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# Innovation in biomanufacturing with single-use technologies:

*Overcoming the challenges through collaboration*

**Jeff Johnson**

New Technology Lead

Global Science, Technology and Commercialization





125  
YEARS  
SINCE 1891

HELPING THE WORLD BE WELL

We are a global healthcare company with a 125-year history of working to make a difference in global health.



**BUSINESSES**  
Pharmaceuticals,  
Vaccines, Biologics  
and Animal Health



**2015 REVENUES**  
\$39.5 billion; 56% of  
sales come from outside  
the United States



**2015 R&D EXPENSE**  
\$6.7 billion; 19 drug  
candidates in late-stage  
development



**HEADQUARTERS**  
Kenilworth, NJ, U.S.A.  
operating in more than  
60 countries



Merck & Co., Inc.  
is our legal name and is  
listed on the New York Stock  
Exchange under the  
symbol "MRK."



**EMPLOYEES**  
approximately 68,000  
worldwide (as of 5/5/16)



We are inspired by a shared vision and a mission to save and improve lives.



## VISION

To make a difference in the lives of people globally through our innovative medicines, vaccines, and animal health products. We are committed to being the premier, research-intensive biopharmaceutical company and are dedicated to providing leading innovations and solutions for today and the future.

## MISSION

To discover, develop and provide innovative products and services that save and improve lives around the world.

Our business focuses on innovation and scientific excellence to deliver vaccines, medicines, and animal health products that can help millions around the world.



## CORE AREAS OF FOCUS

Diabetes  
Hospital Acute Care  
Oncology  
Vaccines

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## ANIMAL HEALTH

Livestock  
Companion Animal  
Aquaculture  
Poultry

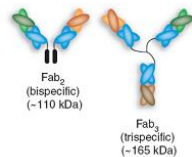
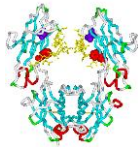
# Continued Momentum of Biologics & Vaccines

Worldwide Biopharma market of > \$190 B, 15% annual growth  
mAb 2013 revenue > \$50 B (BioPlan 2014)

7 of the top 10 drugs are Biologics

High POS for mAbs/TPs

2-5 fold greater than small molecules  
R&D shift to BioPharma  
400 mAbs in development 2013



Continued growth for world vaccine market

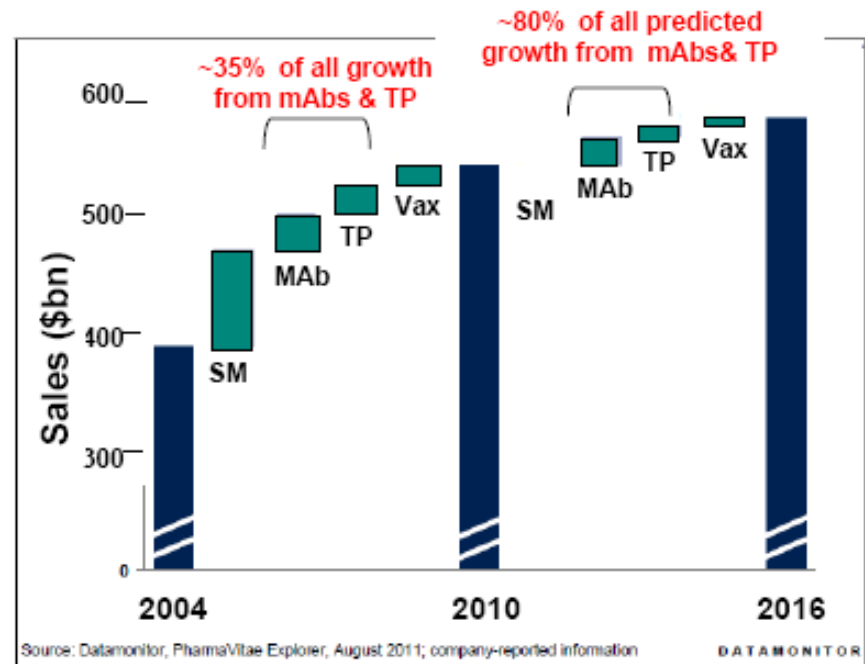
~\$25 bn in 2014 up 9.7% since 2008

Over 200 vaccines in development

Low cost availability to the worldwide is key

(Kaloram Information)

