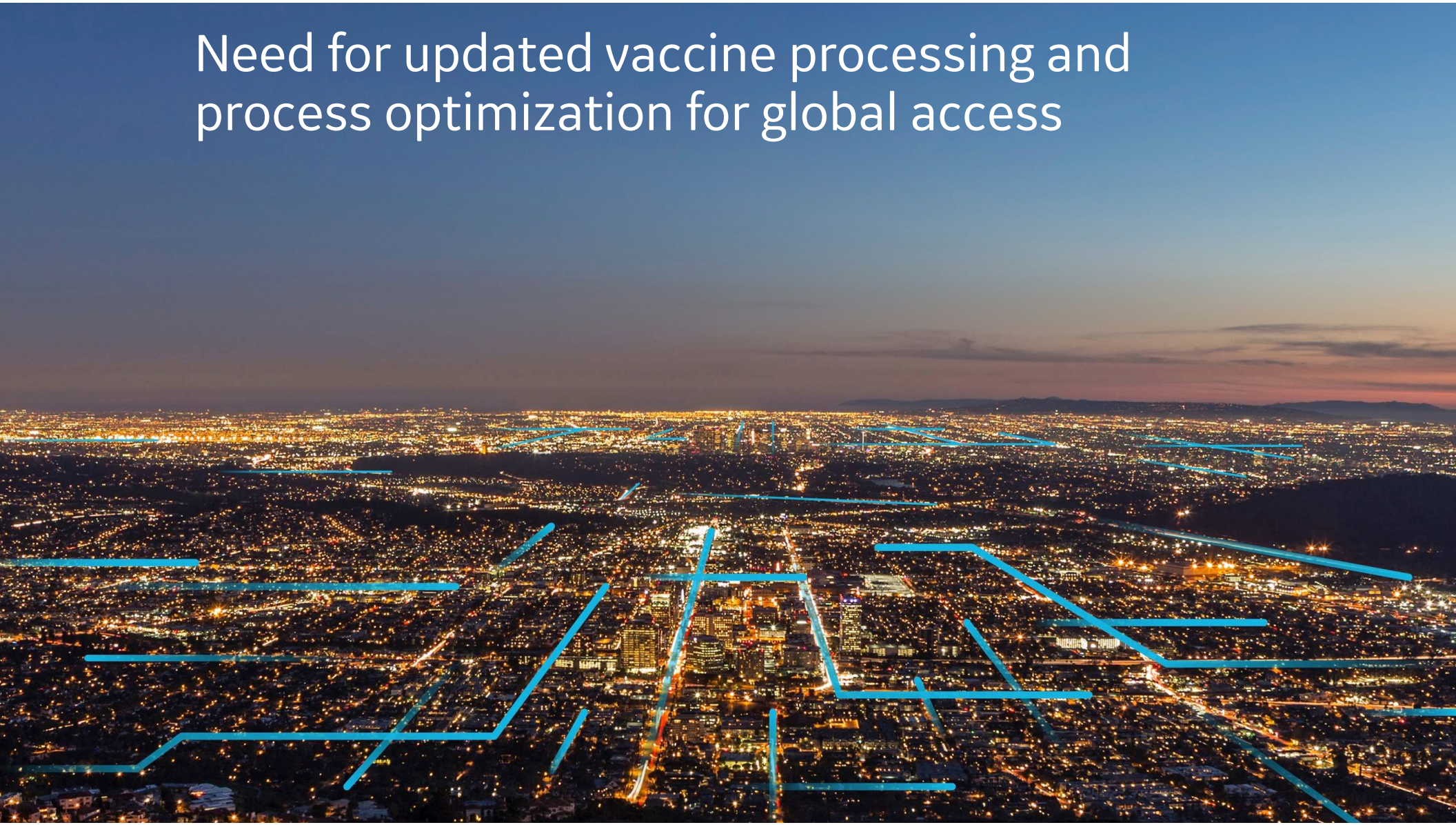
Introduction to process development for vaccine production

DCVMN 10 March 2017

Need for updated vaccine processing and process optimization for global access



Process development and optimization training workshop—DCVMN Taipei

Speakers

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GE Healthcare, Sweden

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Senior Research Engineer, Life Sciences

