Building Efficiencies into Processes

Economies of Scale and Scale-up Technologies

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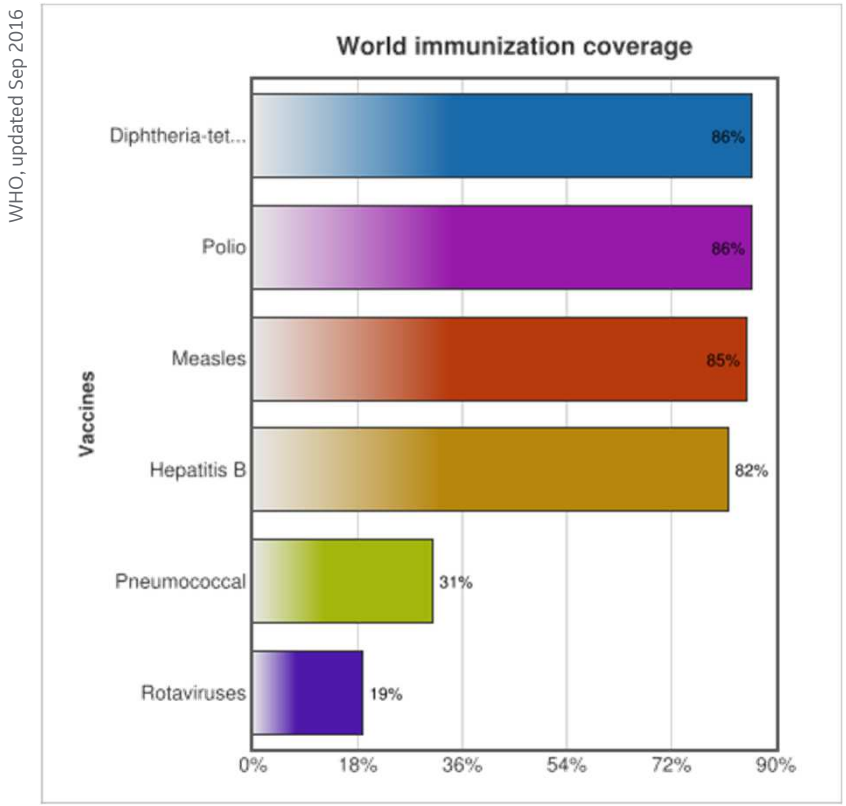
Challenges
Industry and Market Trends
Platforms and Process Improvements
Facility Efficiency
Collaboration

