Enhancing Upstream and Downstream Process Methods Through Implementation of Single-Use Technologies

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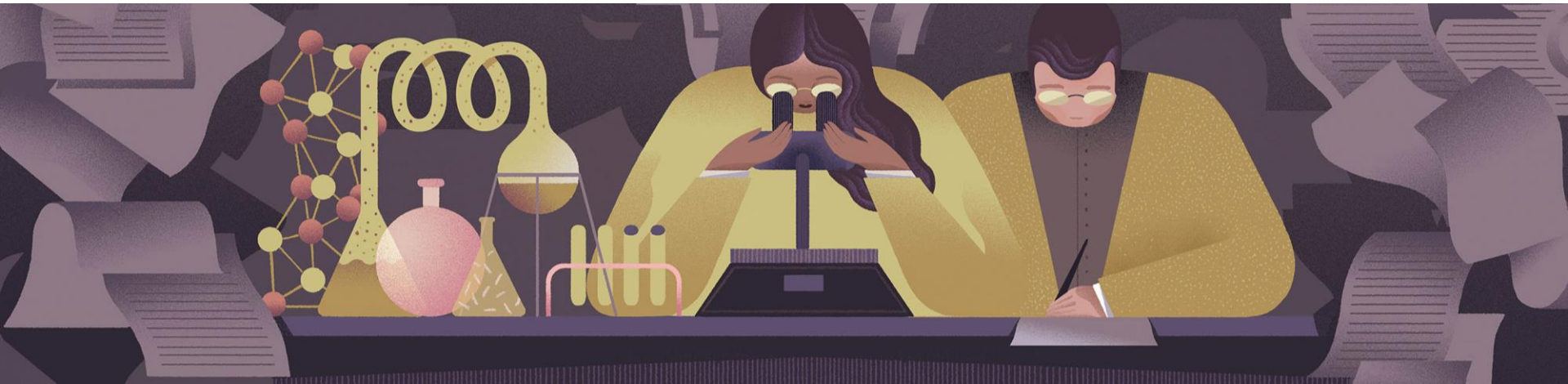
17th Annual
Global Bioproduction
Summit



Overview

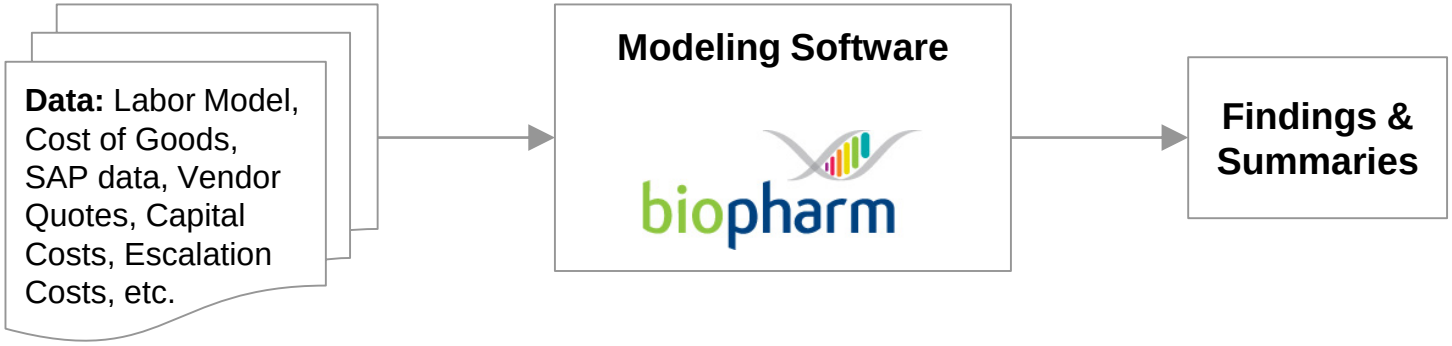
- Single-use technology (SUT) is a rapidly evolving technology that focuses on the application of disposable bioprocessing equipment and accessories for biopharmaceutical manufacturing

- When deciding whether to implement single-use equipment in a biopharmaceutical facility, cost is one of the main factors to evaluate
  - It is important to consider not only the production process, but also HVAC, building costs, running costs, raw materials, personnel, energy, etc

- This presentation will focus on a conceptual analysis of DS manufacturing costs in order to answer the following:
  - Where does it make financial sense to implement SUT?
  - What novel SUT solutions could be worth pursuing?
  - Of the technologies identified - which may still need maturity?

Project Method

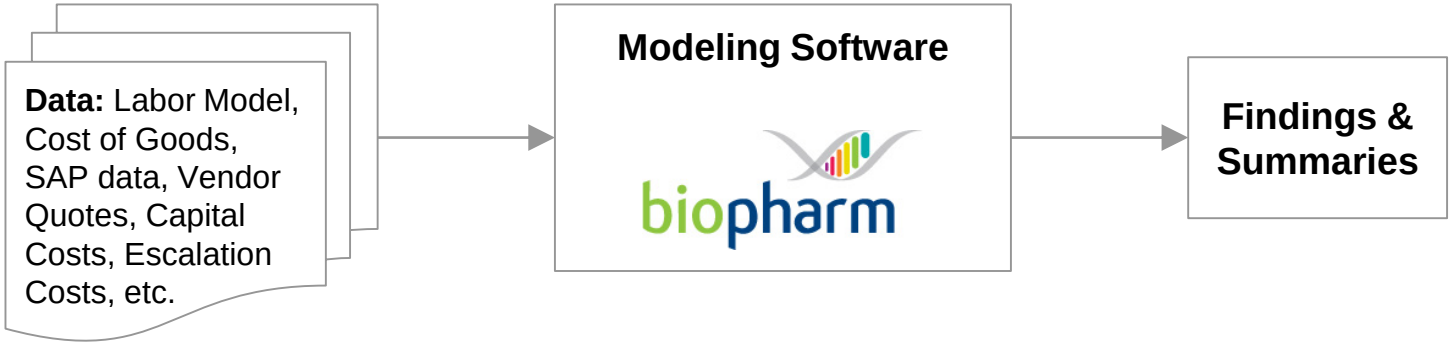
- A conceptual model was developed to identify the most appropriate unit operations for the deployment of SUT to ongoing DS operation
- The model can be used to elucidate cost savings / avoidance and increase agility of the DS network over several run rates, volumes and titer scenarios
- Output
  - Recommendation of feasible SUT applications within a large DS manufacturing network