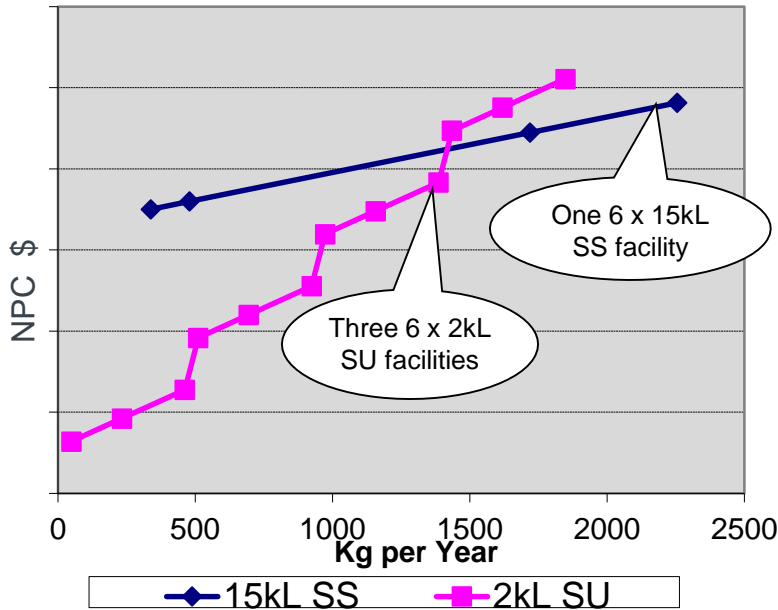
## Sales



# The Multi-Million Dollar Question – Literally!

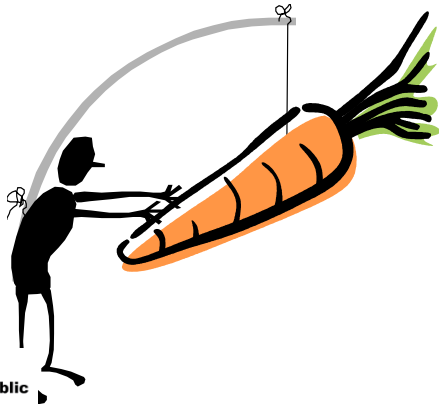
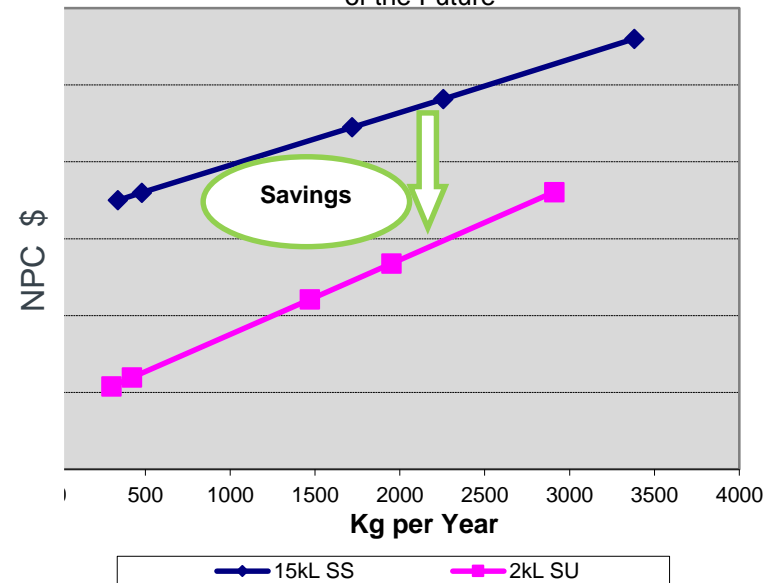
*Can a SU facility produce as much as a large SS facility?*

Bioreactors: 6 x 15,000L vs 6 x 2,000L  
(3g/L Titer)



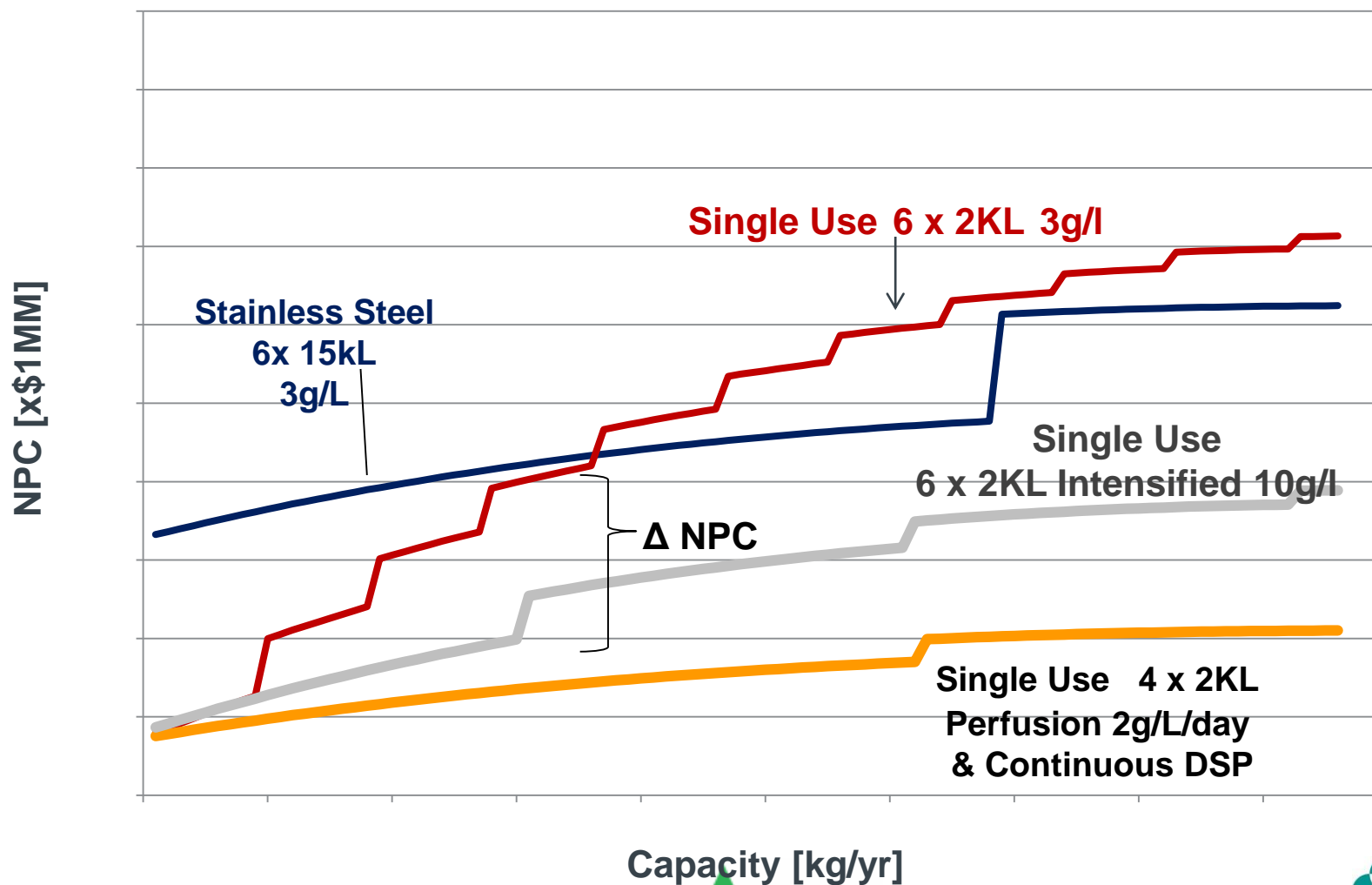
*What if...*

6 x 15kL SS Traditional Facility vs. 6 x 2kL SU Facility of the Future



# Yes! SU Facilities offer Significant Savings over SS!

## Significant NPC savings from SU Intensified & Perfusion Processes

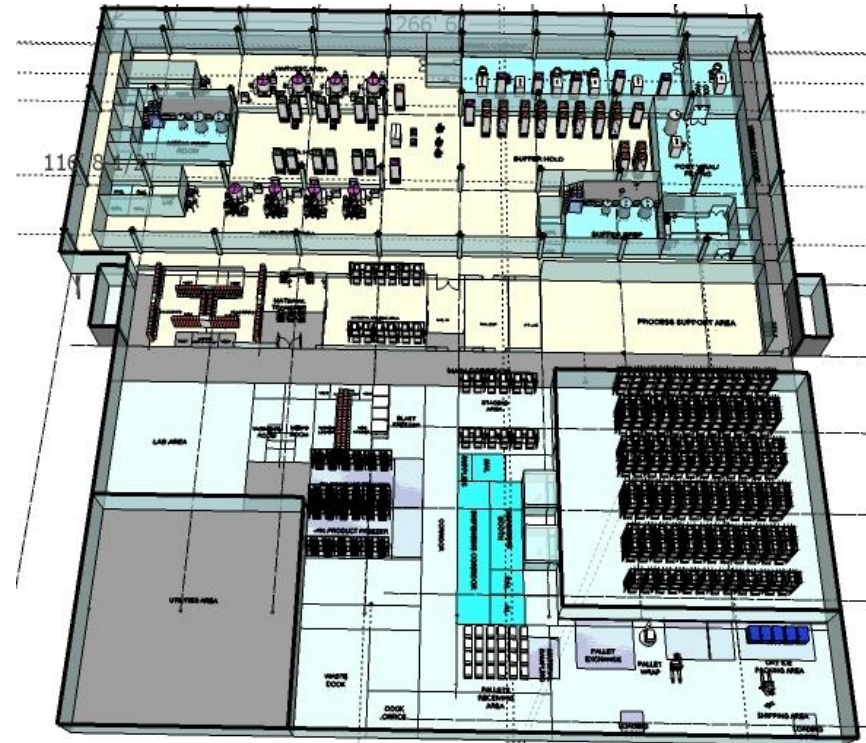


Capacity [kg/yr]