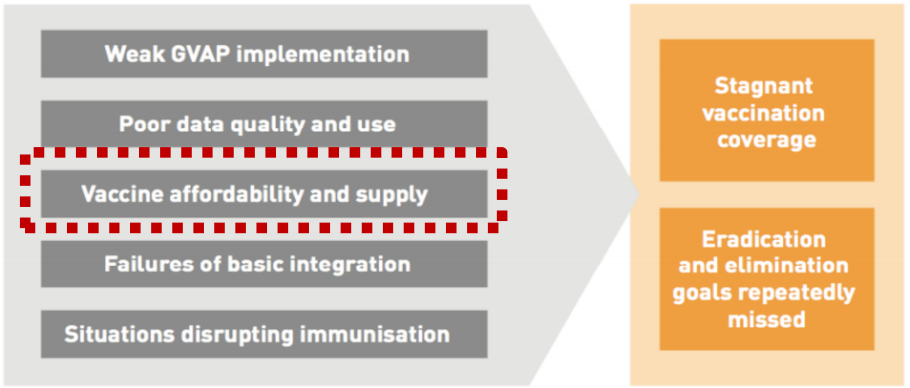
Vaccination access & supply shortages

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

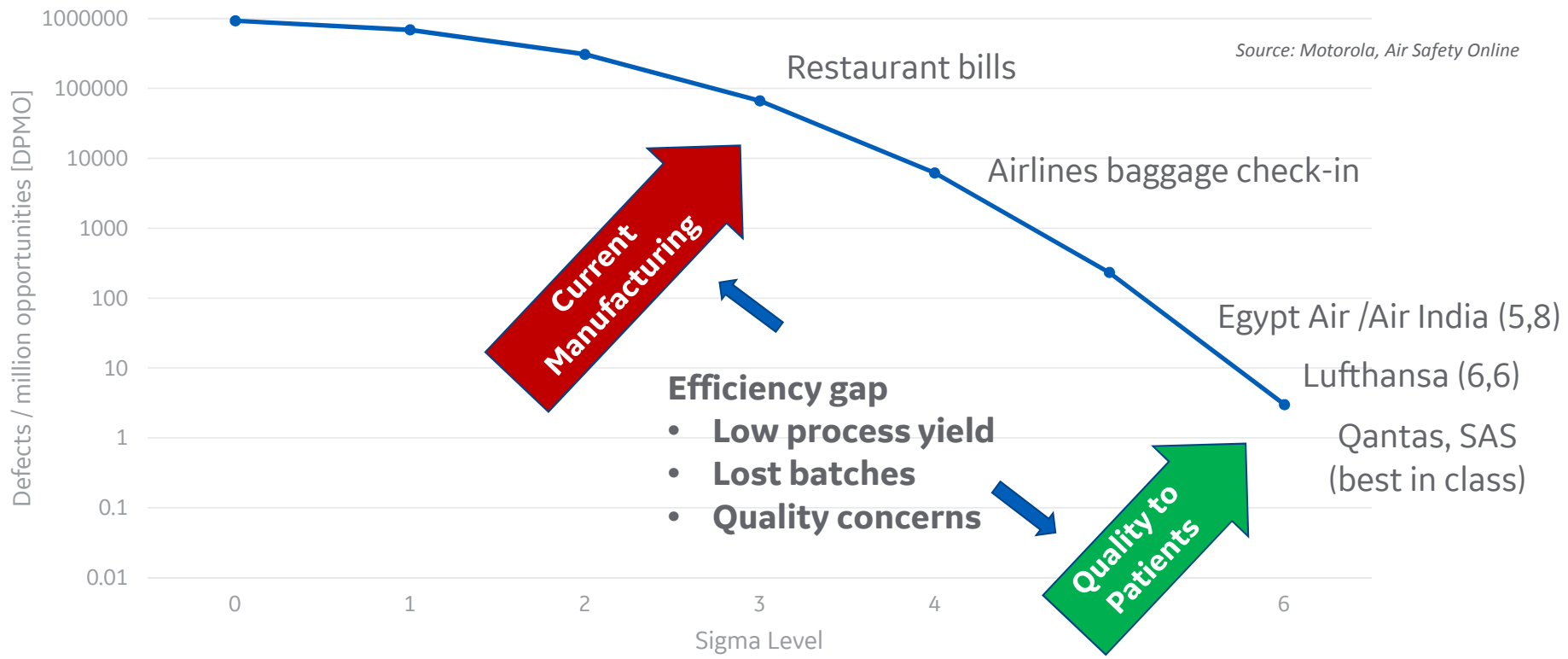
Vaccine Industry Consultation, Unicef, Copenhagen 26-27 October 2015



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Outdated processes with batch failures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

