SINGLE-USE TECHNOLOGIES

STATUS AND NEEDS

Maik Jornitz

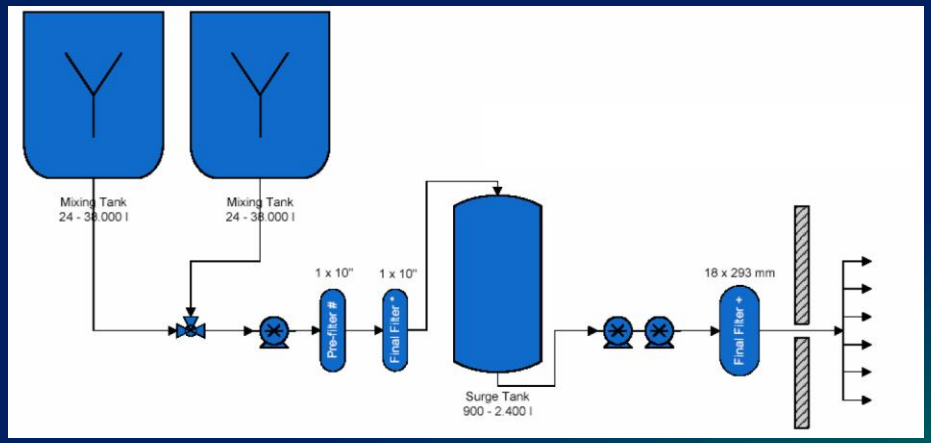
CEO and President G-CON Manufacturing

AGENDA

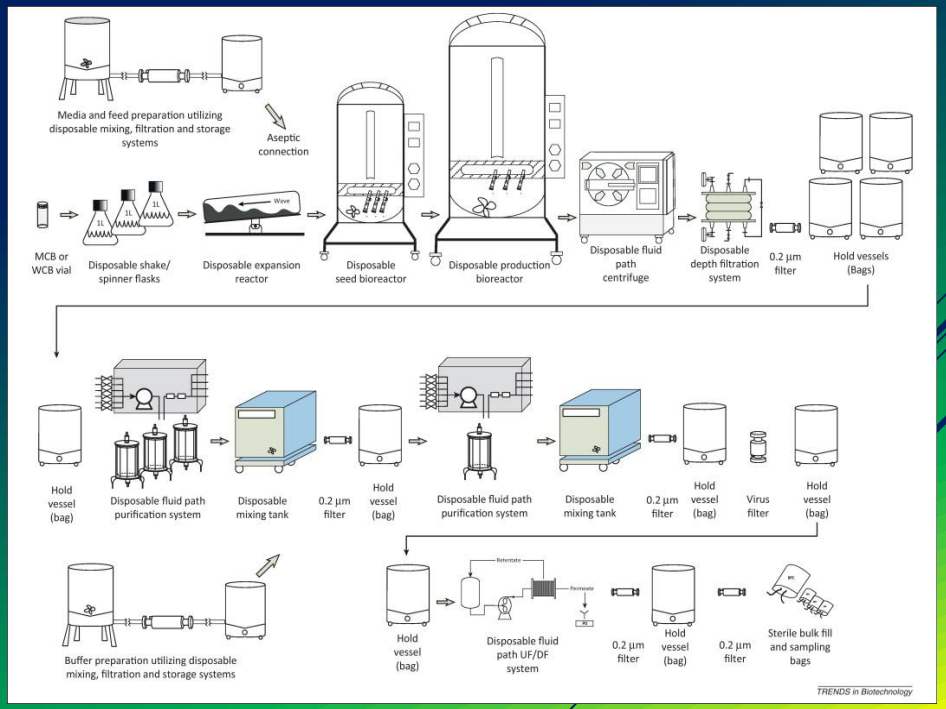
- PRECURSORS
- TECHNOLOGIES
  - Components
  - Benefits
- TASK FORCE
- NEEDS
  - Supplier Information
  - Standardize Extractables/Leachables
  - Integrity Testing

