Process economy for vaccines

DCVMN 10 March 2017

Outline

Vaccine production today and tomorrow

Process economy for vaccines

Strategy for process economy calculations

Case study 1

- Single-use strategy for microbial fermentation

Case study 2

- Evaluation of productivity for modernizing a vaccine process with a different purification technique

Conclusions

Background vaccine production

Need for updated vaccine processing and process optimization for global access

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

Process economy considerations for vaccines

Process re-designs

Low productivity

Technology change

Low yield

Purity issues

Robustness issues

New vaccine introduction

Market size

Cost structure

Expected profit

Will the vaccine be profitable?

Market analysis

Business drivers
- Market size
- Market share/competition
- Market growth
- Profitability
- Uncertainty

Business case

Detailed process economy

What will affect the process economy for a vaccine product?

- Facility construction
- Facility utilization
- Cost structure contributions: USP, DSP, QA, QC, logistics, etc.
- Product titers
- Raw materials

USP = upstream production
DSP= downstream production

Process design will effect process economy

Yield

Robustness

Number or process steps

Unit operations

Automation/smart engineering

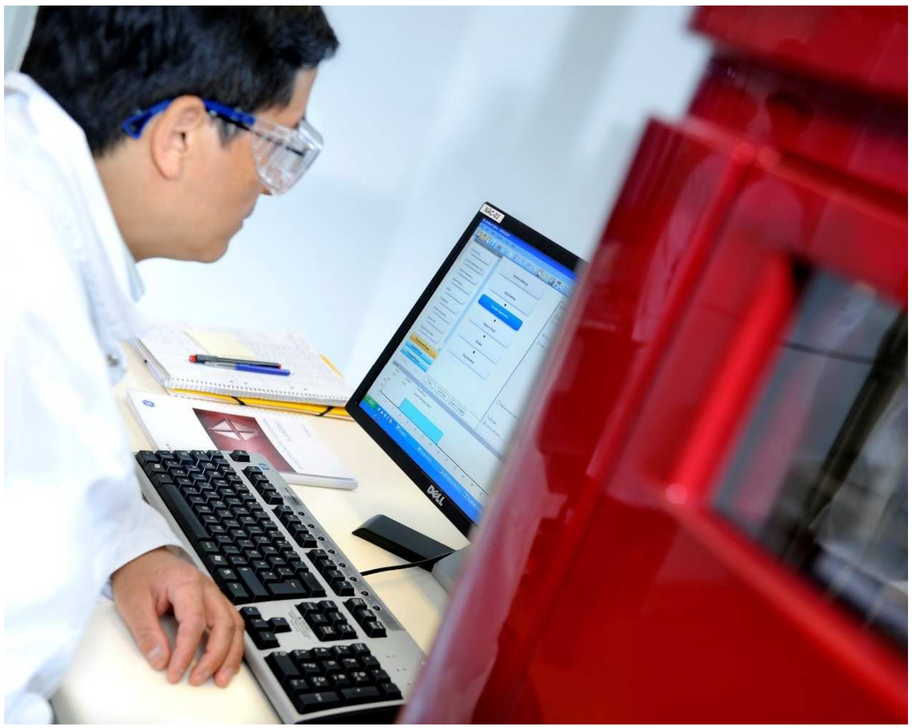
Chromatography resins

Raw materials/chemicals

Platform processes

Disposables vs stainless steel

Process economy calculation tools



Examples of software

- BioSolve™
- SuperPro Designer
- SchedulePro
- Microsoft® Excel®

Process economy outcome…

…will never be better than the input data to simulation model

Strategy for process economy calculations

Proposed workflow for process economy calculations

Scope/objectives

Collect input data—identify differences and similarities

Make assumptions

Identify cost categories to investigate

Calculations

Analyze outcome

1. Scope/objectives → 2. Collect data—identify differences and similarities → 3. Make assumptions → 4. Identify cost categories to investigate → 5. Calculations → 6. Analyze outcome

Case study:
comparing single-use to stainless steel strategies for microbial fermentation

Objectives

Estimation of batch production cost

Stainless steel or single-use equipment

Equipment choice

Effects on the production capacity of the facility

Comparing facility types

Single-product to multi-product facility

Equipment strategy

How does it affect the total annual cost at different facility utilization scenarios?