GE Healthcare, Sweden

Preliminary agenda

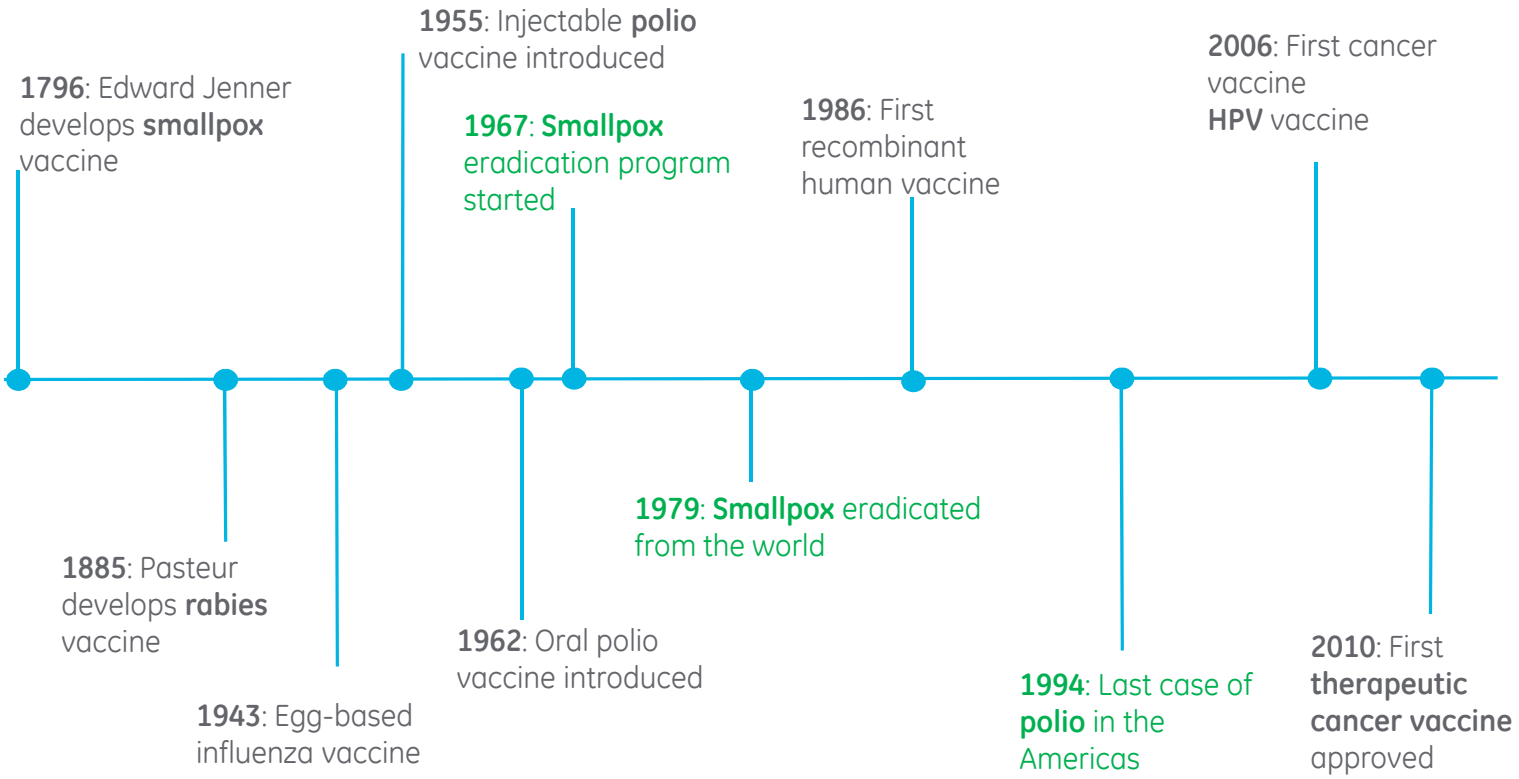
- Introduction to process development for vaccine production
- Process economy
- Group discussion exercise—how to overcome technical and economical challenges in DCVMN companies
- Analytics
- Lunch break
- Upstream process development
- Downstream process development
- Quality by design (QbD) in process 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