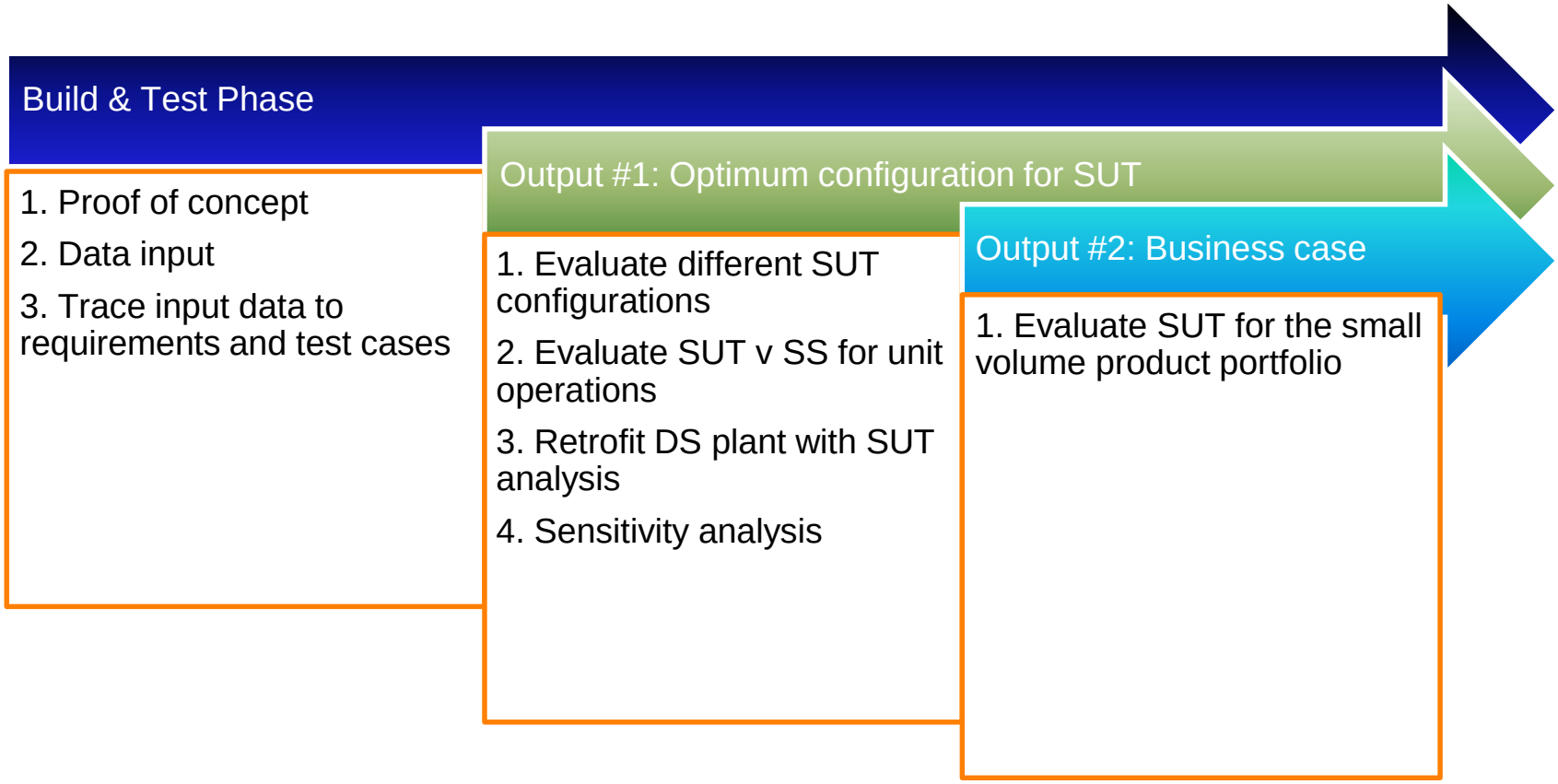
Project Benefits

A conceptual model allowed for the elucidation of opportunities to lower costs, speed, and agility of DS manufacturing operations

- Potential for increased agility and lower capital cost and operating cost.
- Significant cost savings / avoidance by replacing some of the aging assets and using SUT in place of stainless steel in existing DS & clinical operations
- Specific targets for cost saving & avoidance will come from the analysis
- Increase speed for product transfers with SUT
- Building “toolbox” of approved ready to implement SUT solutions for DS sites