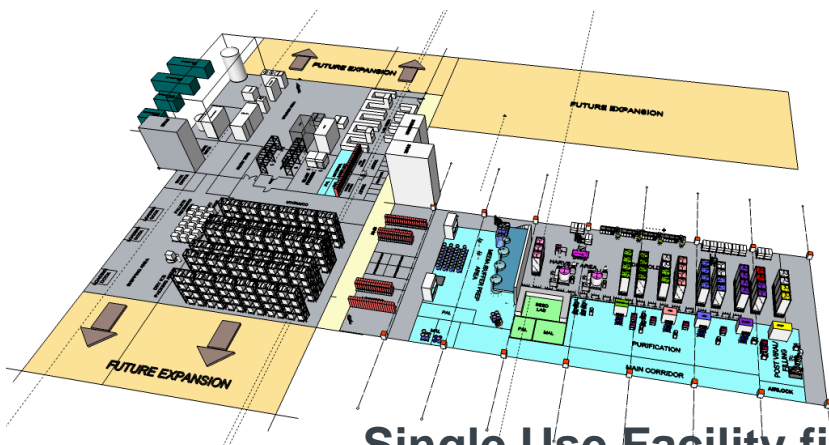


# Facility of the Future Concepts

- SU based Platform at up to 2,000 L scale
  - Intensified fed batch 3-5x titer increase
  - Perfusion with consistent harvest titer
- Modular facility design & construction
  - Scale out rather than scaleup
  - SU allows simpler designs & faster construction schedules
  - Quick to duplicate modules in multiple locations
- Consistent Process Scale allows faster Technology transfer
  - 2,000L SU Bioreactor scale used for all work – clinical, commercialization, launch



**Single Use Facility fit**  
for 6x 2,000L SUBs & Batch DSP



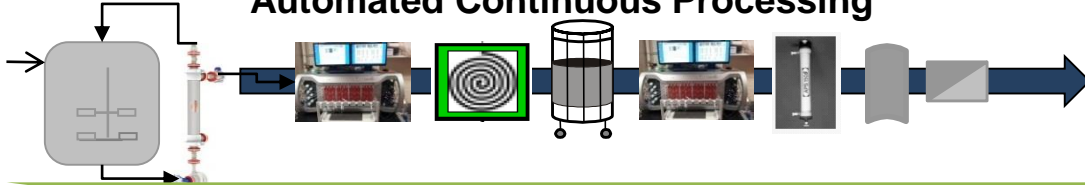
**Single Use Facility fit**  
for Perfusion SUBs with Continuous DSP



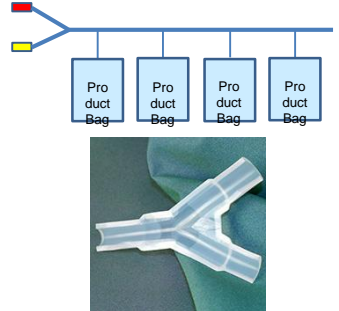
# Facility of the Future

## CHO mAb Processing Vision

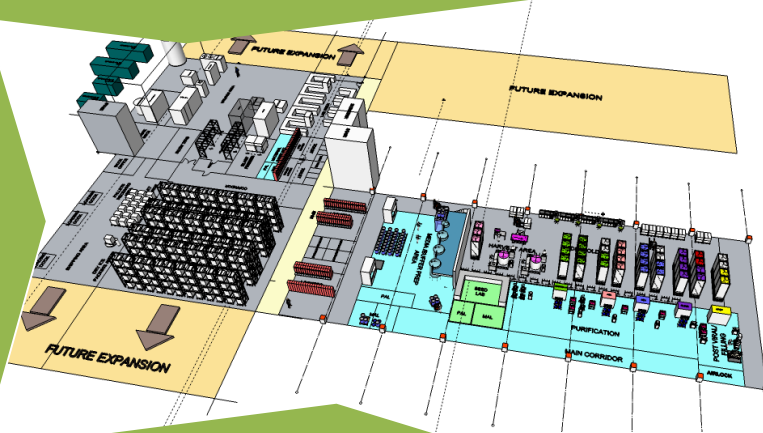
### Automated Continuous Processing



### Component Engng 'lego' building blocks



Molded parts

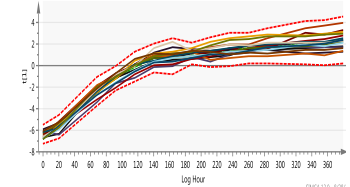


### Adaptive Process Control



PAT tools

Predictive MDVA models

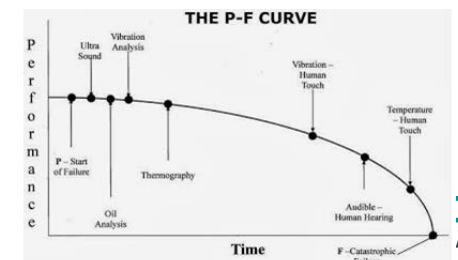


Real Time Release Testing

### Equipment Performance Real time Monitoring

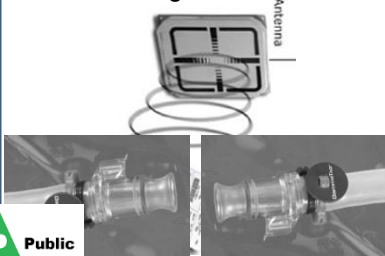
Examples:

- Real time sensing of Pump seal failure, PAT sensor performance
- Proactive preventative maintenance to limit failures
- Eqpt redundancy strategy
- Process flow strategy for deviations