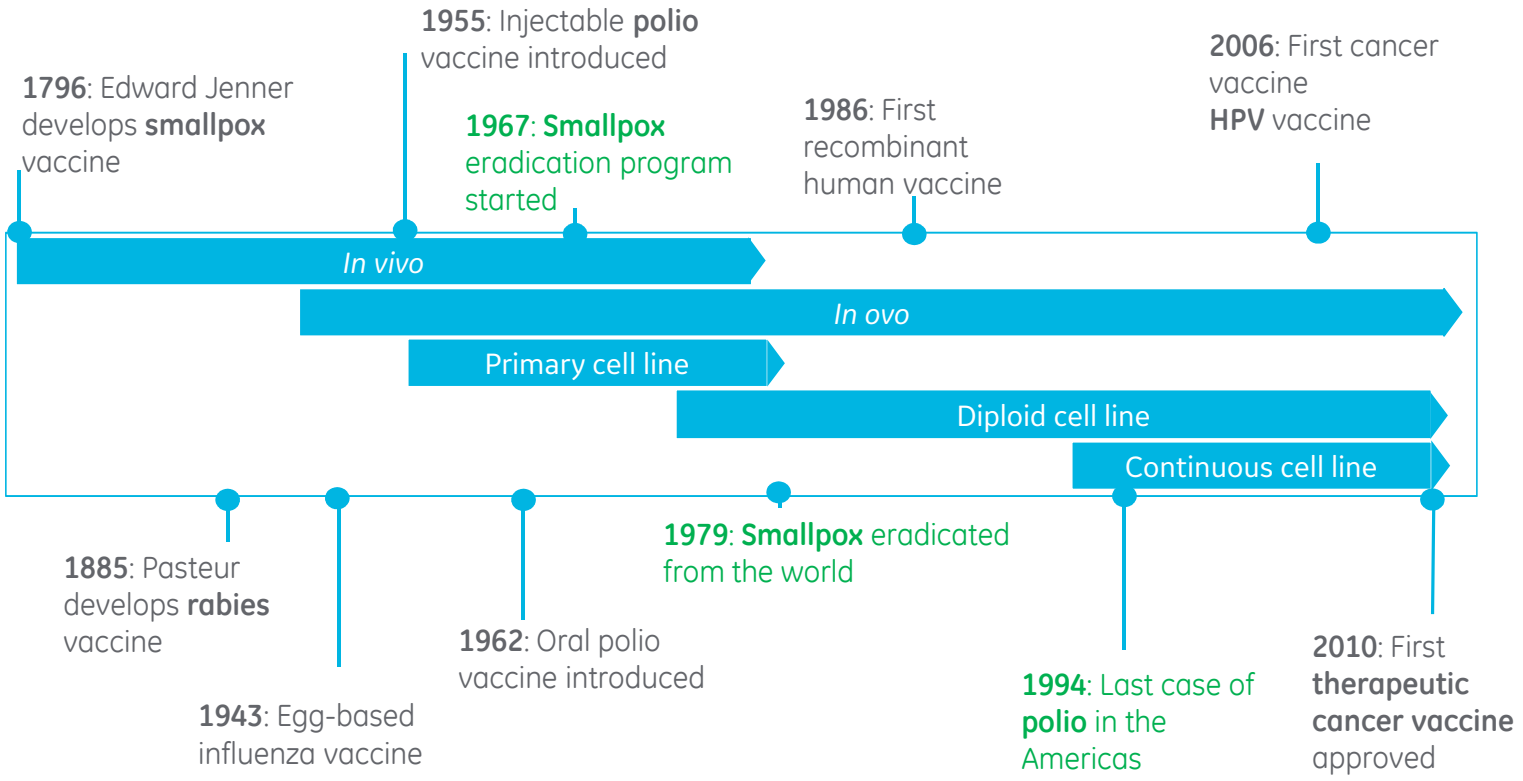
Historic vaccine timeline



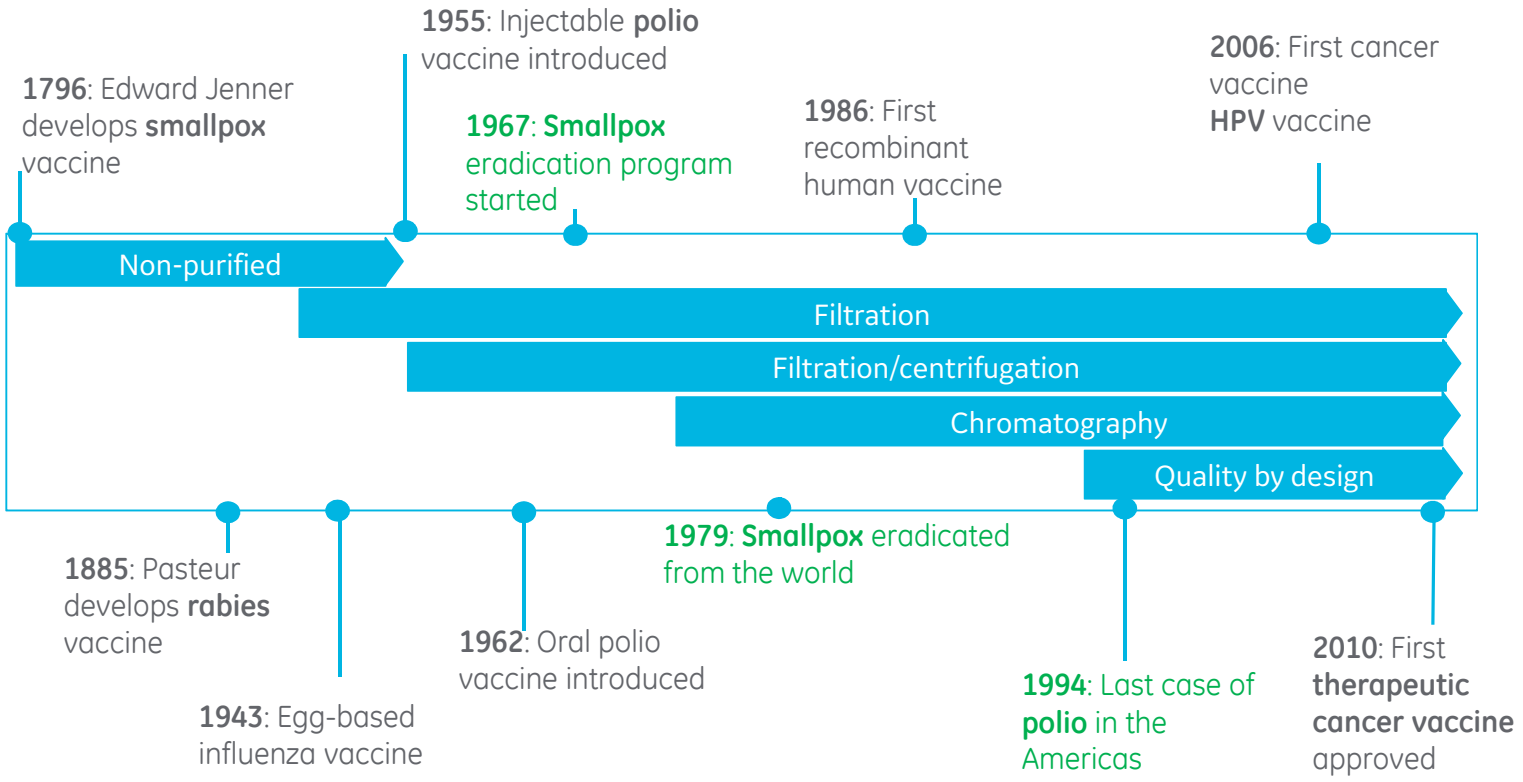
The evolution of vaccine processes

- 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



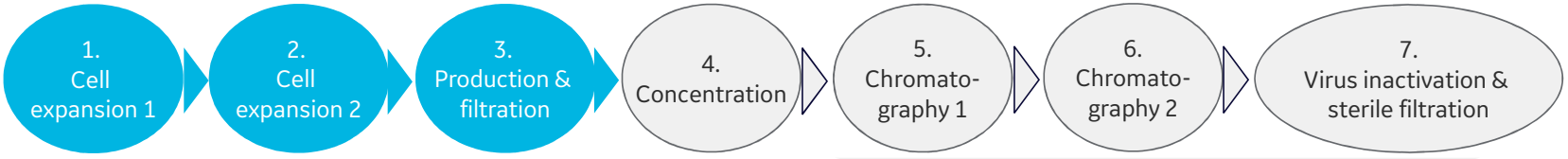
Historic vaccine timeline: purification



The history of polio vaccines and GE

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