Project Approach



Definitions

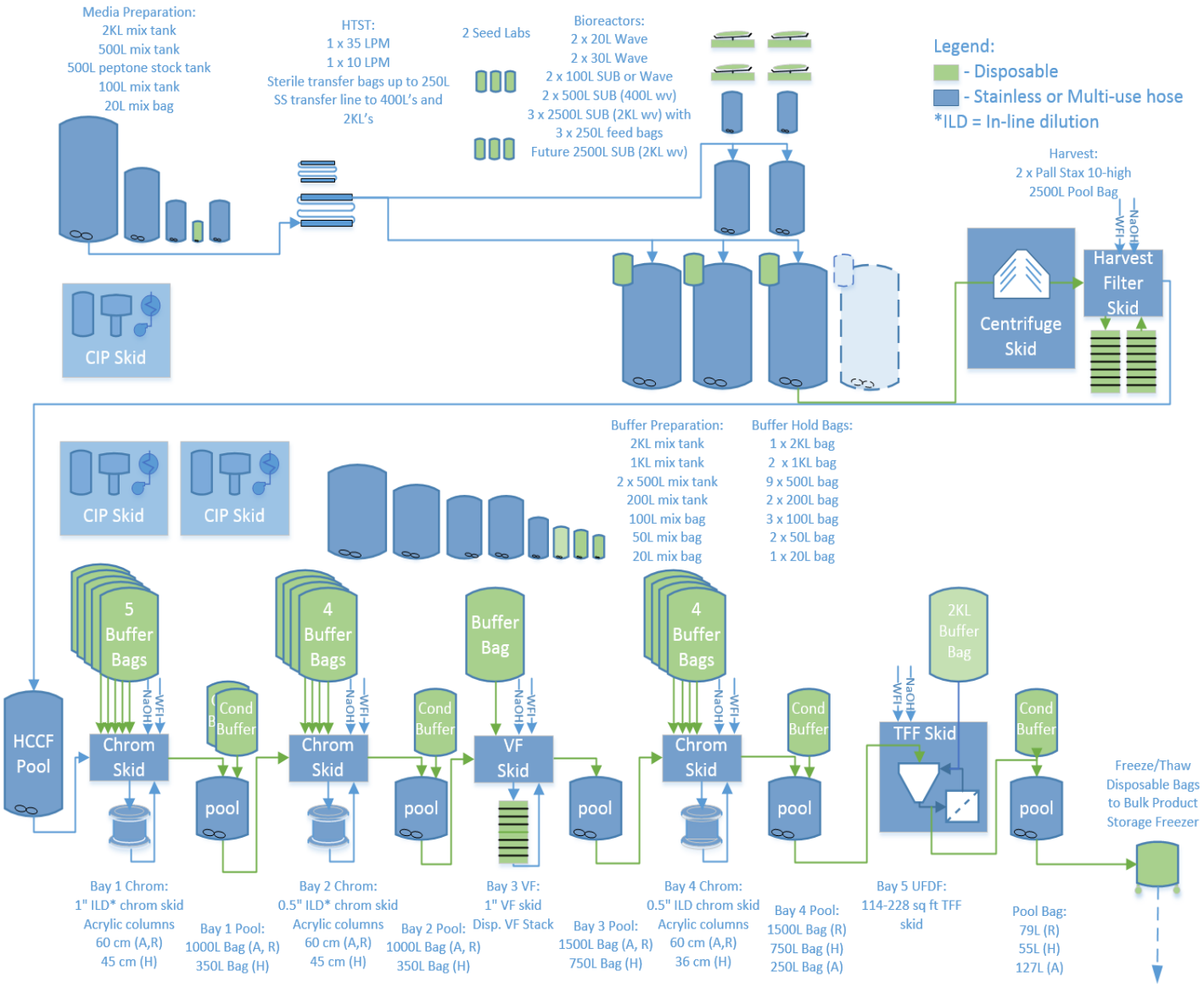
The conceptual model focused on the following scenarios

- Full Stainless Steel
- Full SUT
- Hybrid 1 Stainless Steel + SUT (only 6 unit ops. are steel)
- Hybrid 2 Stainless Steel + SUT (only 2 unit ops. are steel)

	Full SS 2kL Scale		Full SUT 2kL Scale		Hybrid 1		Hybrid 2	
Unit Ops:	SS	SUT	SS	SUT	SS	SUT	SS	SUT
Bioreactors & SL	X			X		X		X
Media Prep	X			X	X			X
Buffer Prep	X			X	X			X
Buffer Hold	X			X		X		X
Pool Hold	X			X		X		X
Harvest	X			X	X			X
Chrom Skids	X			X	X		X	
Chrom Columns	X			X		X		X
VF Skids	X			X	X			X
UFDF Skid	X			X	X		X	

Definitions - Full Stainless Process Flow

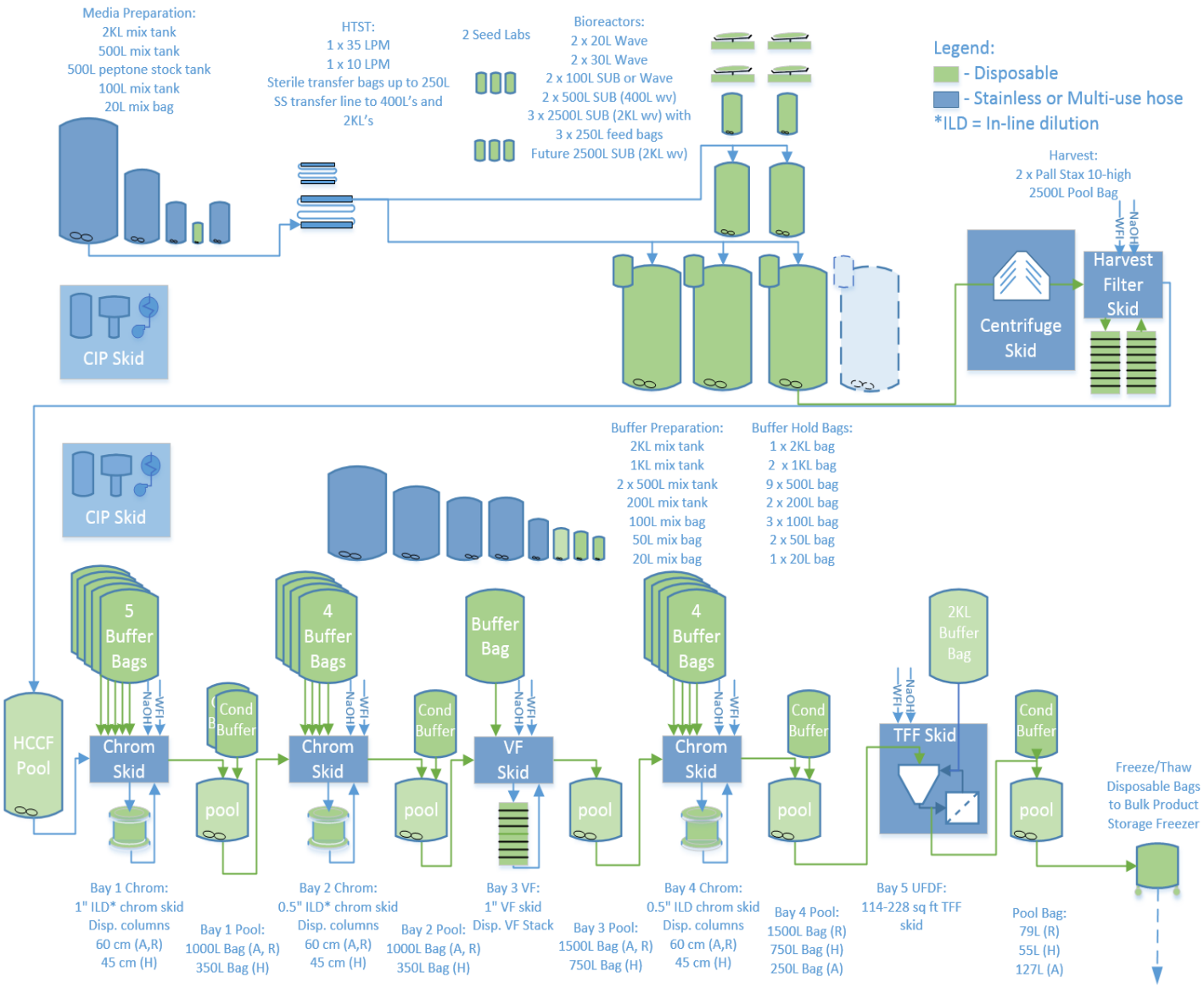
(2kL scale, stainless in blue, disposables in green)