### SU operations

Automated Inventory management

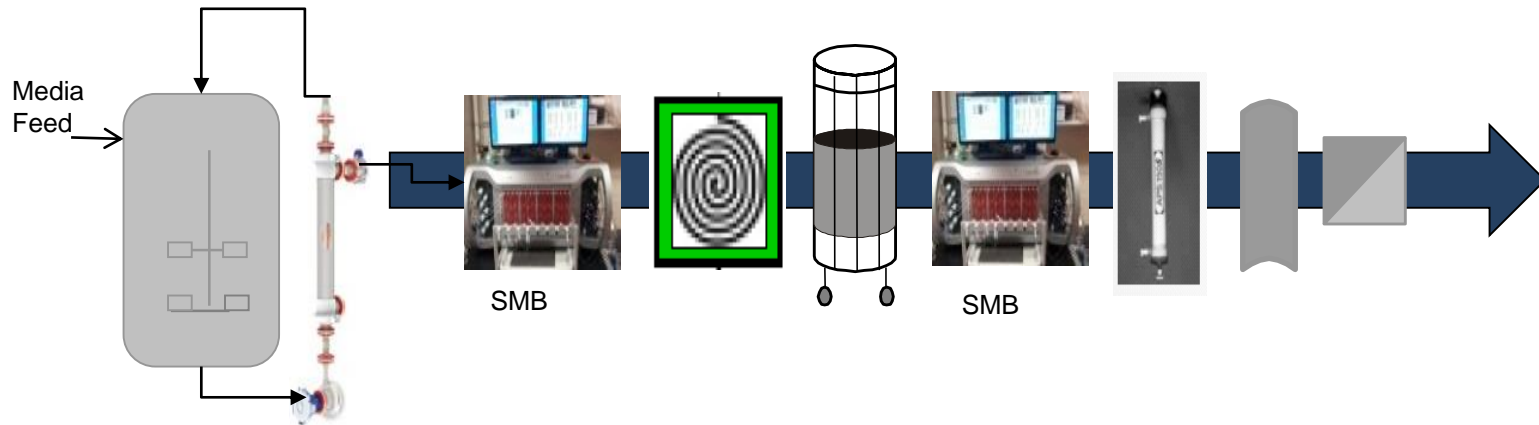


Single use Workflows  
Buffer supply  
Fluid flow management

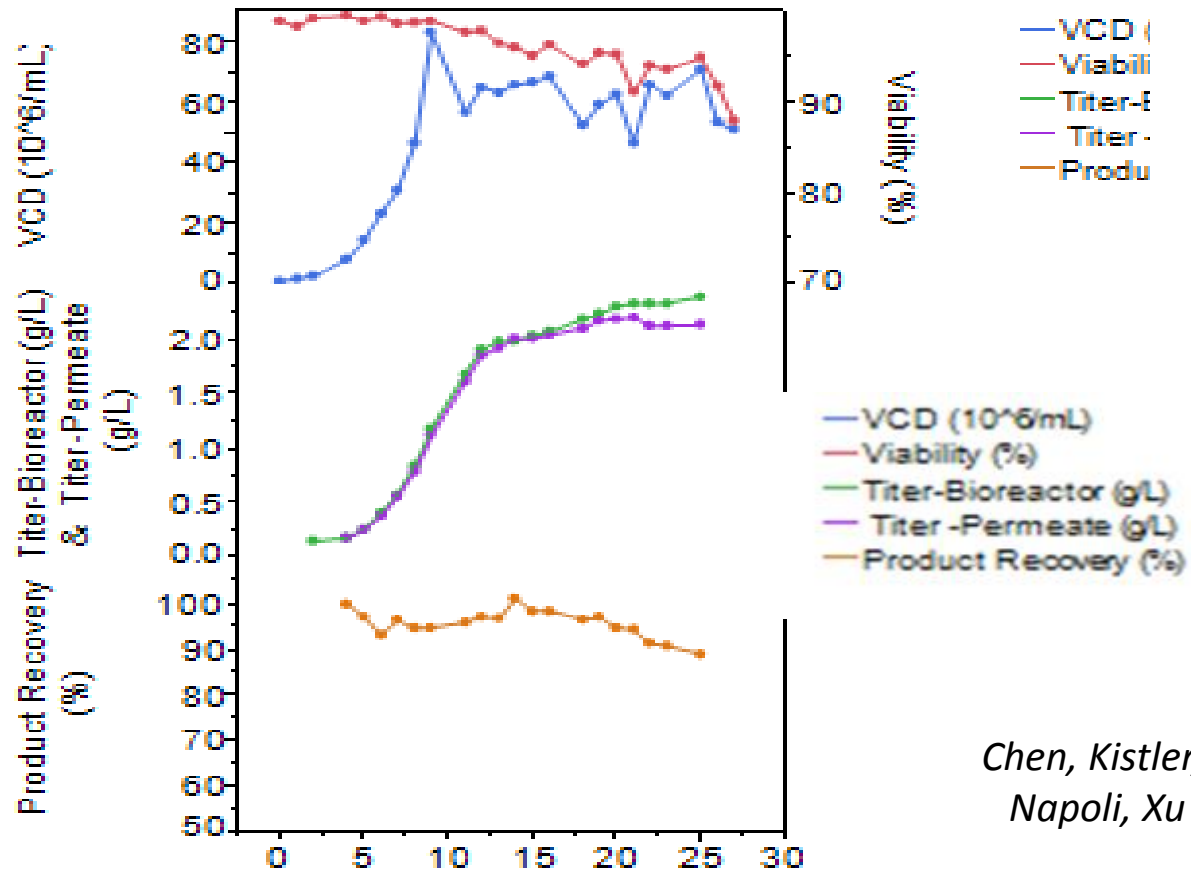
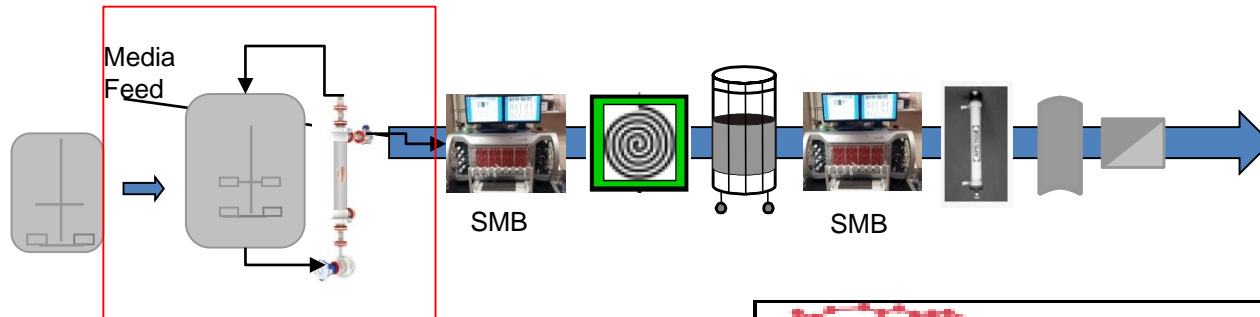


