed system processing—connecting upstream to downstream

- Standard or customized assemblies
- Considerations:
  - Sterility claims
  - Extractables/leachables
- Aseptic processing of large viruses (e.g., pox vectors)
- Improve economics
  - Reduced losses in sterile filtration
Quality must never be compromised

• You always need to spend enough time and money to understand what the process does to the product

• Your process will be most efficient in terms of time and cost if you build its performance on solid understanding
Need for updated vaccine processing and process optimization for global access.