Courtesy of: Carl Johnson

Definitions - Hybrid Facility Process Flow

(2kL scale, stainless in blue, disposables in green)



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Definitions - Full SUT Process Flow

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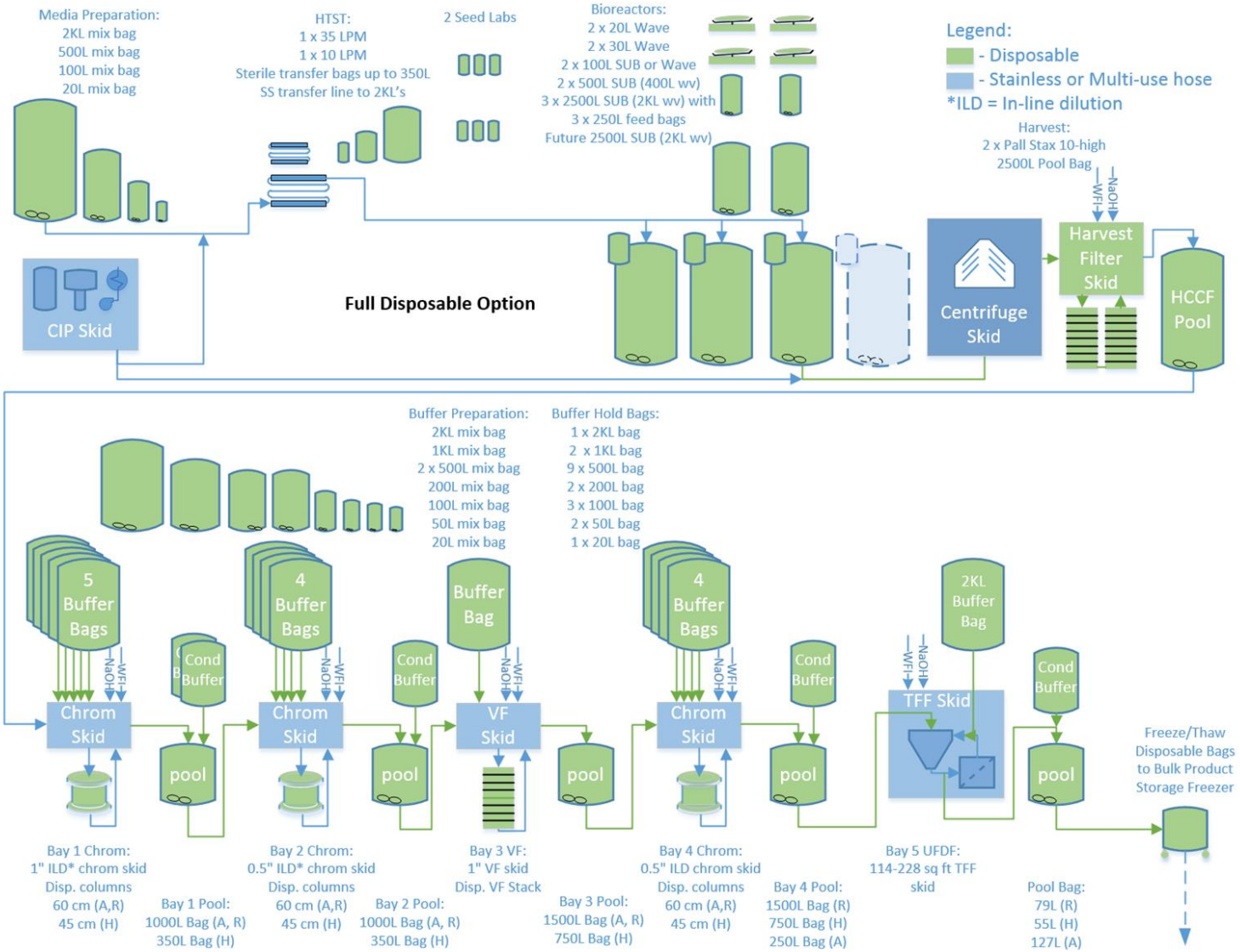
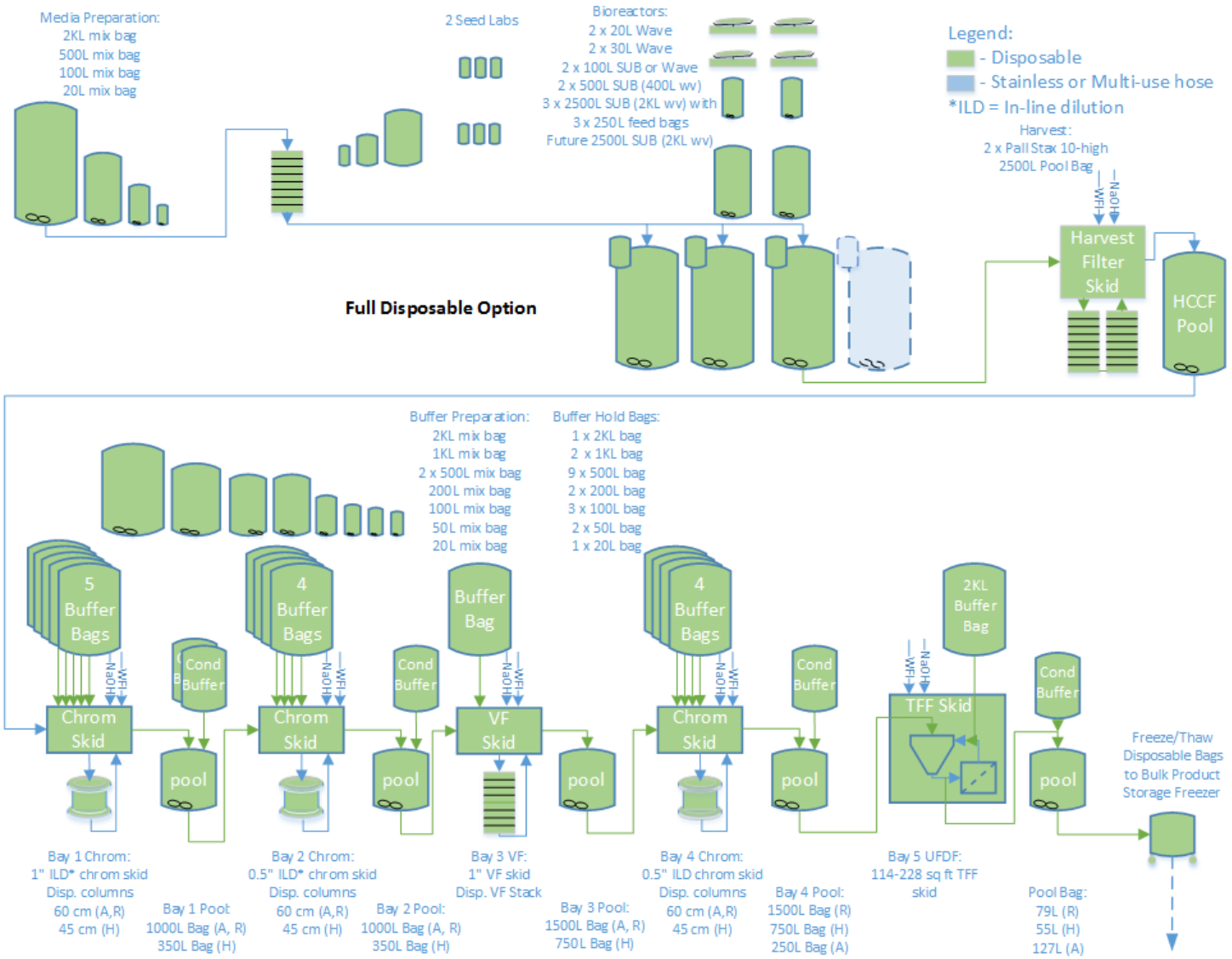