Manufacturing of vaccines is inefficient

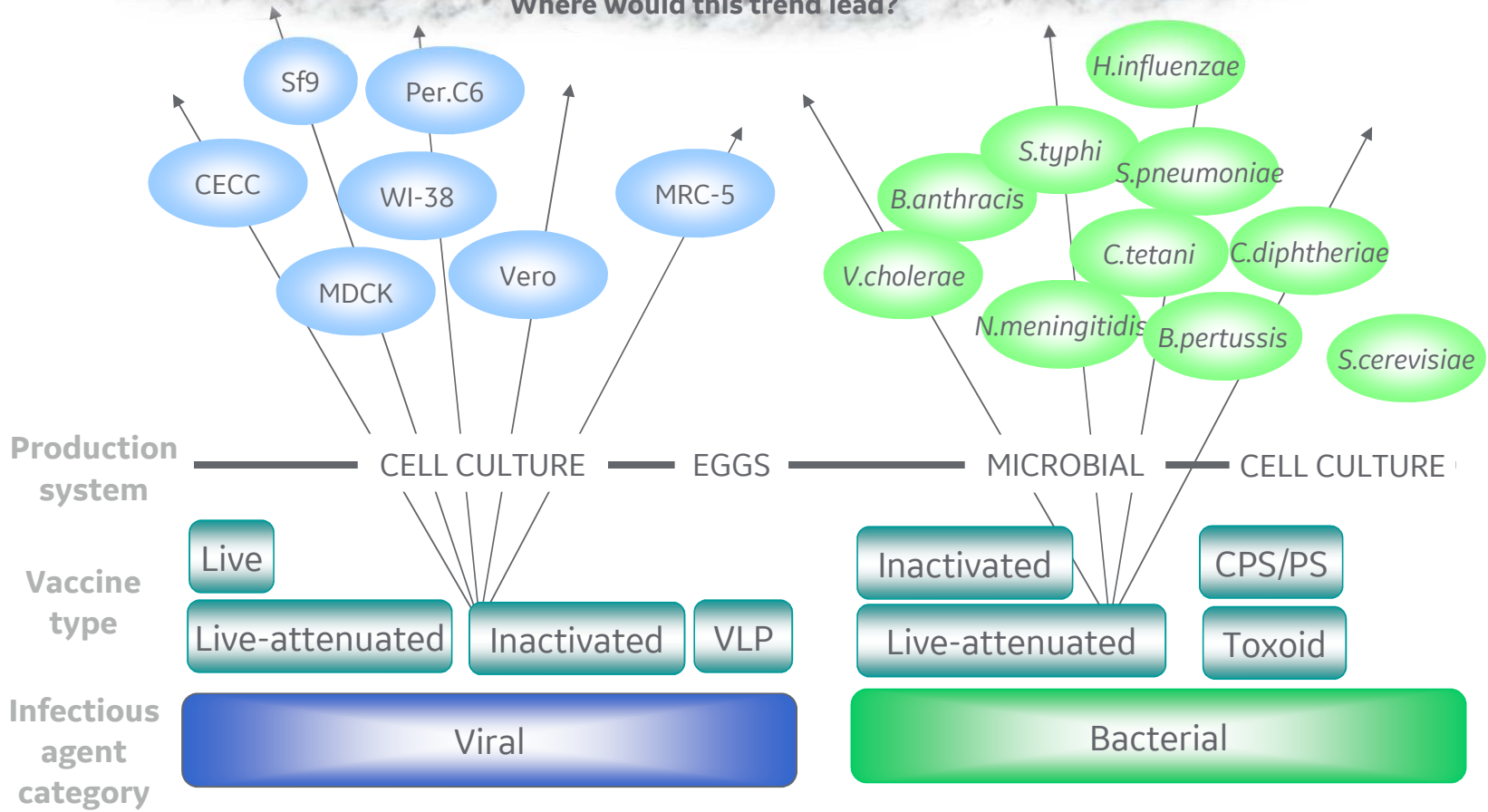
Patient expectation is 6 sigma



Diversification of technology – low efficiency

35-40 vaccines still to be developed

Where would this trend lead?



What are the Issues?

Design of aged processes

- Many “weak steps”, low yield, low robustness
- Lack of use of technology improvements
- 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
- Scale down without losing economic advantages
- Use any technology option to remove non-productive, costly activities
- Overcome lack of flexibility in production infrastructure

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

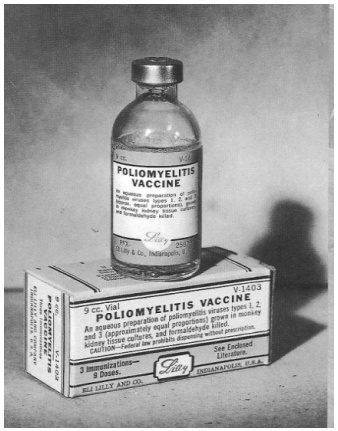
Pursuit of Rapidly Adaptable, Scalable Production Technologies