Process Differences

Past process had a restricted amount of unit operations, but were large

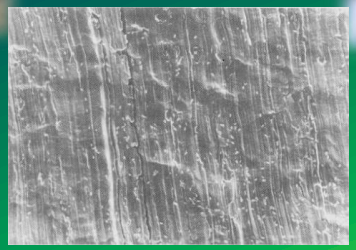


Bioprocesses are complex and have a multitude of unit operations



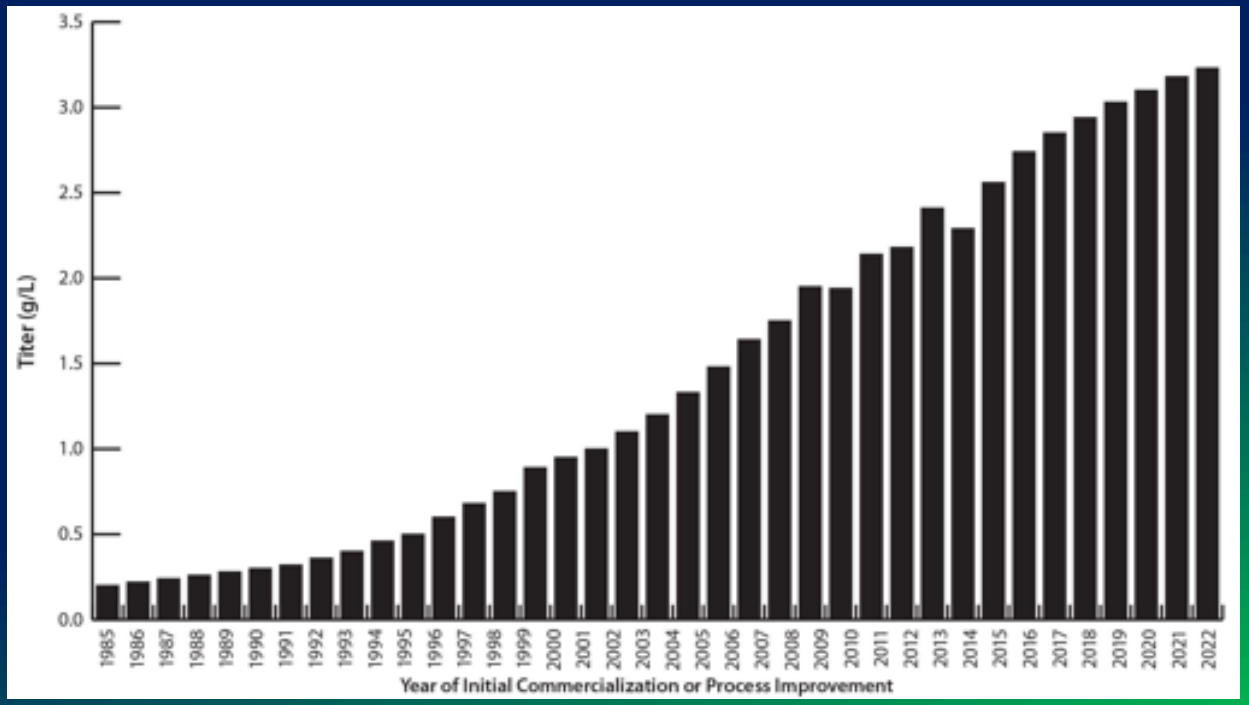
PAST PROCESS TECHNOLOGIES

- The processes were mainly complex re-usable stainless steel systems
- These processes were product dedicated
- Cleaning, sterilization and set-up has been laborious and destined for mistakes and risks
- Process designs had high hold-up volumes
- Large footprint requirements for equipment storage and prep
- These processes were focused on large-scale, large volume manufacturing

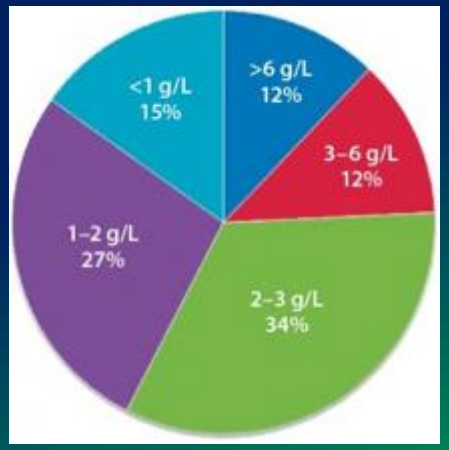


THINGS CHANGED….
PROCESS INTENSIFICATION

Expression rate increases = Lower fluid volumes



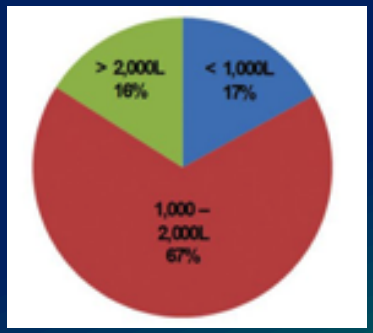
Source: Rader and Langer, 2015



Distribution of current titers for commercial biologics (g/L)