Polio vaccine process



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 × 10^6 cells/mL
   trypsination, 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
7. 0.2 µm

Production system	Vaccine type	Reference
Vero cell line	Polio vaccine (IPV). Naked virus (~ 30 nm). Type 1, 2, and 3 subtypes in the vaccine. (Sabine –OPV, Sabine-IPV, Salk-IPV)	Netherlands Vaccine Institute (NVI) - Vaccine 29, p.7188– 7196, 2011 - www.plosone.org, 1 December 2013, Vol. 8, Issue 12

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

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Adaptation to changing markets

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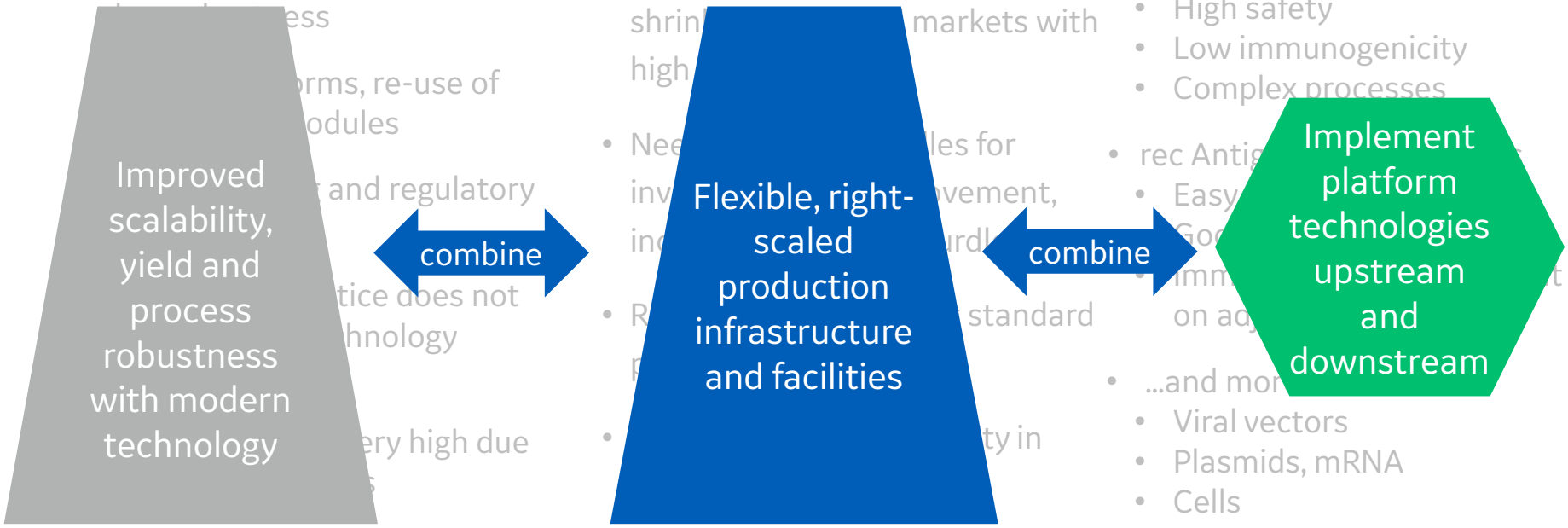
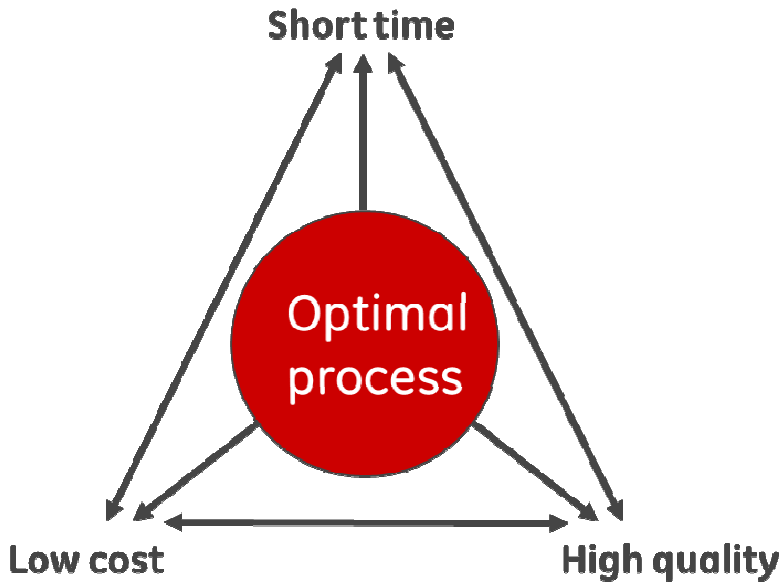