- 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)
- 2012: WHO Endgame Plan: withdrawal of OPV, switch to IPV (2018)
- Global certification of eradication of Polio



Virus-like Particles Technology 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

Scalability and yield, process robustness with current technology

Limited value post-eradication or in shrinking markets ?

combine with

Adaptation to changing markets

Flexible, right-scaled production infrastructure

Collaboration & funding frameworks supporting rise of local markets

Access to new vaccine technology

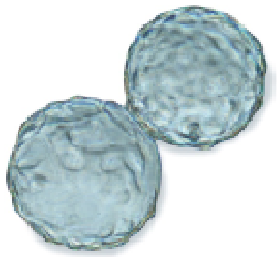
Limited value with pressing short-term challenges

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

  → Development to Suspension cells
- 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~~ → ~~Drain buffer~~ → ~~Wash with cell culture media~~ → Swell in cell culture media

Autoclave (small scale)
Fermenter (large scale)

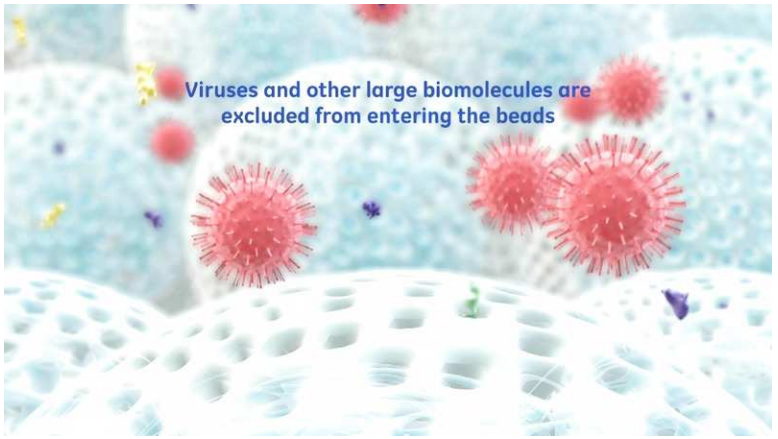
NEW Cytodex™ gamma:

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

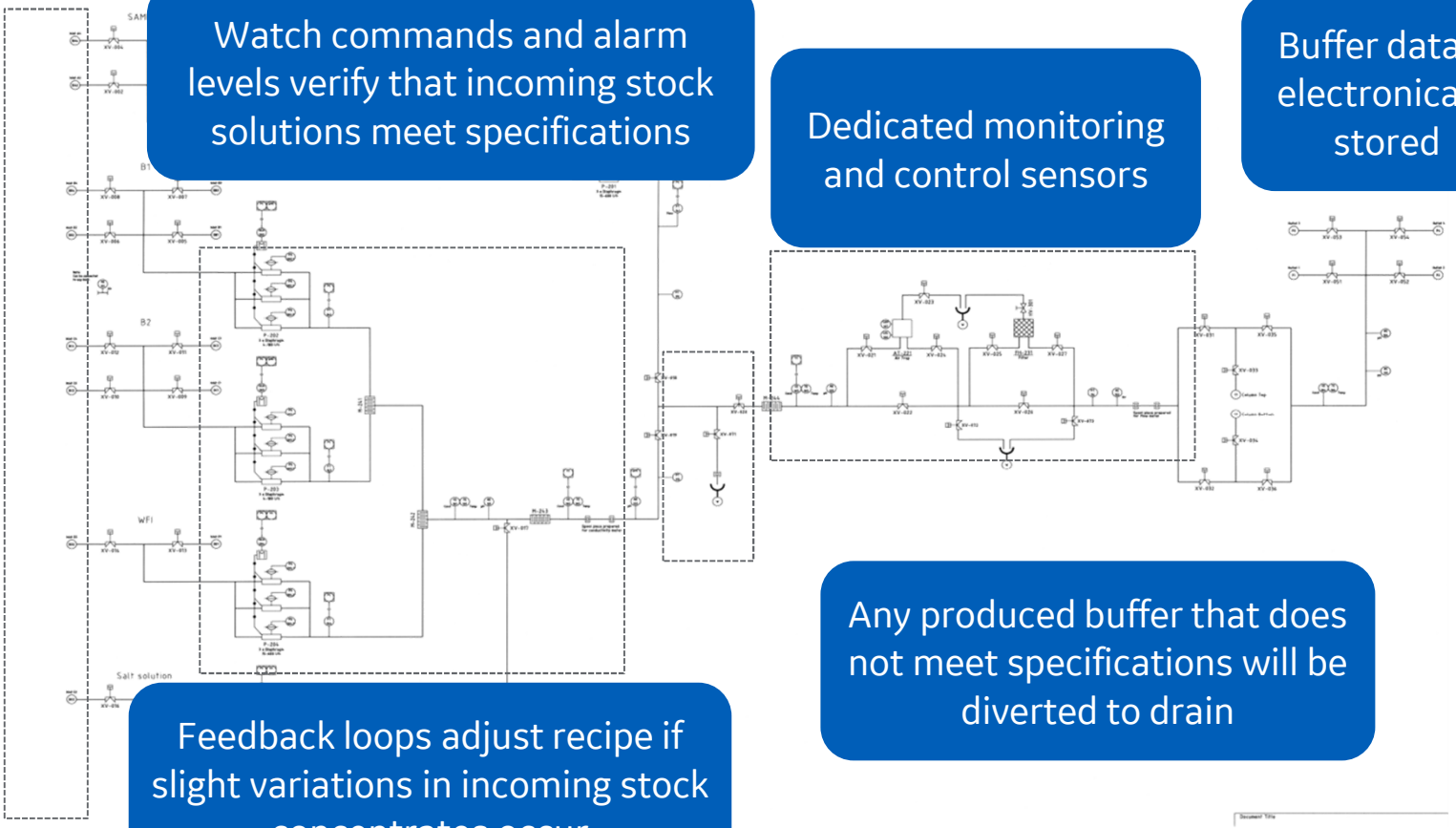
Offline production of buffers into bags

Hold-up tanks and bags

Direct feed to unit operation

Can be fully integrated into the unit operation
(no separate skids)