PAST & CURRENT PROCESSES

From large scale stainless steel to medium volume single-use



2,000L SUT becoming the preferred option

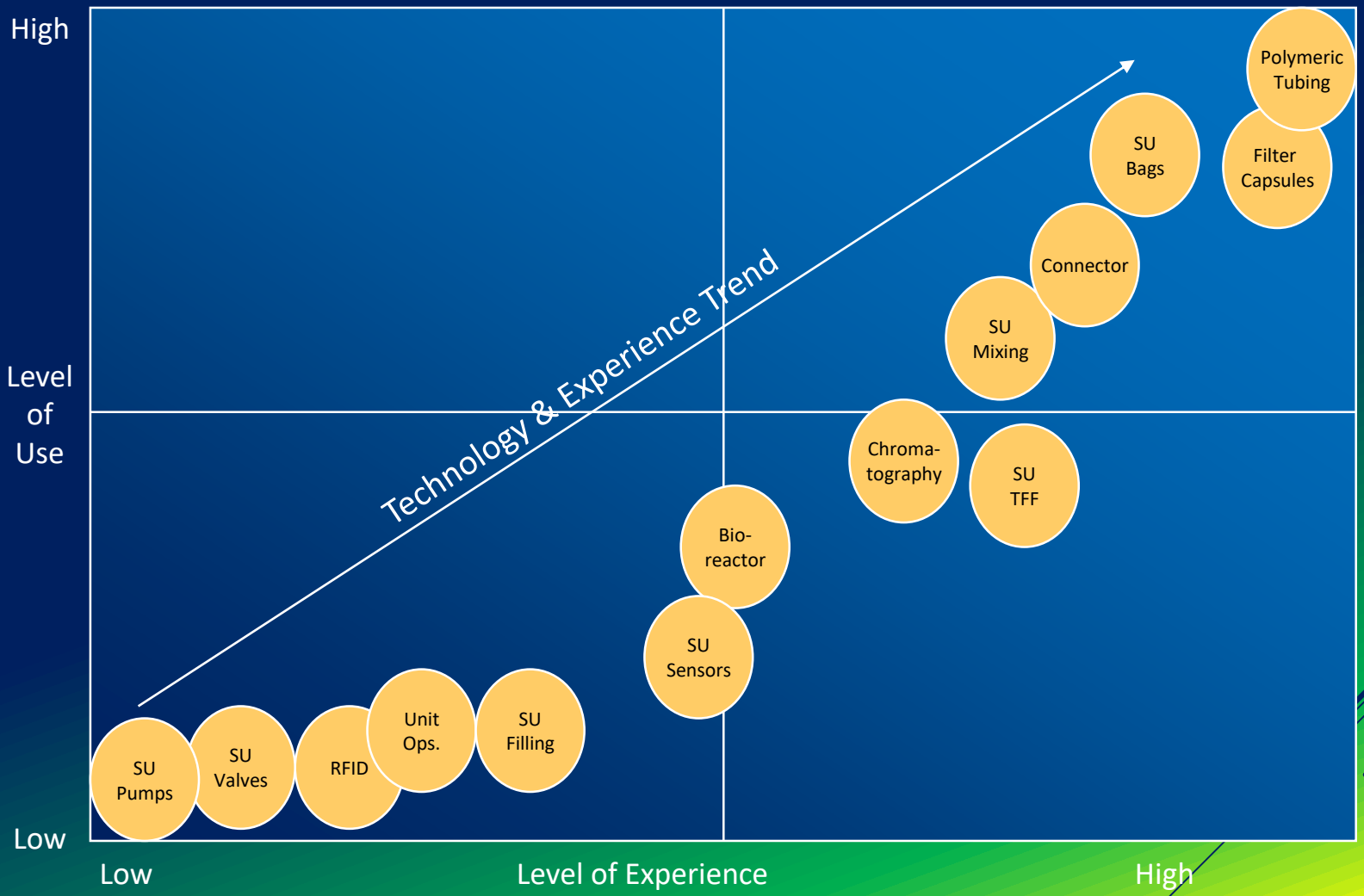
Continuous processing volumes ?

10kL

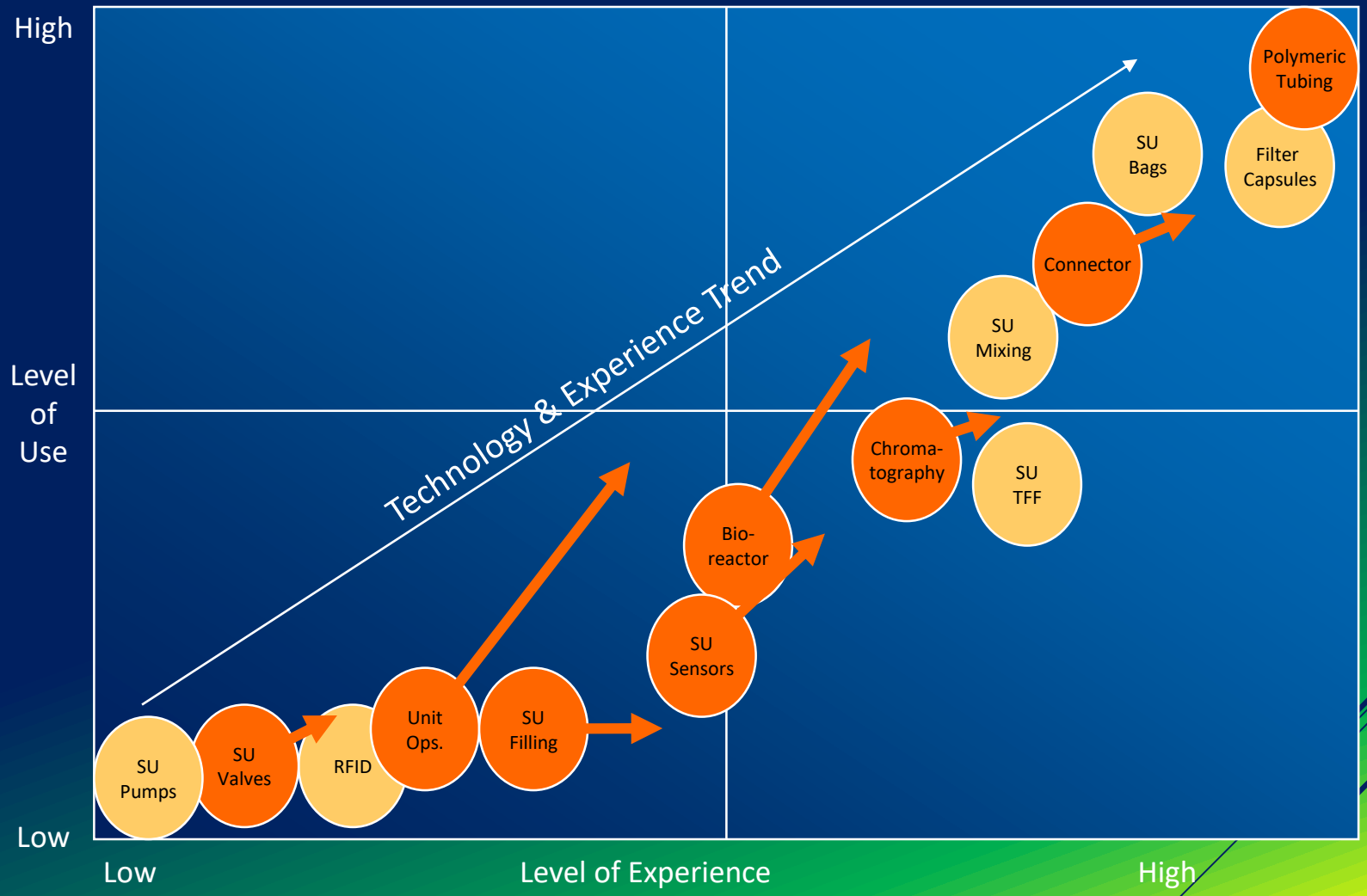
De-risking
Higher flexibility
Faster turn-around
Closed systems
Advanced PAT