1. Scope/objectives → 2. Collect data—identify differences and similarities → 3. Make assumptions → 4. Identify cost categories to investigate → 5. Calculations → 6. Analyze outcome

Differences between systems

Stainless steel system

- Fixed piping
- Valves, steam traps
- Mechanical seals
- SIP and CIP cycles
- Maintenance
- Limited adaptability

SIP = sanitization in place
CIP = cleaning in place

Single-use system

- Flexible tubing
- Integrated filters
- No mechanical seals
- Fast turnaround
- Adaptable

1. Scope/objectives
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Media preparation: example of differences between systems

In stainless steel equipment

- Sterilize-in-place, addition of heat sensitive components aseptically

In single-use equipment

- Option 1: sterile filter
- Option 2: autoclave in separate vessel, add to fermentor aseptically

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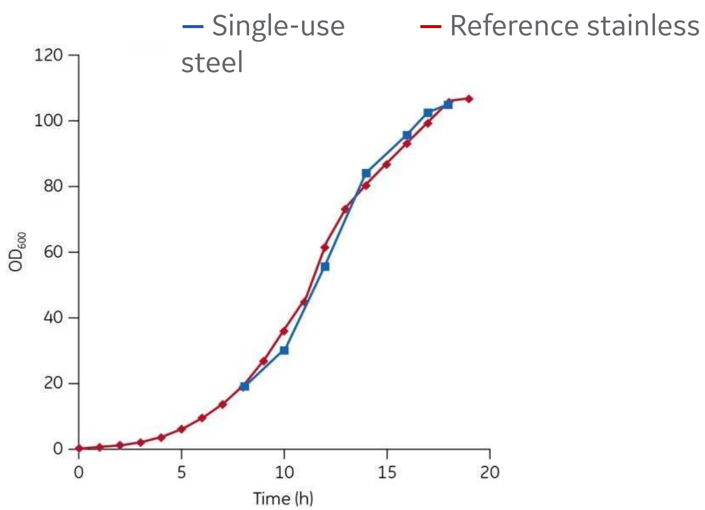
Growth comparison using optical density

Optical density in single-use and stainless steel fermentor



- Comparable growth results from single-use fermentor for same process in 20 L stainless steel fermentor*

* B. Braun Biotech GmbH, Germany (historical data)

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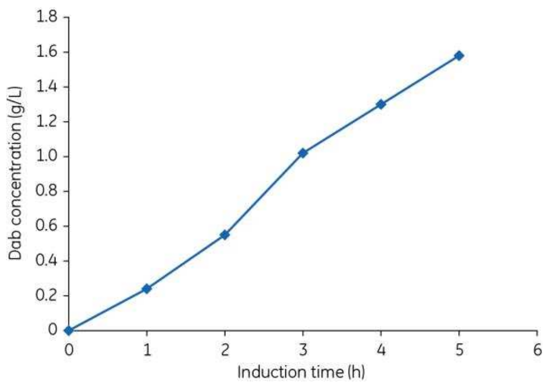
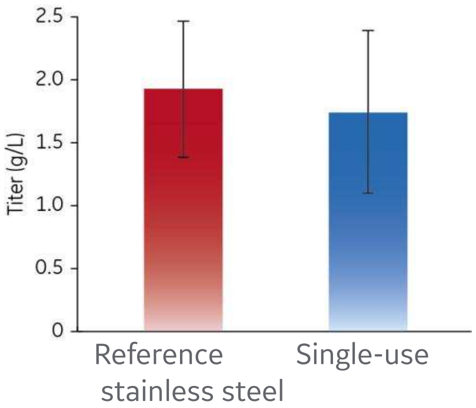
Comparison of dAb expression

dab expression level immediately post induction in single-use fermentor



- Linear expression after induction

dab expression in single-use fermentor and stainless steel fermentor



- Titer comparable with reference
- Some variability, but within expected range

1. Scope/objectives
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General assumptions

- 300 fermentation days/year available
- Cost of labor: 100 USD/man hour
- Labor performed in two shifts
- Batch failure rate: zero
- Capital investments (including 10% interest) and qualification costs will be spread over the number of batches that can be produced over the depreciation time (10 years) for the equipment
- For multi-product, each product is produced in campaigns of five batches