# Protein Refinery Operations Lab (PRO Lab)

## *Fully Automated mAb Drug Substance*

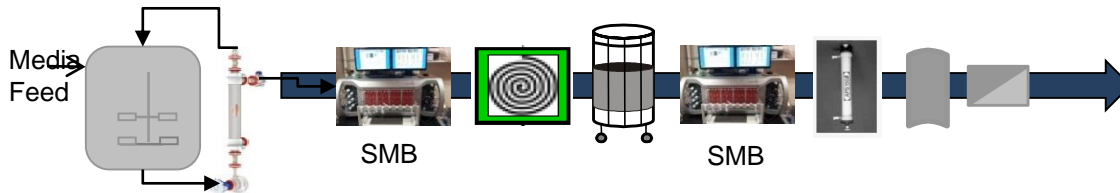


# Next Generation CHO mAb Bioprocessing Perfusion Development

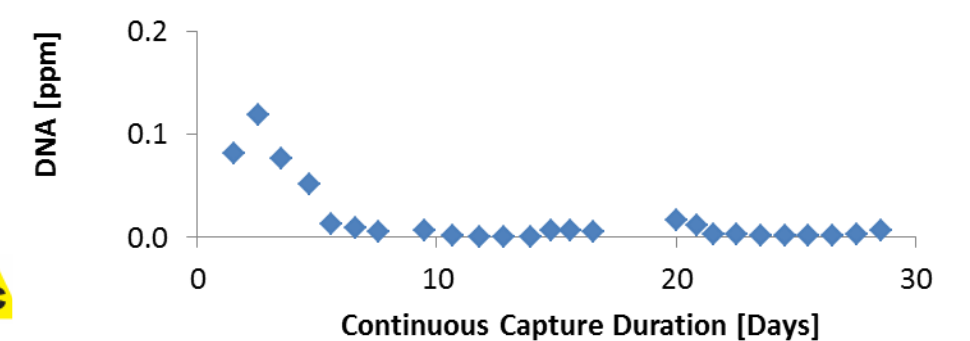
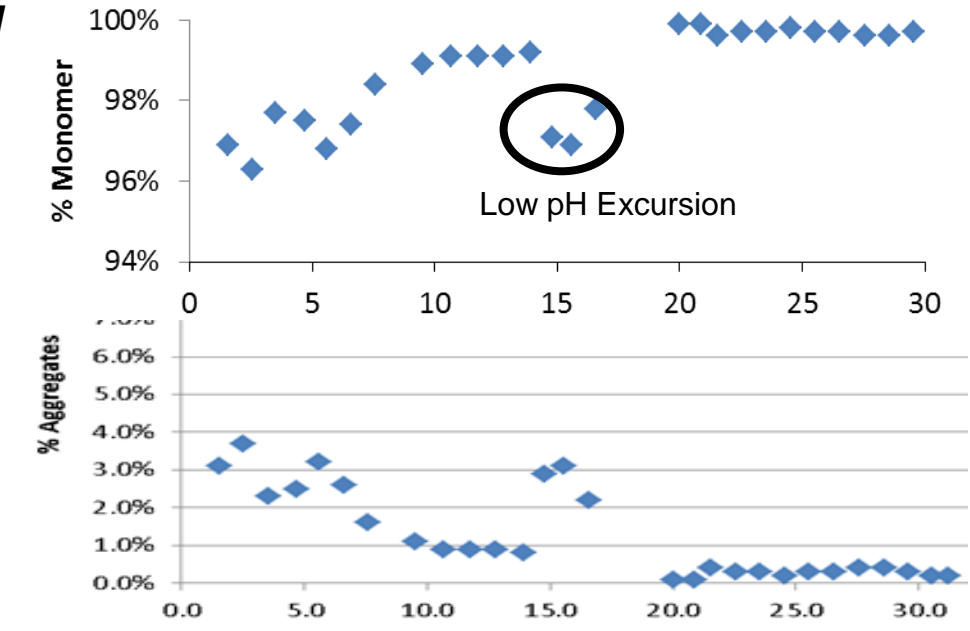
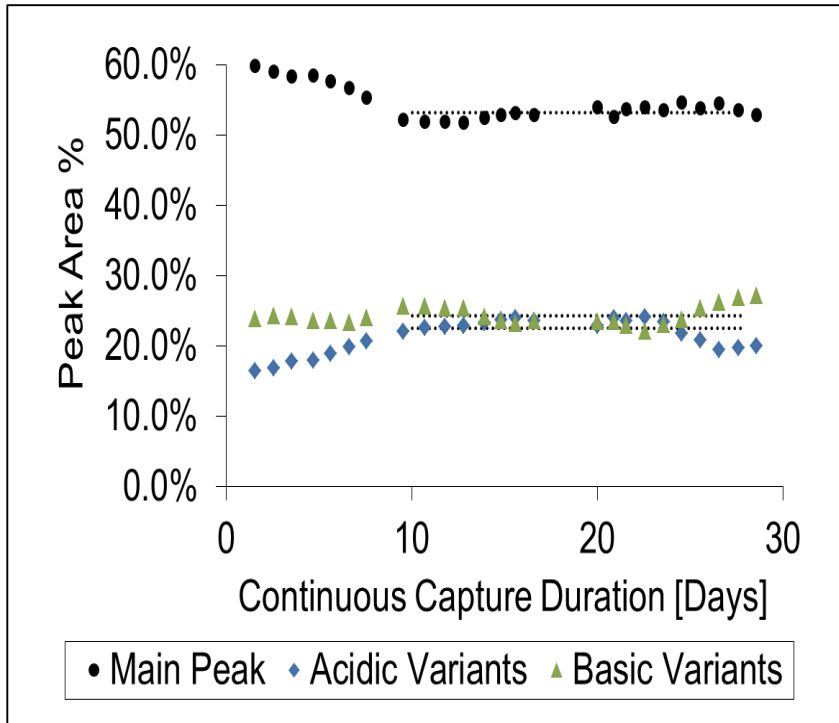