2kL

SINGLE-USE TECHNOLOGY IN 2010



SINGLE-USE TECHNOLOGY STATUS-QUO ON THE MOVE...



End-user requirements create innovative opportunities

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SINGLE-USE TECHNOLOGY ADVANCES

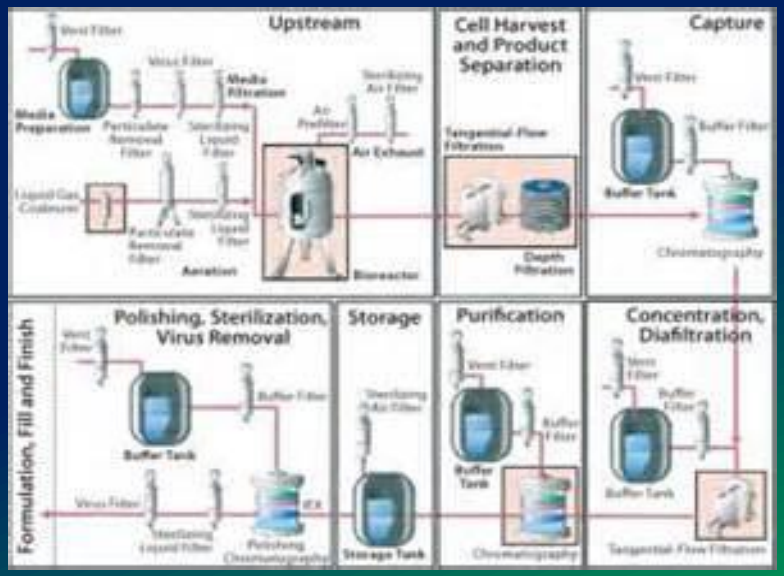
2,000L SU Bioreactors become reality

moving from rocking to stirred

SINGLE-USE PROCESS COMPONENTS

SINGLE-USE TECHNOLOGY ADVANCES

Not just connectors, but high volume connectors, genderless connectors and disconnectors



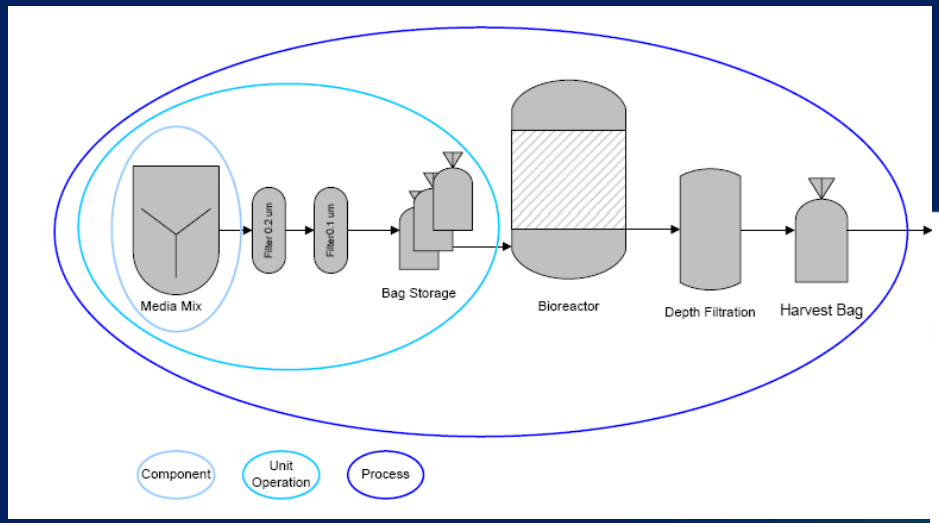
SINGLE-USE TECHNOLOGY ADVANCES

Automatic multi-fill stations and critical fill systems

- Large volume media/buffer fill stations
- SU fill needle/hopper bag assembly
- Robotic enclosed filling

SINGLE-USE TECHNOLOGY ADVANCES

Expansion of the single-use unit operations

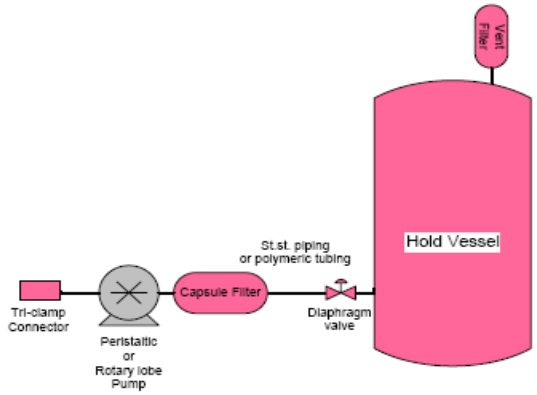


PROGRESS INTO SINGLE-USE PROCESSES

Production sites using single-use & containment technology to produce, monoclonal antibodies and vaccines