1. Scope/objectives → 2. Collect data—identify differences and similarities → **3. Make assumptions** → 4. Identify cost categories to investigate → 5. Calculations → 6. Analyze outcome

Unit operations with identical needs excluded from the model

Examples

- Seed train procedure in shaker flasks
- Type and amount of medium components
- Minor hardware such as scales and tube welders
- Minor disposables such as C-Flex® tubing, pump tubing, syringe filters, vials, and similar

1. Scope/objectives → 2. Collect data—identify differences and similarities → **3. Make assumptions** → 4. Identify cost categories to investigate → 5. Calculations → 6. Analyze outcome

Cost categories

- Capital investments
- Installation and operation qualifications (IQ/OQ), performance qualification (PQ), and cleaning validation
- Production related costs:
  - Preparations prior to fermentation
  - Fermentation process in the production facility
- Disposables, chemicals, water for injection (WFI), steam, and similar
- Annual requalification and maintenance

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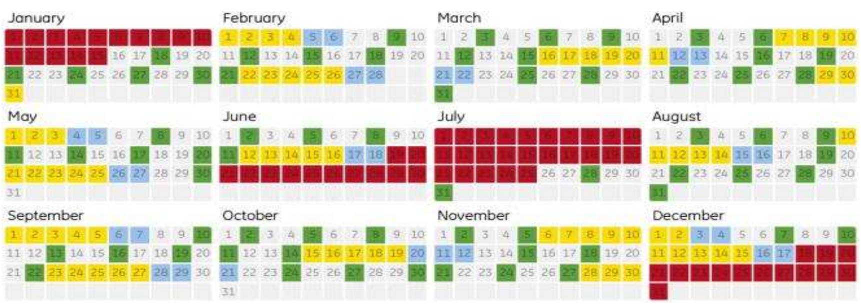
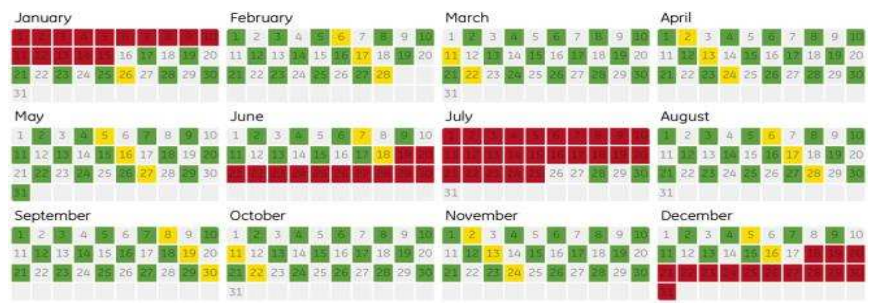
Production schedules for multi-product facility

Stainless steel equipment



- 67 batches/year
- 13 full campaigns/year

Single-use equipment



- 135 batches/year
- 27 full campaigns/year

Harvest days (five batches per production campaign)