Process development—trends and solutions



- 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

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

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

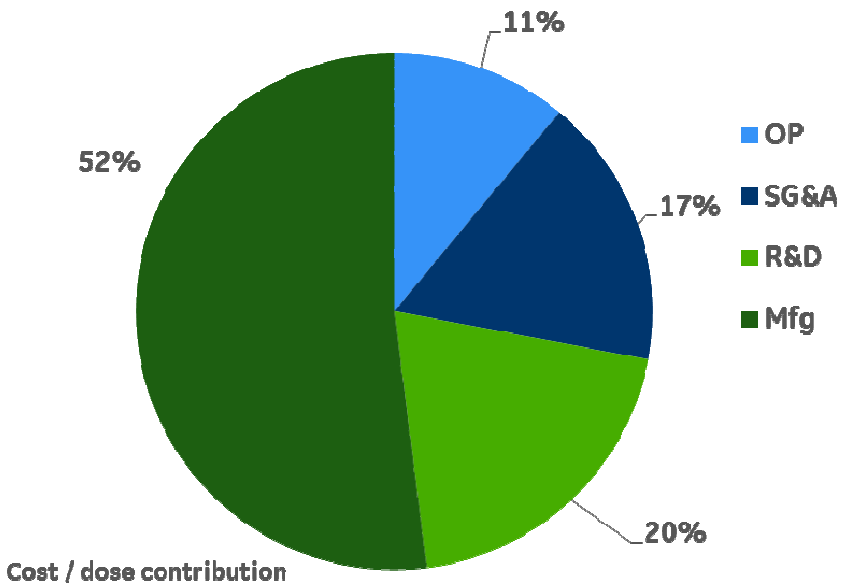
Substantial changes in quality systems and regulatory approaches might be needed

- 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 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 of 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