BENEFIT – SET-UP TIME REDUCTION

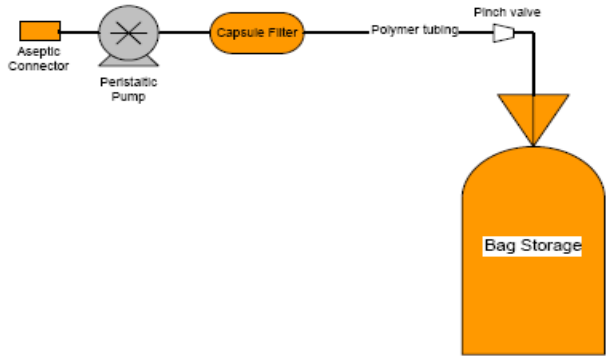
Example: Cell Culture Media Hold



Activities:
- open filter packages
- assemble filters, valves, pipe or tubing to tank
- autoclave assembly
- cool down assembly
- assemble tubing or pipe to pump
- vent liquid filter
- filter media
- close valve to tank
- after use; disassemble valves, pipe or tubing and filters
- discard used filter and tubing
- clean tank, valve, pipework, filter housing (rinse, scrub, rinse, clean, rinse, dry)

Set-up Time

5-8 h



Activities:
- open filter/bag assembly package
- connect filter/bag assembly to media mix
- insert tubing to peristaltic pump
- vent filter
- filter media
- seal tubing between filter and bag
- after use discard

30 min

CLEANING/SET-UP DELAY IMPACT
(ACTUAL CASE)

Biotech facility produces max 4 batches, often only 3
Each batch has an estimated market value of $ 30 Mio

↓

It turned out the bottlenecks are holding tanks:
Cleaning/Set-up/Sterilization Time > 8 hours
additional rinse WFI availability limitations

↓

A disposable holding and/or mixing system
would be set-up in minutes

↓

This improvement would mean:
min 1 batch more/week → $ 1.5 Bio additional revenue

SINGLE-USE VS. MULTI-USE

(TIME TO IMPLEMENTATION)

The time to implement a single-use fermentation system is greatly reduce in comparison to a multi-use system:

2 - 3 years

4 - 7 months

Main reasons for the 5 fold reduction:

- Qualification of the equipment
- Cleaning validation
- Qualification of set-up

Source: Stephen Brown, Vialis, PDA/EMEA Meeting 2009

SINGLE-USE VS. MULTI-USE

(WATER CONSUMPTION W/O STEAM NEEDS)

Capital	Total		57,147,809 €	
	Per Litre of bioreact(		5,715 €/L	
CoG			226.9 €/g	
Water L	**PW**	**WFI**	**Total**	
Process	32,250	22,783	55,033	32%
Cleaning	56,998	62,273	119,271	68%
Total	**89,248**	**85,056**	**174,304**	**100%**

Major cost component:
Water,
also a common
major bottleneck

60 % of the costs
of a re-usable system

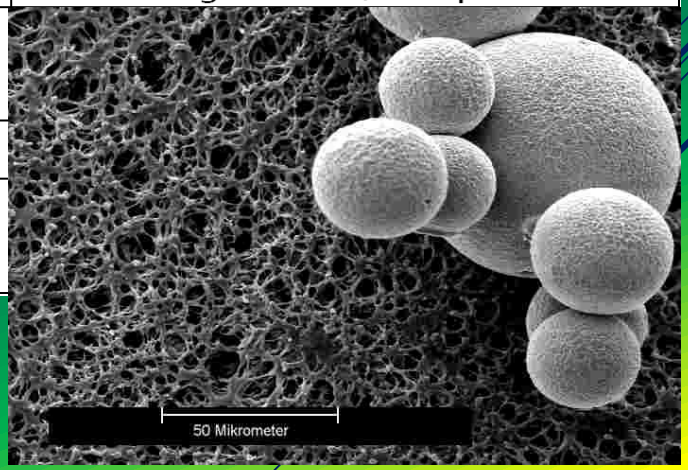
Capital	Total		22,156,225 €	
	Per Litre of bioreact(		2,216 €/L	
CoG			136.3 €/g	
Water L	**PW**	**WFI**	**Total**	
Process	6,730	22,783	29,513	65%
Cleaning	14,465	1,245	15,710	35%
Total	**21,195**	**24,028**	**45,223**	**100%**

Source: BioPharm Services

Costs of Polishing: Resin or Membrane ?