CIP and required analysis

Carry-over calculations, reporting, and quality assurance (QA) approval

Maintenance

1. Scope/objectives
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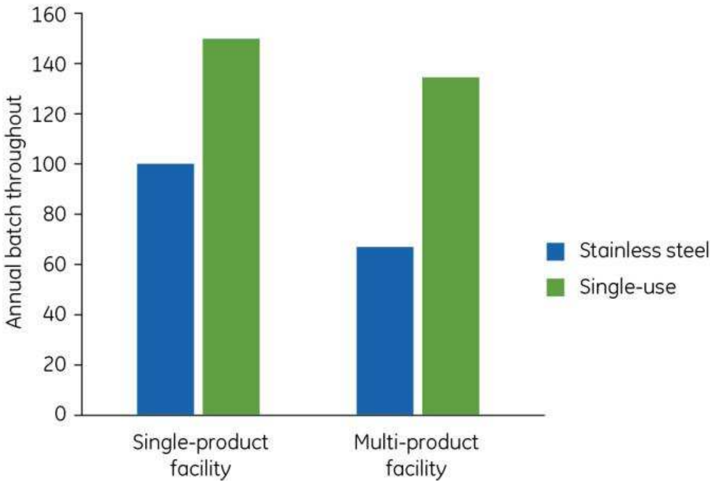
Production capacity



Single-use equipment enables higher throughput in both types of facilities

Doubled production capacity enabled in multi-product facilities with single-use equipment

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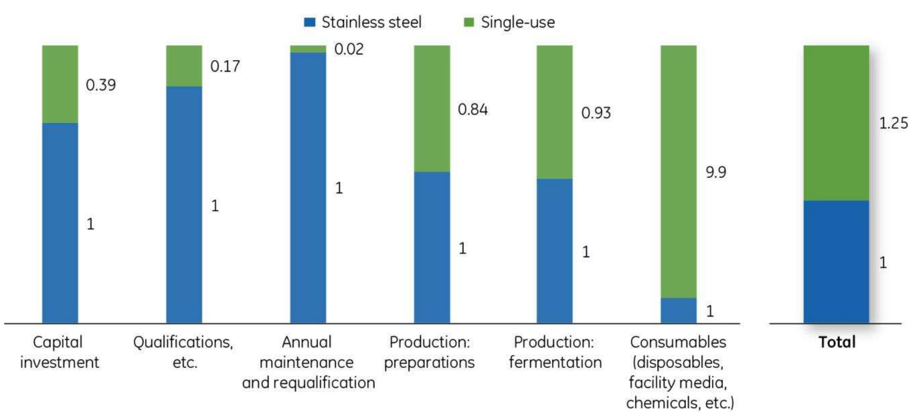
Cost per batch: multi-product facility

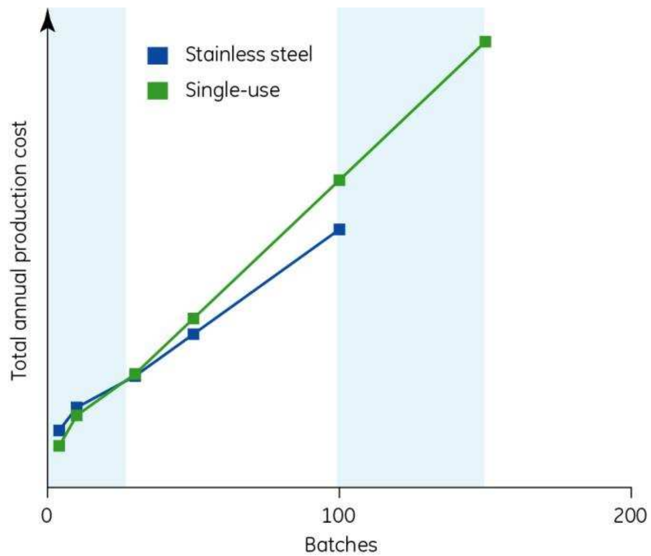


- Stainless steel cost is higher for
  - Capital investment
  - Qualifications
  - Annual maintenance and requalification
- Equal cost for
  - Production (preparations and fermentation)
- Single-use cost is higher for
  - Consumables (disposables, facility media, chemicals, etc.)