Chen, Kistler,  
Napoli, Xu

# Continuous Process Performance

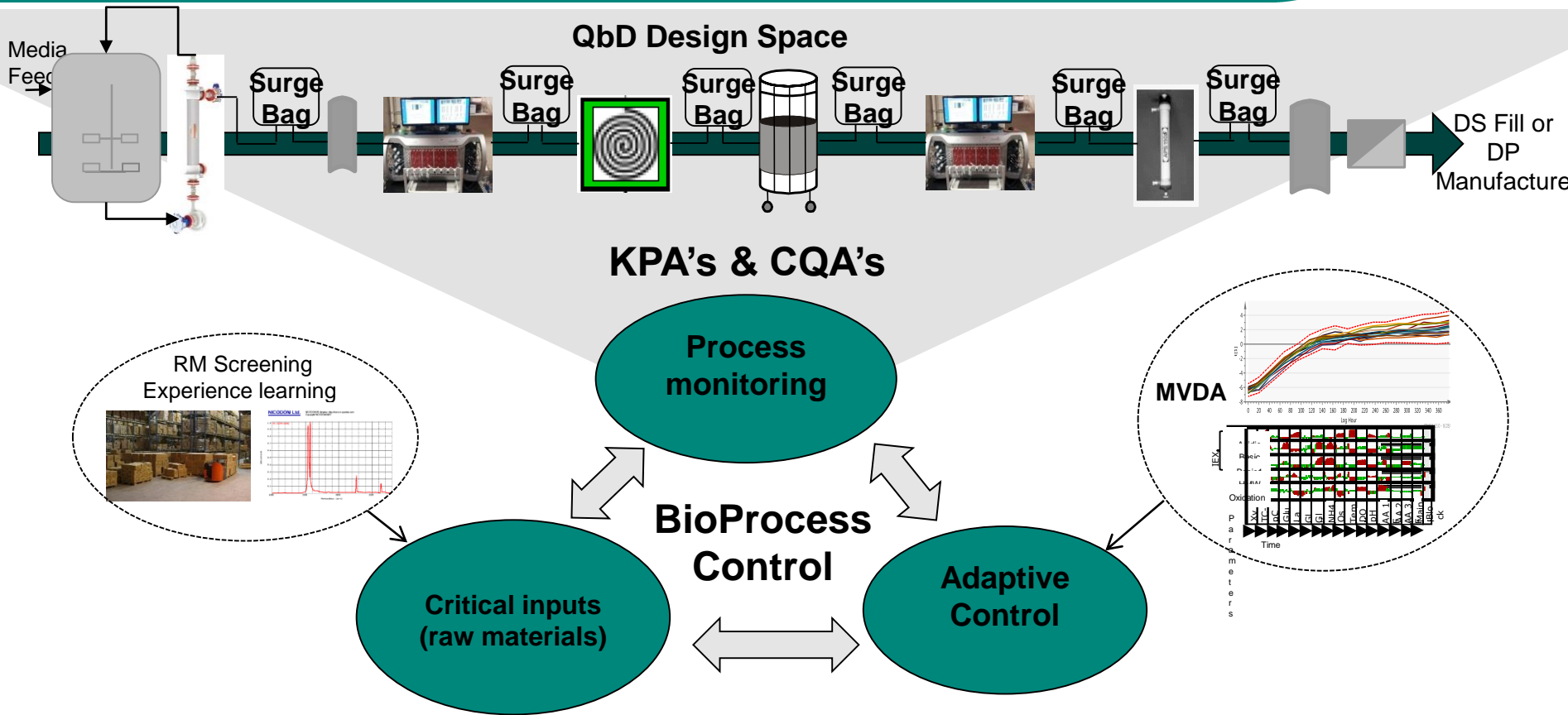


*Upon reaching steady state, purity and quality attributes remain consistent*



# Continuous Processing:

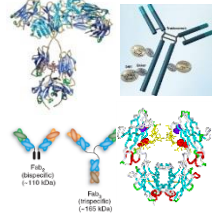
## PAT, Automated Control & Real Time Release



- End Product Testing transition to Real Time Release Testing
- Real time automated control: process responds to variability & disturbances
  - End to end prediction models for complete process
  - RM control → Process input → Product quality & yield

# Elements for Success : Collaboration between Suppliers & End Users

## Novel Pipeline



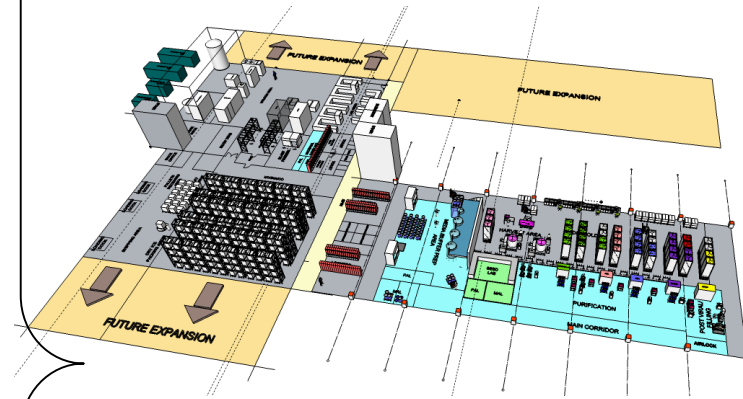
## Innovative Next Gen Process Dev



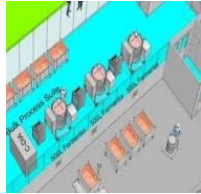
## Process Economics Tools



## Low Cost mAb Flexible Manufacturing



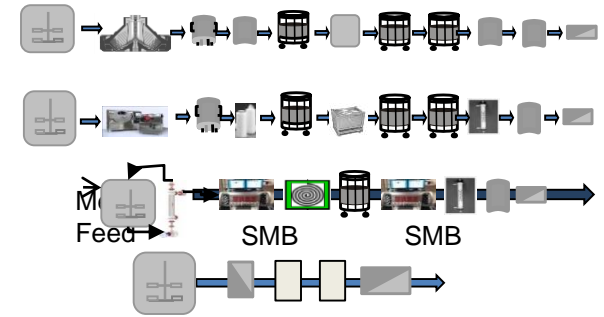
## Facility design SU Operations



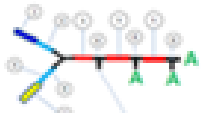
## Material handling



## Waste handling



## Component Engng



## SUN CoP



## Supplier Partners



## Standardized testing & hardware



## Industry Aligned



## Technology improvement



# Benefits & Obstacles to SU Technology Implementation

Potential benefit	Experienced obstacles
Contamination reduction with closed systems	Leaks, particles, integrity testing and non standard design qualification approaches
Sterile, pyrogen free	Irradiation validation practices vary – despite standards
Flexibility of Facility Tech transfer is easier Facility schedule reduced	Managing Supplier Complexity Lead time of supply, Design-to-deployment takes too long (12-24 months, typ.)
Processes are flexible for new products & processes	Limited connectivity for different supplier hardware Implementation speed : extractable / leachable testing
Lower capital cost with faster construction/ validation schedule	“One-off” tubing management and automation solutions Higher Expense - Unit cost & inventory holding cost Higher solid and packaging waste stream
Reliable and reproducible	Leaks, visible particles, delivery problems erode end user confidence, change control & supply chain concerns



***Reducing Risk Increases the rate of SUS Industry Adoption***  
***Working together, we can lower these risks***



# Industry Landscape

## Networks created to improve internal alignment & control

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### Current Situation

- Sourced at site level
  - SUS specified by many groups
  - Inconsistent user requirements
  - Site experience vs. best practice
- Complex supply chain
  - Many 'overlapping' designs
  - Many suppliers

### Trends emerging

- Strategic commodity
  - Central team with oversight/guidance
    - Component Engineering
    - SUN
  - Company requirements
    - SU Guideline Documents
- Some simplification
  - Part and supplier rationalisation
  - In-house SU Catalog
  - SU Standardization Efforts