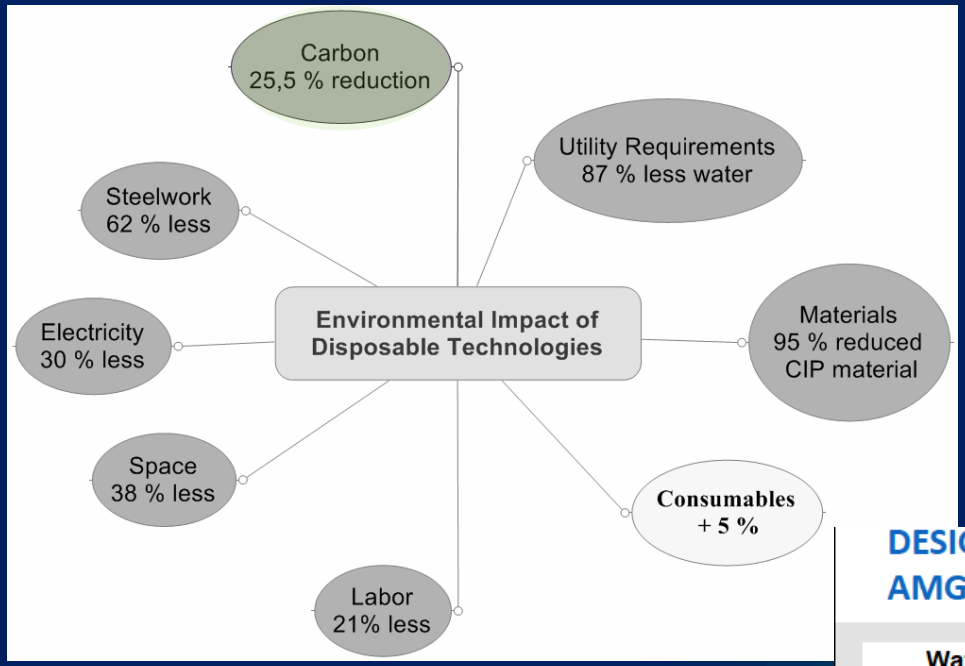
Anion exchanger polishing step (flow through) for the removal of DNA, HCP, Protein A and endotoxins

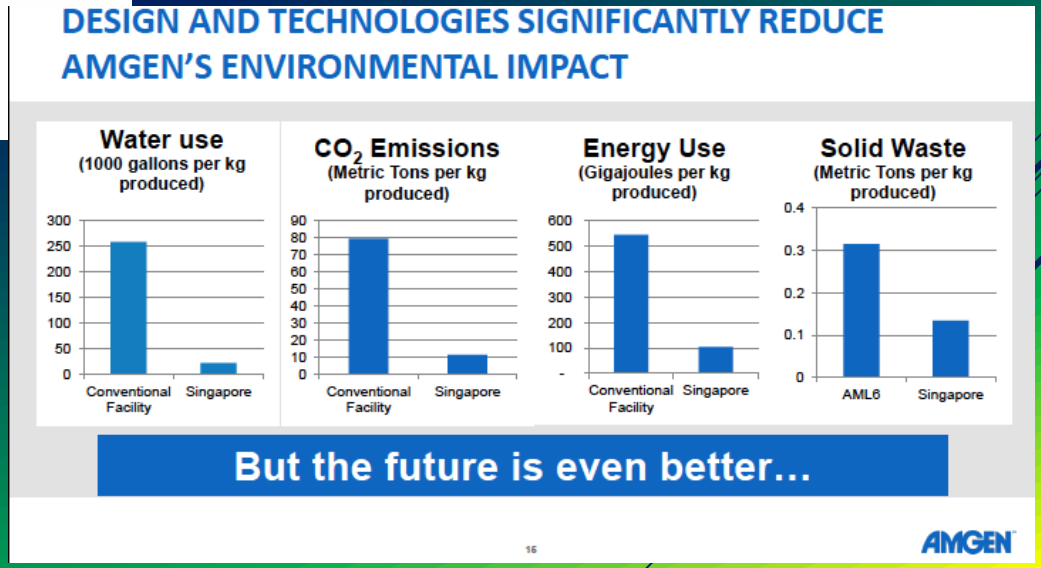
	Q Resin	Q Membrane	Cost/Saving Assumptions
Flux/flow rate	100-150 cm/h	450-1000 cm/h	10 fold cut in processing time
Capacity (large molecules)	50-100 g/l	10 kg/l	100 fold capacity increase
Buffer use	100 %	2-5 %	40 l resin buffer use 700 l Cost per l buffer = approx. $ 15 Saving ~ $ 10,000 per run
Contaminant removal	Good	Excellent	
Set-up time	~ 15 h	~ 0.5 h	
Cleaning validation	Yes	No	



Source: Gottschalk, PhD

BENEFIT – ENVIRONMENTAL IMPACT ?





Source: Sinclair; Leveen, et.al.; The Environmental Impact of Disposable Technologies, The Biopharm International Guide, 11.2008

Van Trieste, PDA Europe Annual Meeting, June 2016

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TECHNICAL REPORT

- Need for clarification of technical terms
- Requirement to find alignment of the statements made for single-use technology to reduce confusion
- Definition of needs from vendors
- Description and sync of validation activities
- Case study on the determination of the economic benefits
- Implementation example and lessons learned

TECHNICAL REPORT - TEAM

PDA Application of Single-Use Systems in Pharmaceutical Manufacturing Technical Report Team

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All Task Force teams are commonly composed from experts of the industry, suppliers, consultants and regulators. To abbreviate the timeline and make the activities move along the Task Force team was a smaller group.