Courtesy of: Carl Johnson

Definitions - Full SUT Process Flow 2

(2kL scale, stainless in blue, disposables in green)



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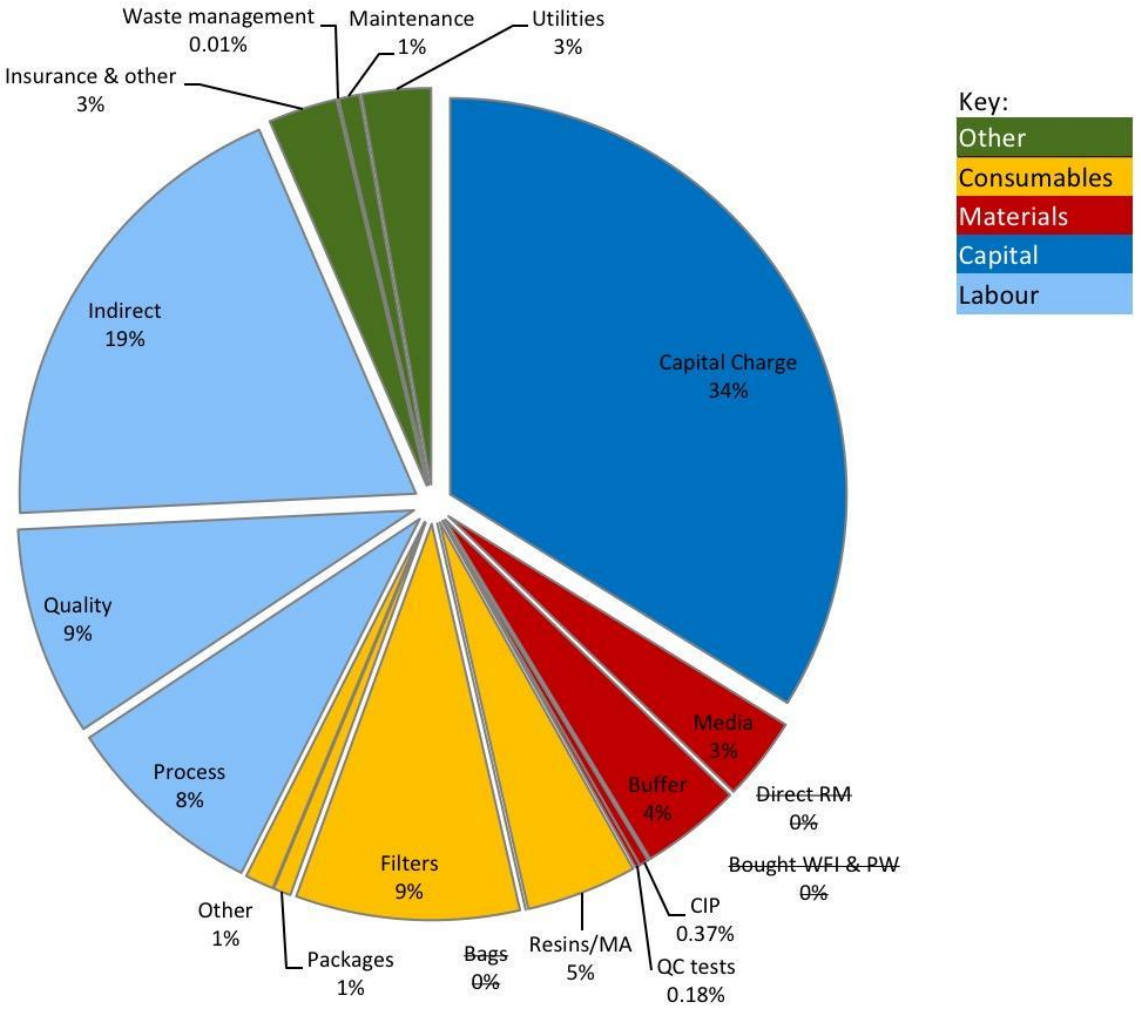
Harvest	X			X	X			X
Chrom Skids	X			X	X		X	
Chrom Columns	X			X		X		X
VF Skids	X			X	X			X
UFDF Skid	X			X	X		X	