1. Scope/objectives › 2. Collect data—identify differences and similarities › 3. Make assumptions › 4. Identify cost categories to investigate › 5. Calculations › 6. Analyze outcome

Annual production cost in microbial fermentation

Total annual production cost



Comparison stainless steel and single-use equipment

- Single-use equipment is advantageous:
  - if facility utilization rate is low or
  - when a high production capacity is needed
- Stainless steel equipment is advantageous:
  - at mid-facility utilization rates and when capacity is not a limiting factor

1. Scope/objectives → 2. Collect data—identify differences and similarities → 3. Make assumptions → 4. Identify cost categories to investigate → 5. Calculations → **6. Analyze outcome**

Evaluation of productivity for modernizing a vaccine process with a different purification technique

Study objectives

Evaluate the effect on productivity by replacing a size exclusion chromatography (SEC) step with a core bead chromatography step in a vaccine process in different production scales

1. Scope/objectives
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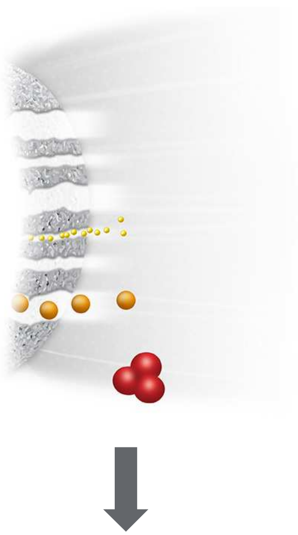
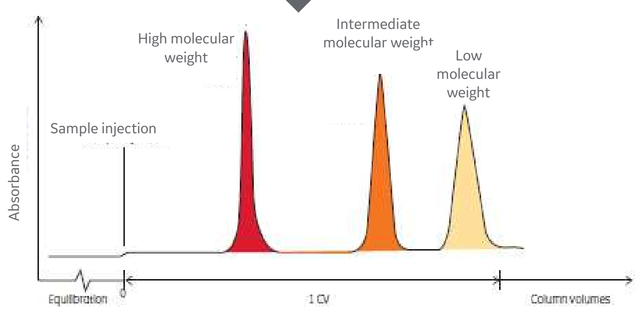
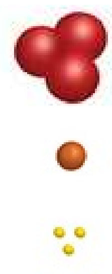
Size exclusion chromatography (SEC)