TECHNICAL REPORT - CONTENT

1. Introduction
2. Glossary of Terms
3. Points to Consider for Single-use System Manufacturing Strategy
4. Single-use Technologies and System Integration
5. Qualification and Verification of Suppliers, Materials, Components, and Completed Assemblies
6. Business Drivers for the Adoption of Single-use Systems
7. Implementation of a Single-use System
8. Appendix I: Overall User Requirement Specification Example
9. Appendix II: Project Execution Plan Example
10. Appendix III: Training Requirements Example
11. References

TECHNICAL REPORT – OVERVIEW GRAPHIC

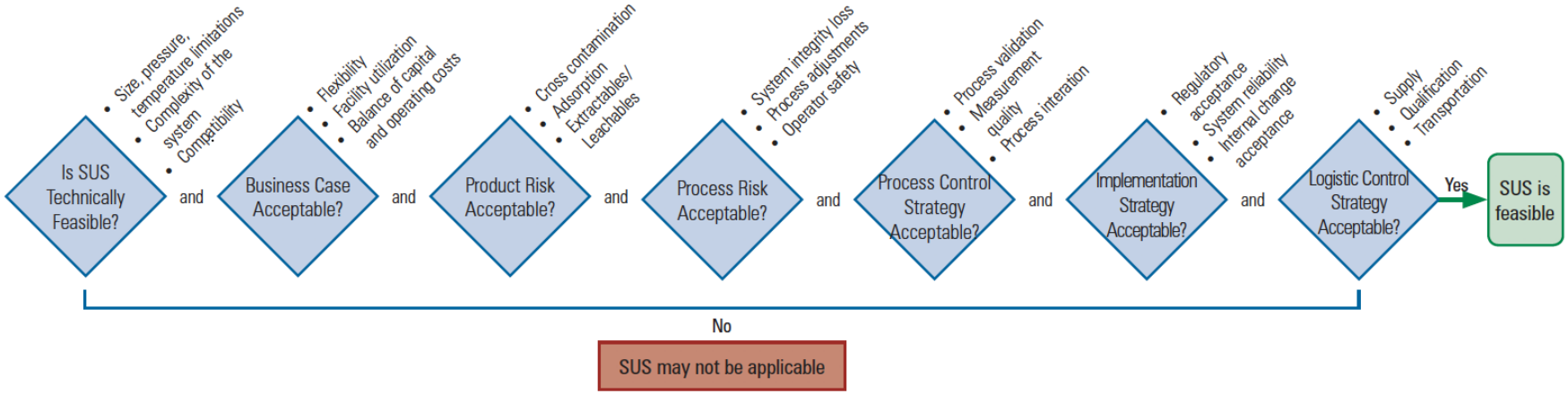

Figure 3.0-2 Proposed SUS Decision Pathway

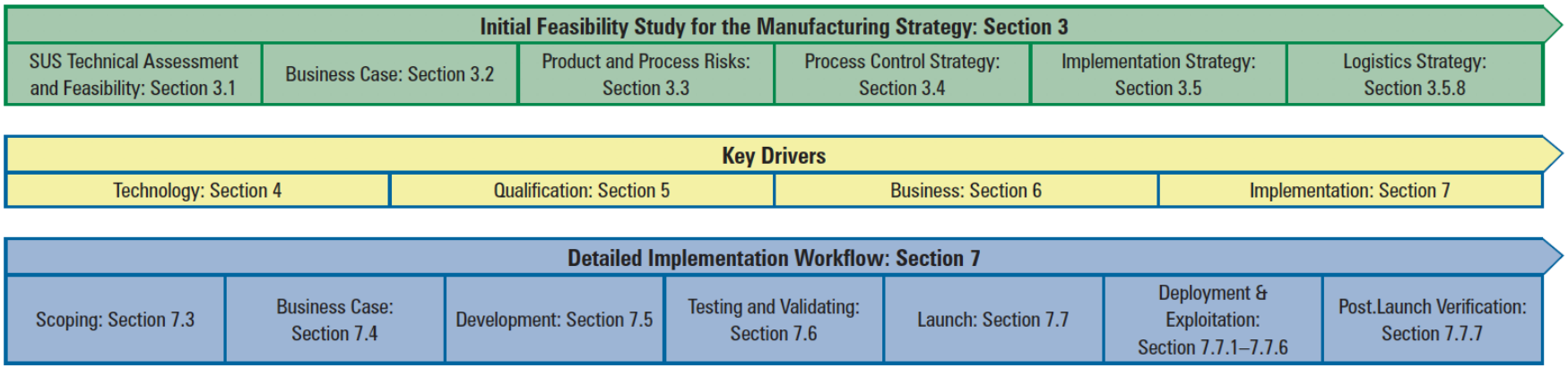

Figure 3.0-3 Technical Report Structure Overview

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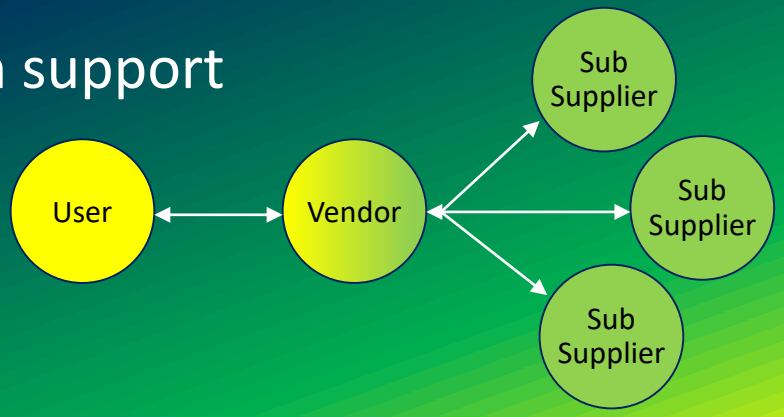
END-USER REQUIREMENTS

- Thorough qualification testing and documentation
- Long-term supply assurance (health of the company, take-over target, etc. pp.)
- Timely change notifications and comparability studies/ documentation
- Appropriate Quality System (reliance on vendor data and raw material supplier audits)
- Process validation support