# Industry Landscape

## Suppliers need to transform to meet end user commercial cGMP requirements

### Current Situation

- Legacy of clinical expectations
  - Majority of applications now in R&D or clinical space
- Innovation focused
  - No standard 'standards'
  - Product / supply chain complexity is an operations problem
- Opaque supply chains
  - Low volumes and influence with resin and film producers



### Desired state

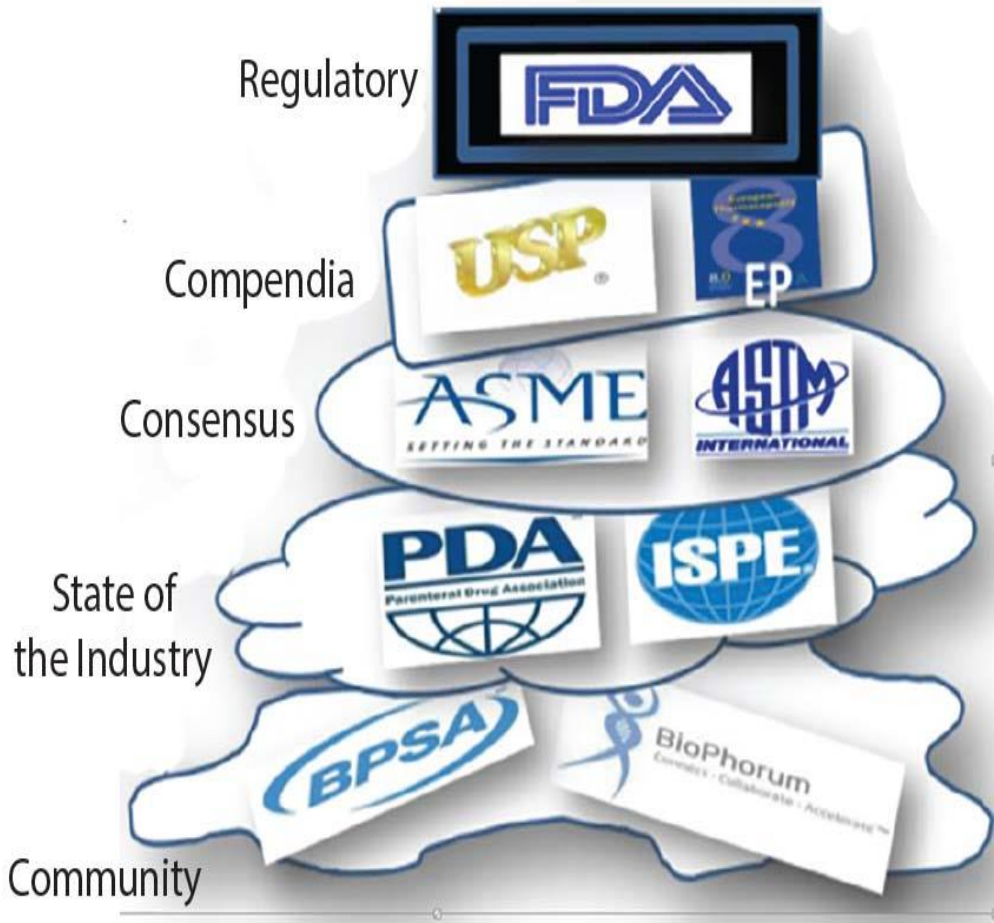
- Systems set up to support commercial GMP needs
- Service / Innovation Balance
  - Customer centric 'standards'
  - Supply chain complexity is managed
    - Standardized commodity items for simple, well established uses
    - Innovate on less developed areas
- Transparent supply chains
  - Well managed Change Control
- Reliable and consistent supply



Slide adapted from Tony White, BioPhorum



# The Hierarchy of the Alphabet Soup



Courtesy of Jim Vogel and BioProcess Institute

# BioPhorum Operations Group (BPOG) Disposables Workstream

## BPOG Disposables – Single Use Systems



# Merck SUN committed to Conquering Change through a Collaborative Single Use Community

## BPSA (Bio-Process Systems Alliance)

- Defined guidance on particulates
- Initiating two task forces: Change Control, Integrity Testing
  - Mark Petrich is Merck representative and BPSA Second Vice Chair



## ASTM E55 team is:

- Working on SU Extractables Standard
- Planning to issue SU testing standards



**ISPE:** working to publish a single use guide.



**PDA** published Technical Report 66 on Single Use Systems



# Develop SUS Best Practices and Physical Standards

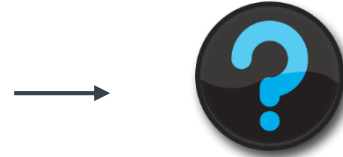
Model:



SS “near standards”



“Code 7”



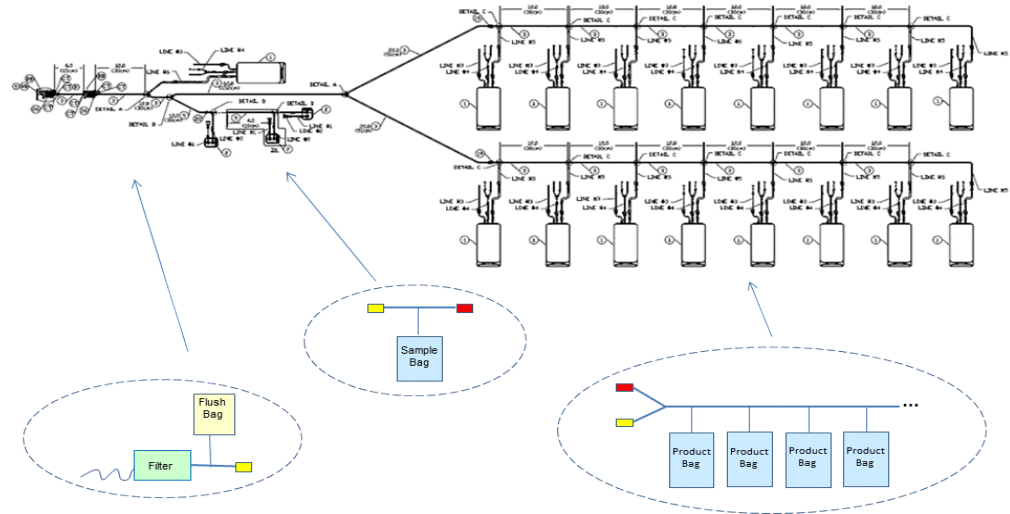
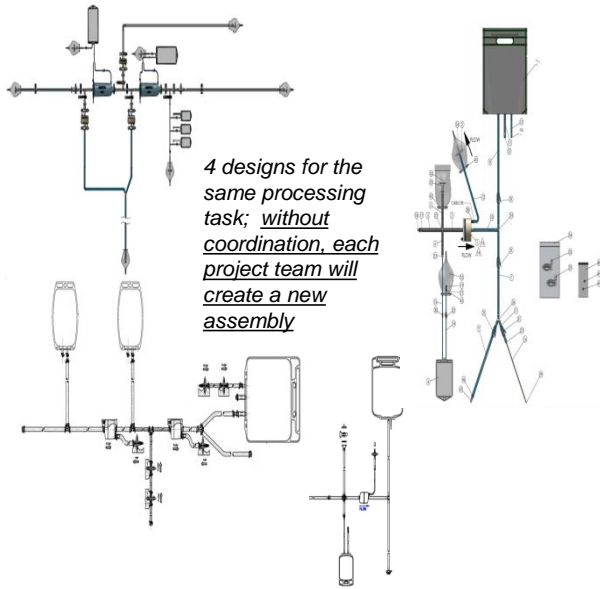
# SU Standardization Efforts