Single Use Facilities Case Studies

Cost of Goods - Breakdown Details by Unit Operation

For a 12 kL Stainless Steel Plant, Assuming 3.5 g/L Titer, 70% Recovery



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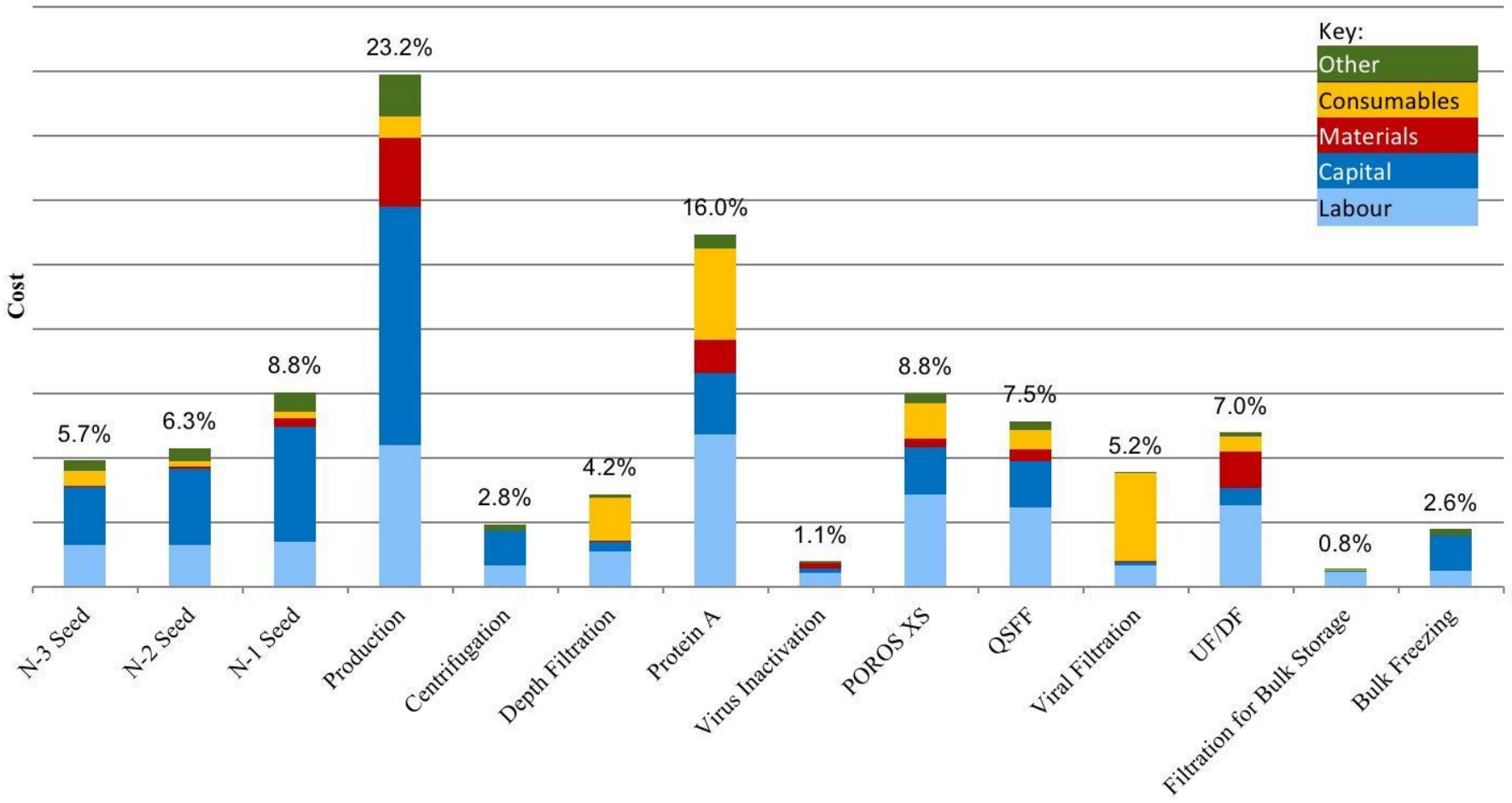
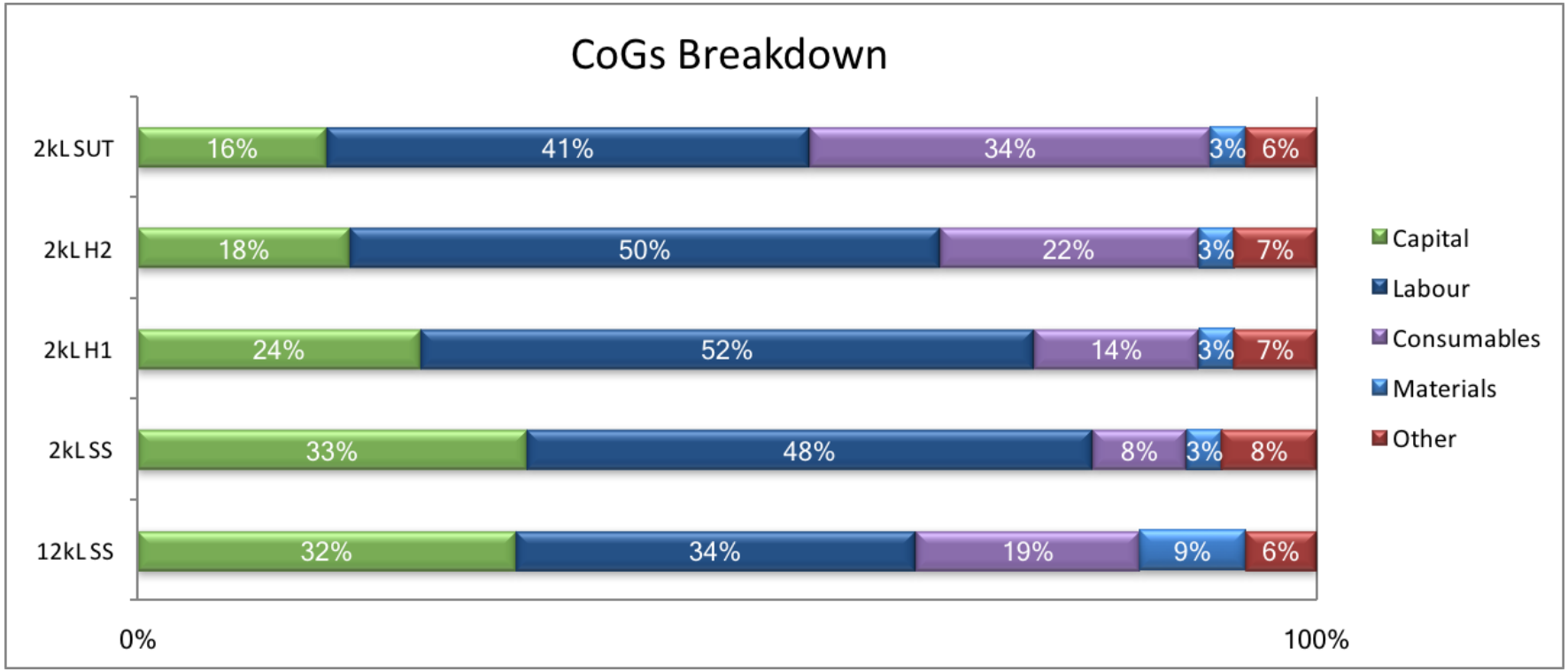
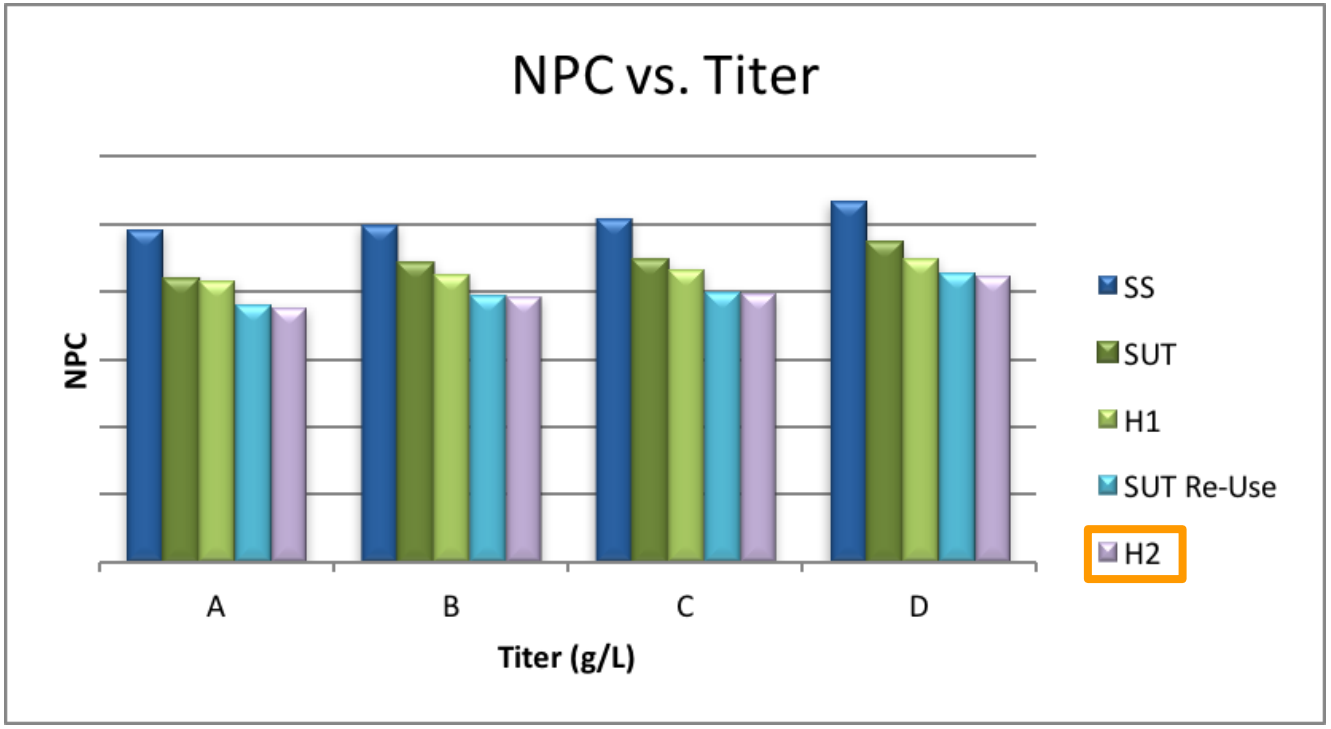