QUALIFICATION REQUIREMENTS

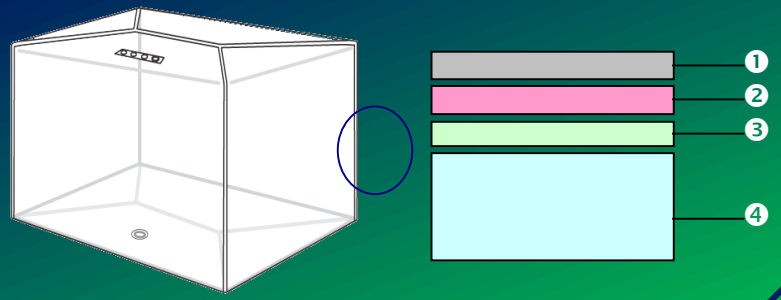
- γ Sterilization Validation
- Extractables Analysis
  - Actual Product Contact & Duration
  - RP-HPLC, GC-MS, FTIR
  - USP Class VI
- Chemical Compatibility
  - Physical Testing

    Burst Test

    Leak Test,

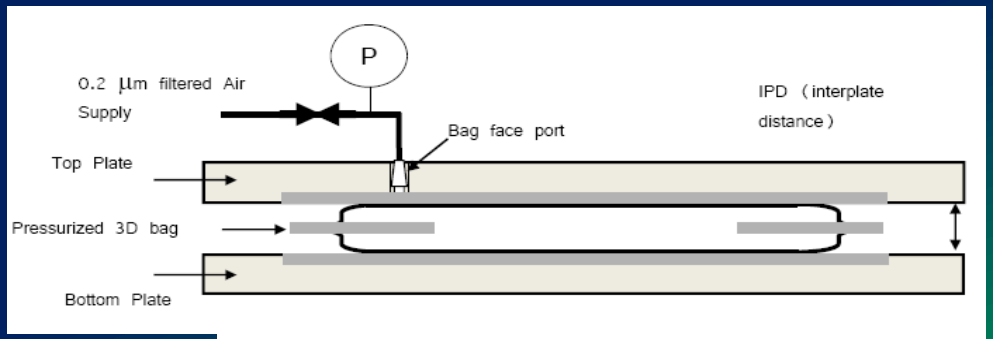
    Seal Strength

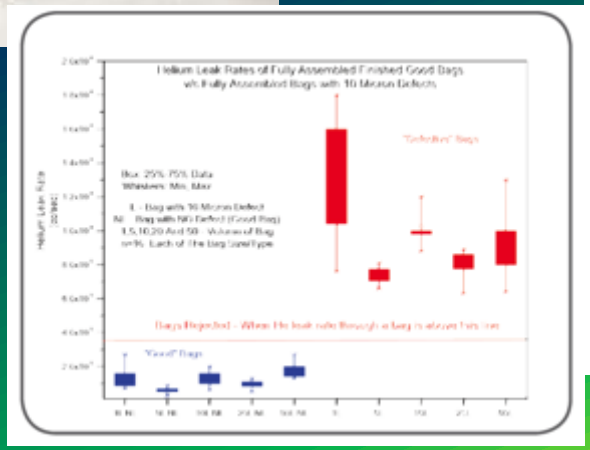
    Film Thickness
- Endotoxin Testing
- Permeation Analysis
- Long-term Shelf Life
- Unspecific Adsorption
- Particle Release

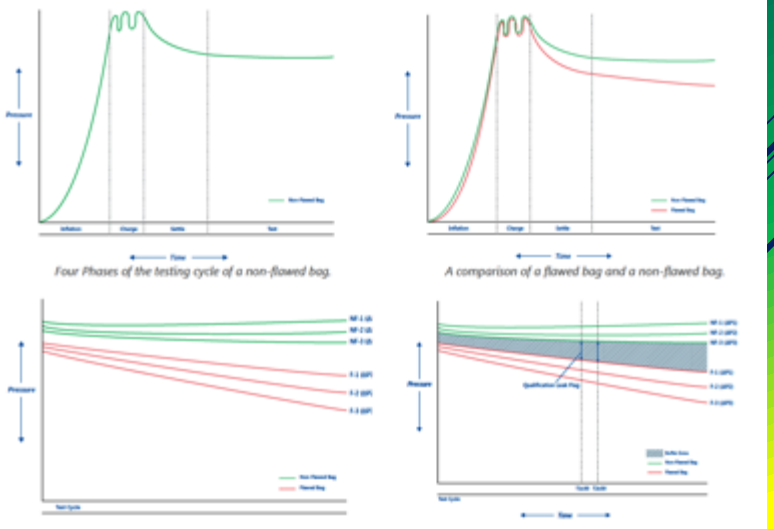


SINGLE-USE TECHNOLOGY ADVANCES

- Bag and fermentor bag integrity test are published
  - Production release and end-user integrity tests are offered
  - Bacterial ingress/flaw correlations are done, but inconclusive







CONCLUSION

- The single-use technology status is rapidly shifting and implemented
- 5 years ago, single-use unit operations were the newest “hit”
- Self-contained process steps or entire processes are very real
- Vendors are not only asked to supply products, but require to support products with an appropriate quality system
- Trade organizations start supplying aligned science & technology documents

A PESSIMIST SEES THE DIFFICULTY IN EVERY OPPORTUNITY; AN OPTIMIST SEES THE OPPORTUNITY IN EVERY DIFFICULTY.

SIR WINSTON CHURCHILL

THANK YOU !

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