Annual Report 2009: Crucell, incl. Berna Biotech

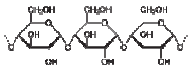
Typical vaccine business

- 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

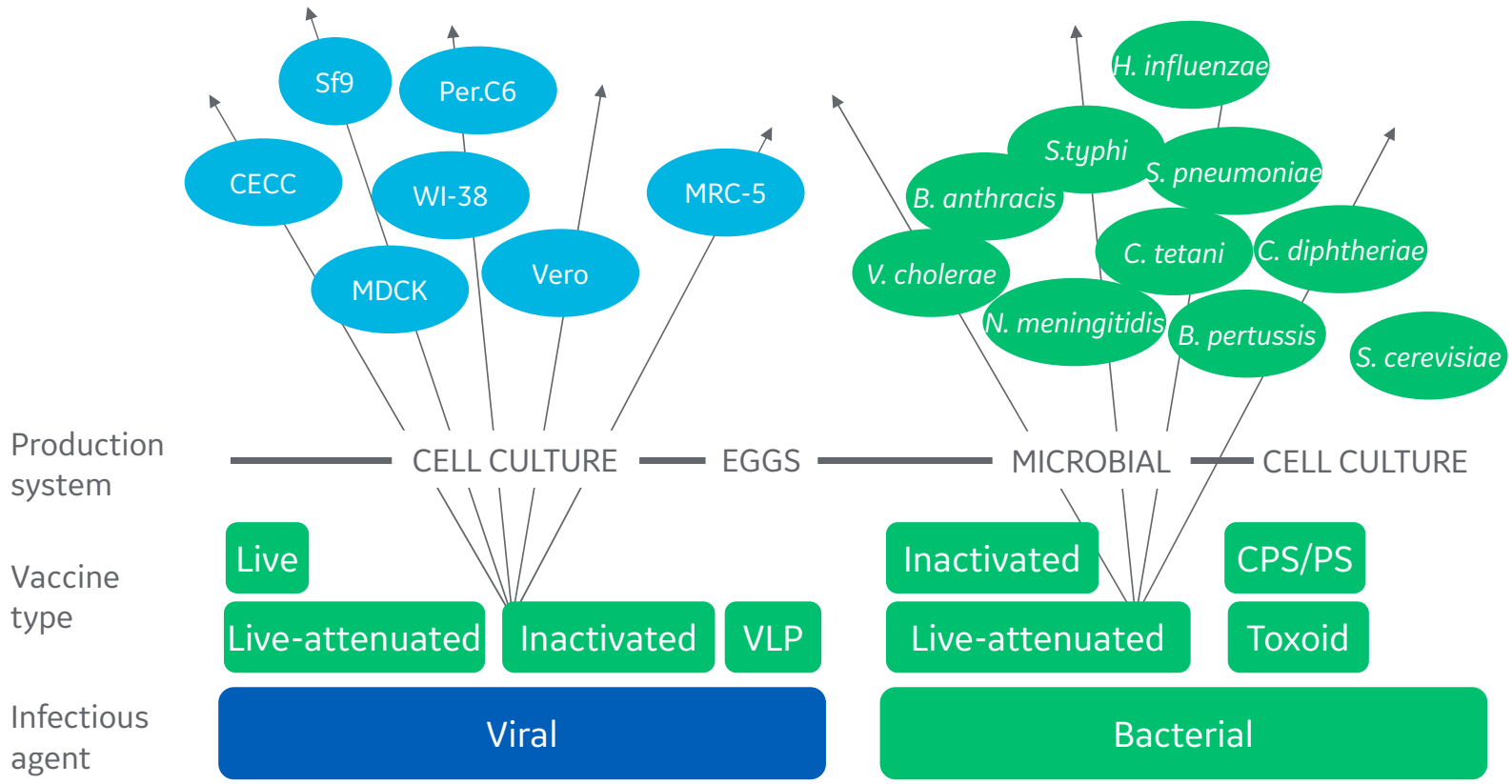
- Bacteria based 
- Virus based 
- Protein based 
- Polysaccharide based 

The manufacturing process

- Cell culture/ fermentation
- Purification
- Fill and finish
- Analysis (QA/QC)

E. Coli Bacteria from NIH Image Library
Influenza virus by Kat Masback.

Diversification of technology—low efficiency



Vaccine production today

Processes developed decades ago

Old cell substrates or eggs

Limited purification

Significant expertise required

Processes difficult to scale up

Centrifugation

Fixed installations

Roller bottles

Unfavorable process economy

Low yields

Long process times

Labor-intense processes

Dedicated facilities

Increased regulatory requirements

Open handling

Batch variability

Serum supplementation

Vaccine production tomorrow

Processes developed decades ago

Platform cell lines

Efficient purification

Processes difficult to scale up

Scalable technologies enabled by, e.g., single-use technologies

Unfavorable process economy

Efficient and rational process design

Flexible facilites

Increased regulatory requirements

Closed handling

QbD

Chemically defined cell culture media

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

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