Key Financial ROI Savings



- Labor is the largest component of cost for all scenarios
  - Labor demand decreases with single use due to smaller scale and simpler operations with less automation and facilities support
- Capital cost component decreases with plant configured towards increasing SUT
- SUT greater variable cost to fixed cost ratio – scaling advantage

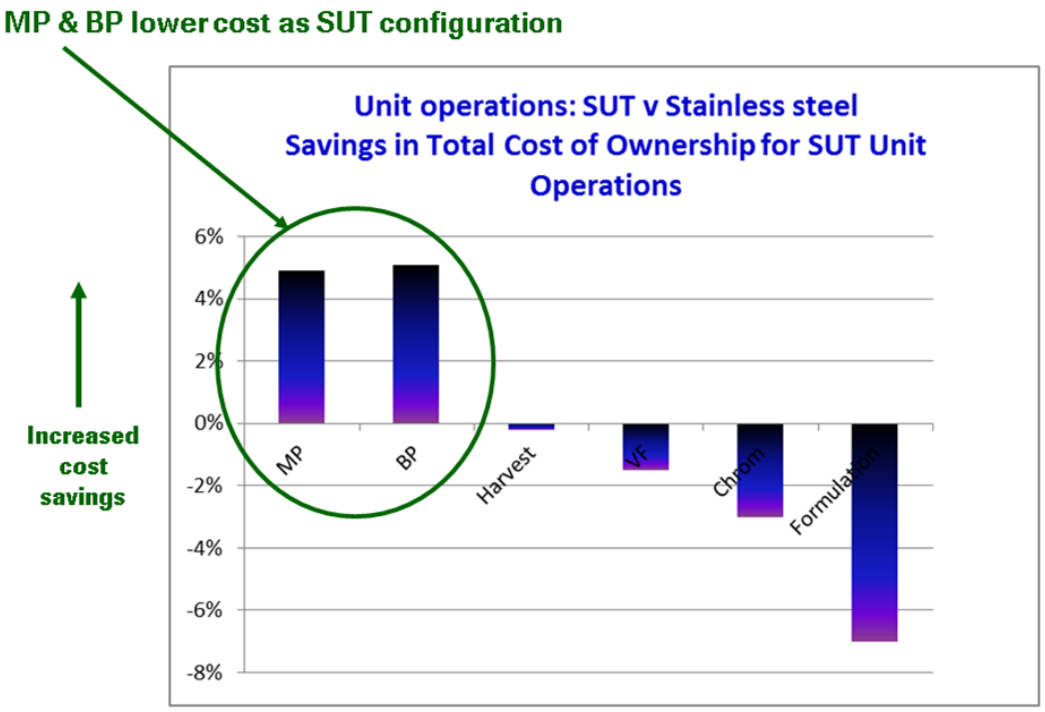
Key Financial ROI Savings



- Titer increases from left to right (A < B < C < D), analysis is for constant production for a year, 6 x 2kl bioreactors, 100 run starts
- "Hybrid 2" configuration has the lowest cost for all titers
- Slight increase in cost at higher titers is due to more buffer prep & hold consumables & materials required
- Stainless configuration has the highest cost

Single Use Facilities Case Studies

Hybrid 1 Scenario Compared to Stainless Steel



- SUT for Media Prep and Buffer Prep provide the greatest savings
- Lowers total cost of ownership (NPC) by approximately 5%
- Assumes constant production for a year, 6 x 2kL bioreactors, 100 run starts
- Single-use UF/DF skids followed by single-use Chrom skids, are the least favorable
    - High cost per gram for single use UF/DF skids and Chrom skids is associated with the cost of consumables for these units (i.e. membranes)

Outputs and General Findings

- Fully SUT facility was not always the most financially feasible
  - Some SUT may not be fully developed or favorable for plant and process needs (e.g. UFDF and chrom skids)
- Labor demands are a major consideration for CoGs
- Capital cost is dramatically reduced for a SUT facility
- ROI on some SUT unit operations are made difficult based on the pricing of the SUT components vs steel / cleaning
- “Hybrid 2” configuration gives the lowest cost of ownership & initial investment
  - All SUT except “stainless steel” chrom & formulation (harvest & VF are relatively neutral to costs)
- Cost of tech transfer to SUT appears less than “stainless steel”

Single-Use of the Future

What are the remaining gaps for SUT?

Chromatography

- Optimize the ability of SUT chrome skids to be able to provide Inline dilution of larger scale buffer concentrates to enable SU facilities to employ smaller hold bags vs larger steel hold tanks for chrome buffers and regeneration solutions
- Larger systems to employ faster / higher flow rates with increased psi capabilities

TFF

- Reduction in price points for both Single Use TFF and Chrome tubing sets to enable purchasing the capital to compete with cleaning traditional steel skids
- Larger ID systems to allow for higher over all Kg runs and high concentrate low volume pools

New Advances in SUT

Current Landscape of Freeze Technologies

Small volume bulk freeze systems have been introduced in commercial and clinical since 2009:

- Sartorius Celsius® FFTp 6L
- Thermo Fisher (Aegis 5-14) 5L bag
- Thermo Fisher (CX5-14) 5L bag and 20L bag

SSB FFTP

CX514 system

Large Freeze Thaw (LFT) system

- No commercial system available
- SSB/RGNE co-development (2012-2015)

SSB LFT system

New Advances in SUT

Areas of Opportunity for Freeze Technologies

- There is no current solution for large bulk freeze applications in the industry
- The current stainless steel tanks generate risk, require excess labor, coordination, and investment
- The current landscape of single-use freeze technologies are not fully developed to meet process and facility requirements
    - A sustainable system is needed to improve freeze capability in a single-use format

New Advances in SUT

Frozen Accelerated Seed Train

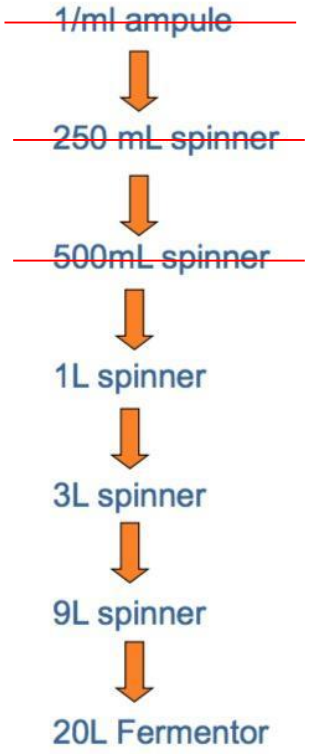
- Ampoules of frozen cells from a released cell bank (MCB or WCB) are thawed and then expanded in 20L perfusion bioreactor (with an ATF system for cell retention)
- Upon reaching target cell density, the cells are mixed with freezing medium, and filled into 150-mL cyrobags which are then frozen down using a rate-controlled freezer
- When needed to support a manufacturing campaign, the bags are thawed and inoculated into the N-3 inoculum train bioreactor
- The inoculum train and production bioreactor culture are essentially unchanged from the current operating paradigm
- Using SUT, this process saves time in upstream processing by accelerating the seed train process

New Advances in SUT

Frozen Accelerated Seed Train

- Freeze production of CHO cells in Freeze-Pak ™ Biocontainers
- Followed by thaw into the inoculum train to initiate cell culture manufacturing campaigns
- No vial seed expansion, no need for cracking vial under laminar flow
- No wait, ability to remove N-5 to N-4 scaling

→ Saves 15-30 days of cell culture expansion



New Advances in SUT

Octane Bioreactors

- Full-circle automation from ‘donor-to-product’
- Cell isolation, proliferation, wash & concentration, scaffold loading, graft production
- Another step towards personalized medicine
- Interlinked bioreactors combine all processing events in a closed and automated single-use customized cassette

Conclusions

- Biosolve analysis has shown strong financial positive returns for SUT drug substance manufacturing
- Several key SUT platforms have been successfully launched from leading vendors
- Many of the technologies while they are capable at increasing scales, their ROI does not necessarily show a positive return depending on the scenario which it is used in
- Additionally, several of the SUT platforms, while being innovative, still do not compete in their technical capability vs. SS systems
- Our key partners (vendors) are continuously innovating both DSP and USP applications to meet our technical needs

Acknowledgements

- Ken Hamilton
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