Quality features in an Inline Conditioning system



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

Dedicated monitoring and control sensors

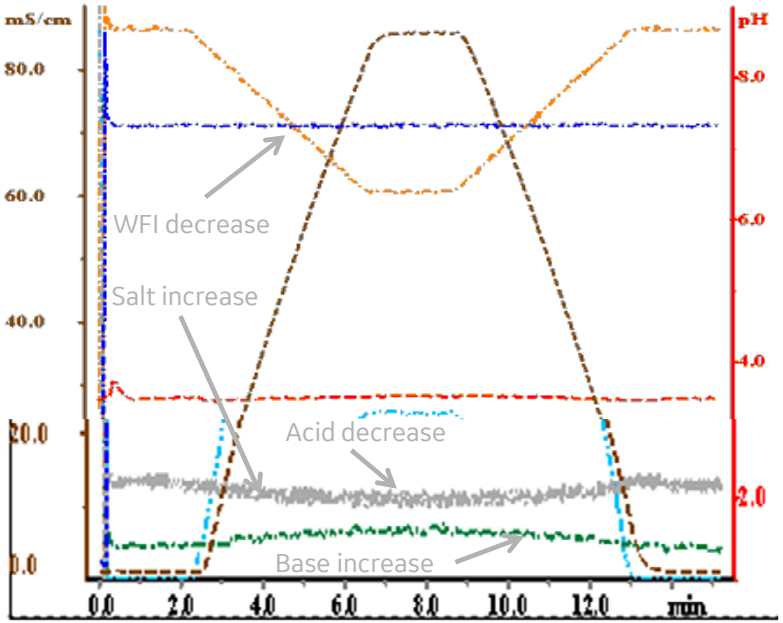
Buffer data is electronically stored

Any produced buffer that does not meet specifications will be diverted to drain

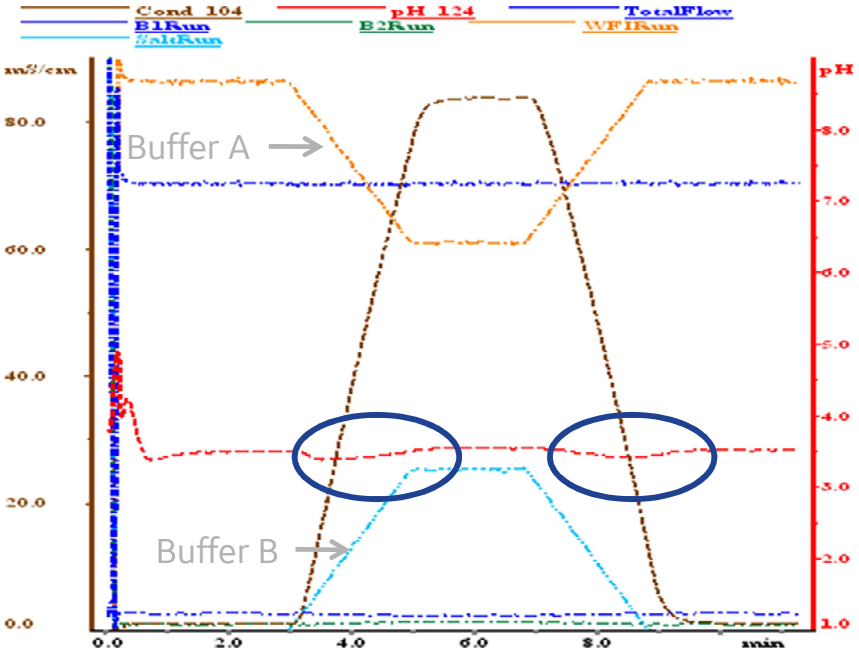
Feedback loops adjust recipe if slight variations in incoming stock concentrates occur

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



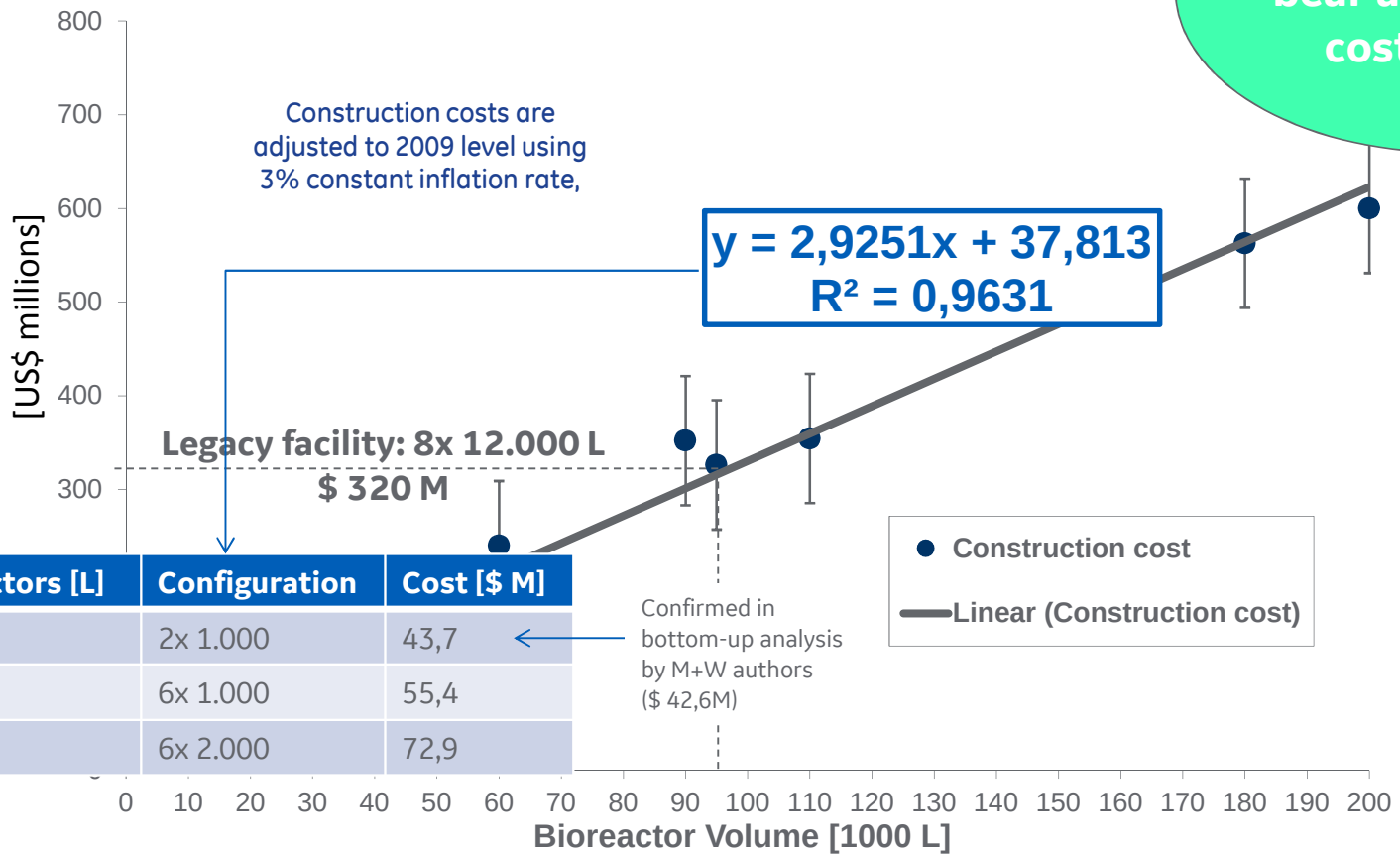
A two-pump solution leads to pH variations along the gradient