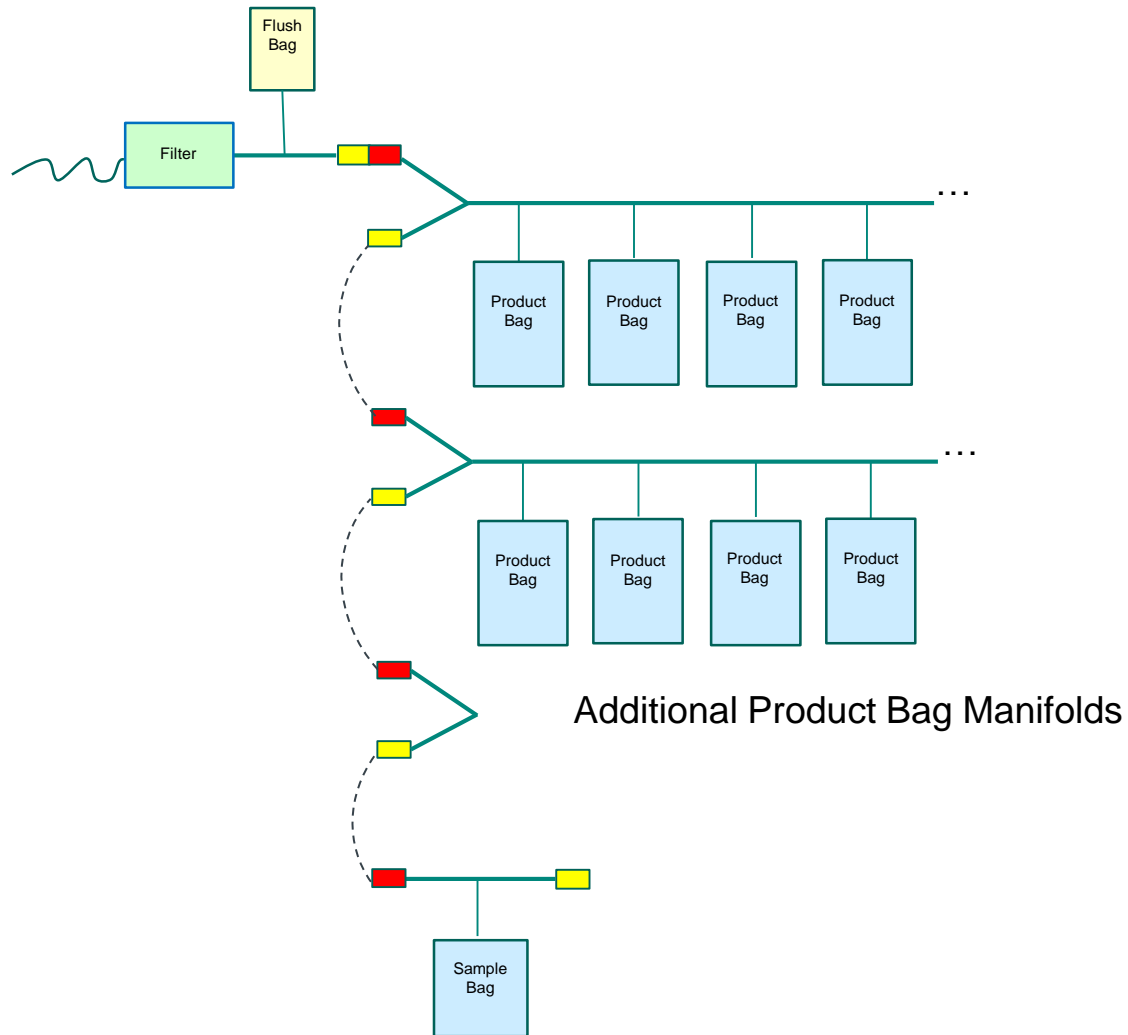
## Standardization efforts are starting:

- SUN is helping to drive SU Standardization within Merck
  - Network wide VTN, Sub-teams, and Strategy
  - Single Use Equipment Guidelines
  - Single Use Catalog
- Industry-wide Standardization is starting to gain some traction
  - BPOG Standard Extractables Protocol is making progress
  - BPOG Letter to ASTM on SU Hose Barb Standardization
  - PM Group Standard Disposable Design (SDD) effort
- Lack of alignment among SU users makes for slow progress
  - BPOG is one possible forum for alignment between end-users
  - BPOG and BPSA Collaboration is starting to make progress towards SU Standardization

# Why Standardize – Current State Drivers



# • Modular Design





# Why Standardize – Current State Drivers



**Think holistically, the entire user experience**

Integration of SU Components,  
Tubing Management, and  
Automation Hardware & Software  
Needs Industry Wide Solutions

# Summary:

**Innovation in Single Use enables faster and lower cost facilities**

**Merck is actively developing Single Use approaches to Biologics and Vaccine production**

**Merck Single Use Network (SUN) is aligning best practices across the Merck Network**

**Component Engineering and Standard Components can strengthen the supply chain**

**Innovation is still needed in Single Use process design and implementation**



## Beneficiaries

**Patients : reliable supply of lower cost medicines and vaccines**

**Suppliers: expanding sales with a fair share of a much larger market**

**Regulators : clear standards and inspection expectations**

**End Users: Reliable cGMP supply  
Simpler, Faster, & Lower Cost**

# Acknowledgements



- Dave Pollard
- Clay Reilly
- Mark Petrich
- Bobbijo Redler
- Chris Smalley
- Sabrina Restrepo
- Chris Gross
- Mark Brower
- Doug Richardson
- **SUN!**



BioPhorum  
Operations Group  
Connect · Collaborate · Accelerate

**Tony White**  
**Andy Orr**  
BPOG Disposables Working Group



Bio-Process Systems Alliance  
*Advancing Single-Use Worldwide*

# *Questions?*