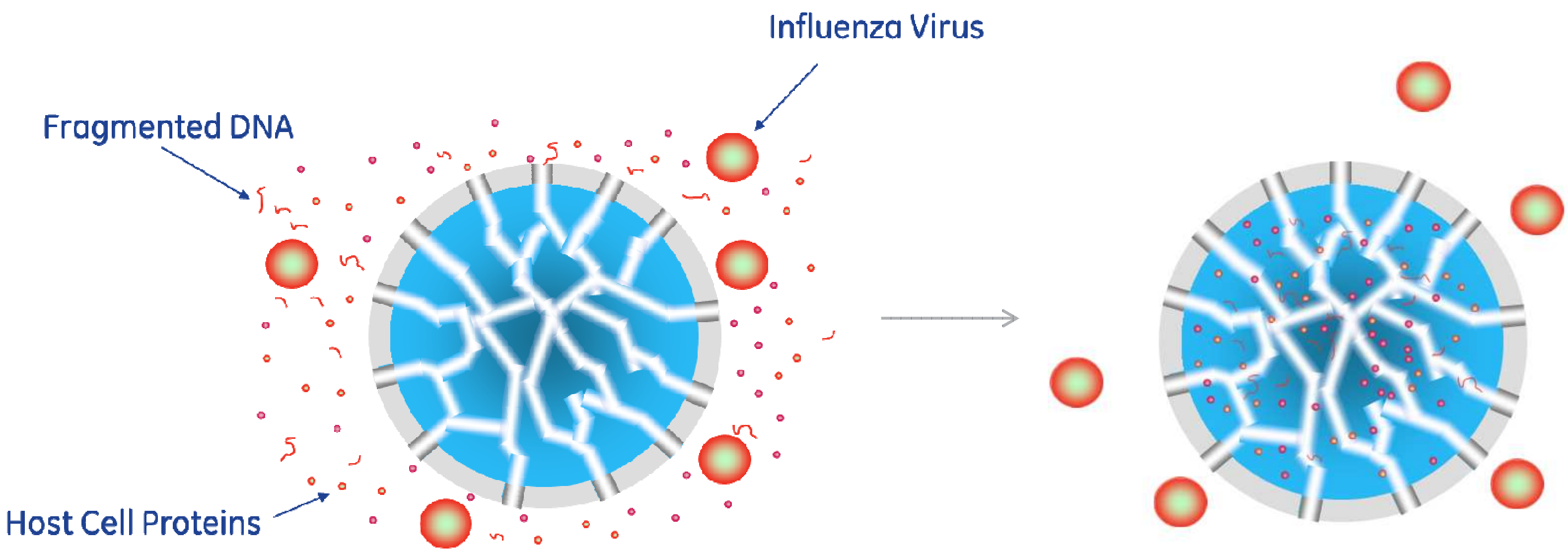


Exluded from pores

Enter a fraction of the pores

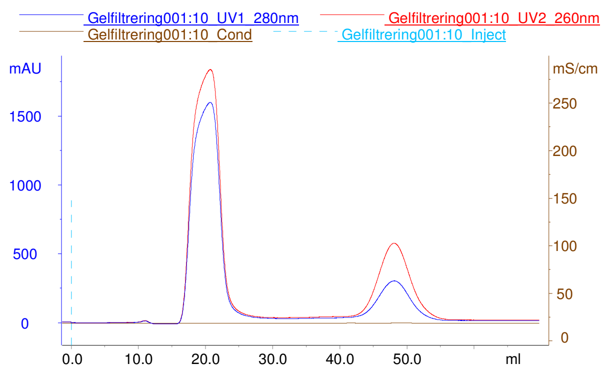
Enter all pores

Core bead chromatography: host cell proteins and DNA fragments bind to the core and viruses stay in the void

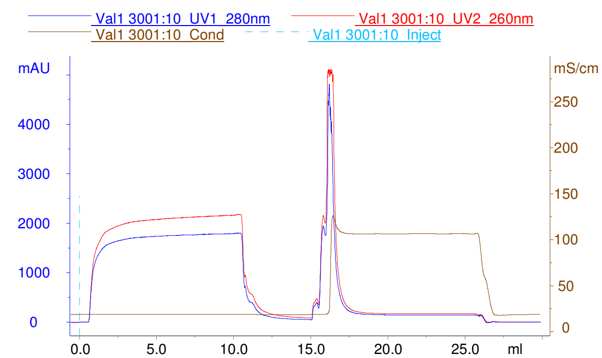


Data collection for comparison of SEC and core bead chromatography: lab-scale experiments with influenza virus

SEC	
CV (mL)	47
Load (CV)	0.1
HA yield (%)	86
HCP removal (%)	31



Core bead chromatography	
CV (mL)	1
Load (CV)	10
HA yield (%)	85
HCP removal (%)	32

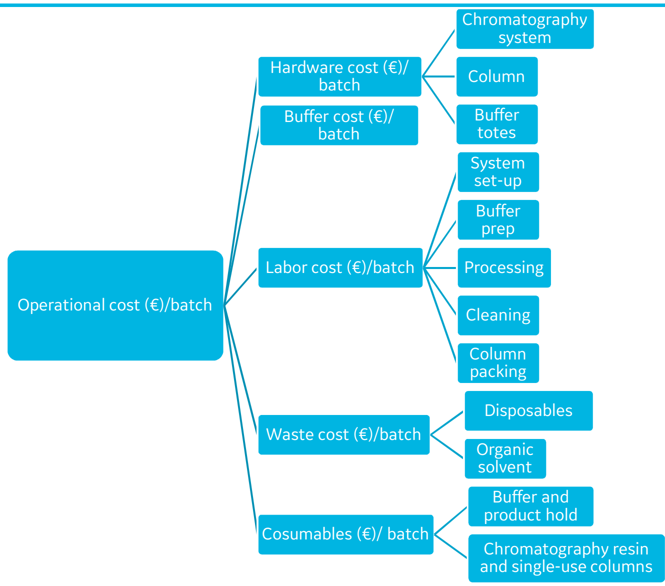


CV = column volume
HA = hemagglutinin
HCP = host cell protein

1. Scope/objectives → **2. Collect data—identify differences and similarities** → 3. Make assumptions → 4. Identify cost categories to investigate → 5. Calculations → 6. Analyze outcome