Facility related efficiencies

Reduce facility investment cost

Legacy facilities bear a huge fixed cost burden

CAPEX can be 30% lower for single-use facility

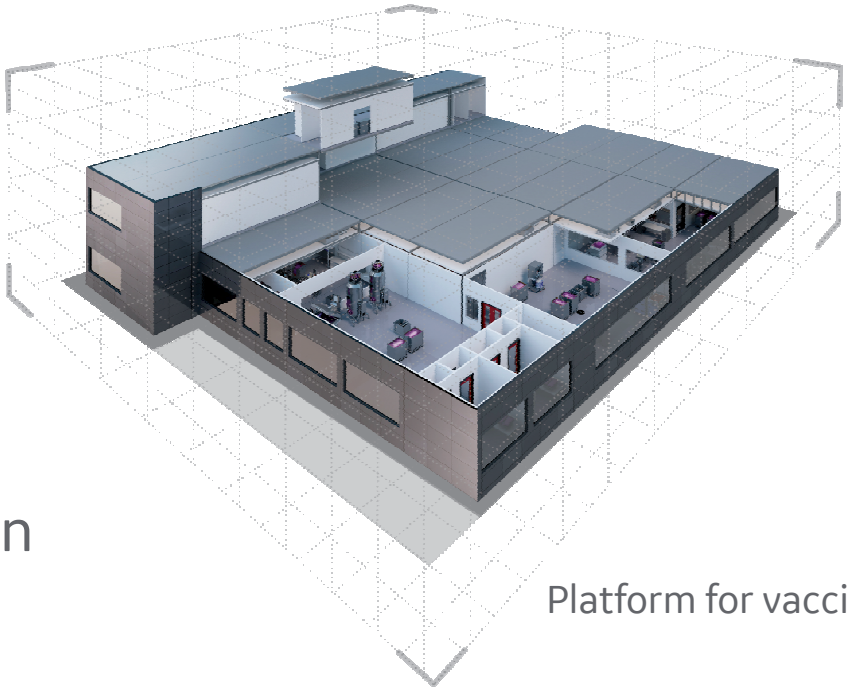


Bioreactors [L]	Configuration	Cost [$ M]
2.000	2x 1.000	43,7
6.000	6x 1.000	55,4
12.000	6x 2.000	72,9

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