Assumptions for comparison of SEC and core bead chromatography

Included



Not included

- Facility-related costs
- QA/QC costs
- System validating costs
- Cost for ex-class facility for Capto™ Core 700

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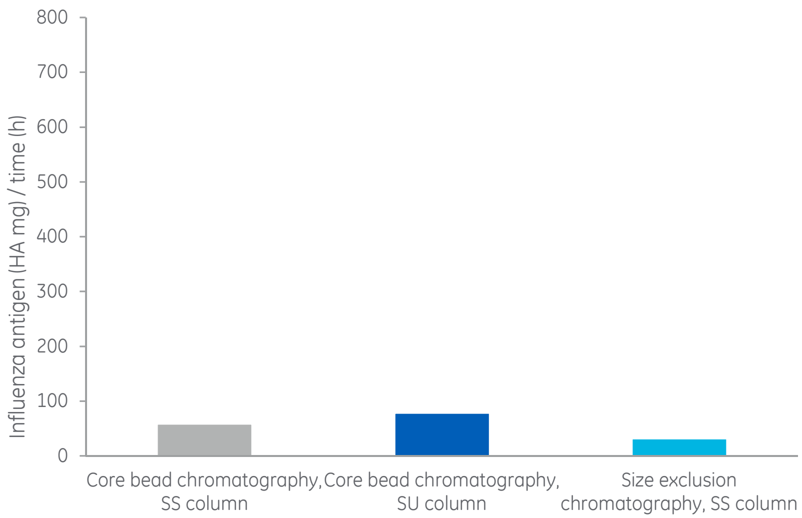
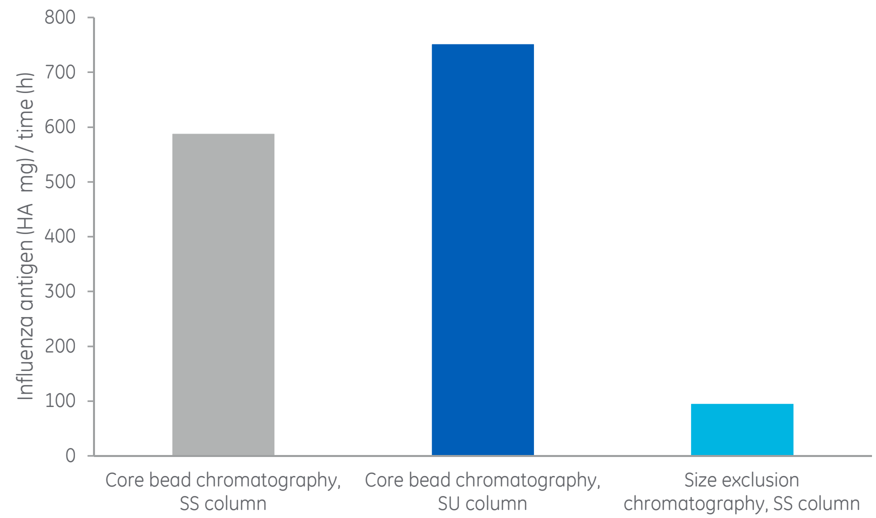
Productivity for SEC and core bead chromatography

200-L scale



2000-L scale



HA = hemagglutinin, SS = stainless steel, SU = single-use

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Cost comparison stainlesss steel versus single-use technologies

Single Use vs Stainless Steel savings

User reports – compiled data from publications and conference presentations

Users reports – last 5 years
Savings with Single Use versus Stainless Steel

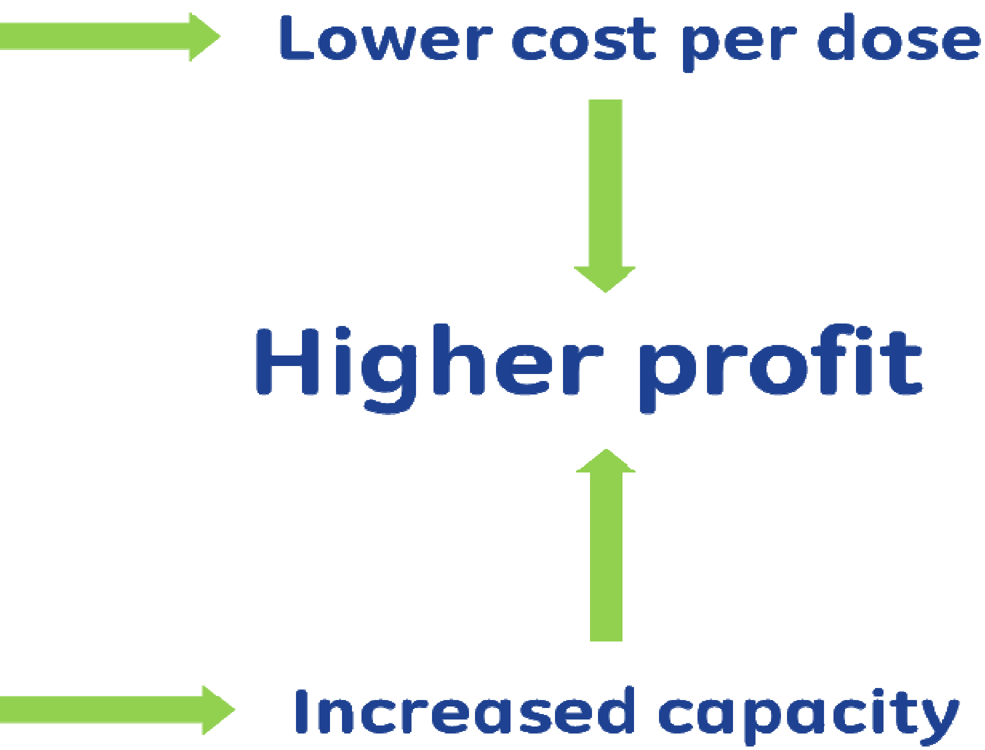
Company	Consumables	Facility Cost	Facility footprint	Labor	Time to build	Turnover time	Water /Energy	Capacity increase	COGs
Large Vaccine	+200%	-40%			-50%		-70% / -45%		-40%
Small Vaccine		-75%							
Large pharma	+120%	-50%	-25%	-48%		-70%		+30%	-57%
Large Pharma		-60%				-50%			-25%
Large biotech		-75%	-75%		-50%		-80% / -80%		-67%
Large Biotech		-25%	-35%		-25%		-85% / -25%		
Small biotech	+250%			-45%	-25%				-25%
CMO	+50%	-50%		-10%	-50%	-25%			-30%

Substancial savings by using SUT despite increased consumables cost

Single Use $ savings - reports from users 5 years

- Facility cost savings, footprint reduction
- Facility build-out time savings
- Equipment cost savings
- Labor cost savings
- Cycle turnover time savings
- Water, chemicals and energy savings

Benefits of single-use technology



- Less handling can reduce the required FTEs, leading to lower labor cost.
- Lower capital investment as some equipment can be omitted.
- If the production process is not limited by the equipment, more batches can be produced.
- Eliminate cleaning requirements and time consuming QA/QC, for faster campaign turnaround time.
- Excluding of some equipment allows for smaller facility, reducing capital investment.
- Less chemical consumption and waste.

QA/QC = quality assurance/quality control

Conclusions

Conclusions

Paradigm shift for vaccine production—from lab bench process to rational design

Start early with process economy in process development

Integrate process economy as a part of process development

Use a strategy for process economy calculations

Productivity can be increased by rational process design gelifesciences.com

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