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# ADAPTING SINGLE USE/STAINLESS HYBRID SYSTEM FOR FLEXIBLE MANUFACTURING

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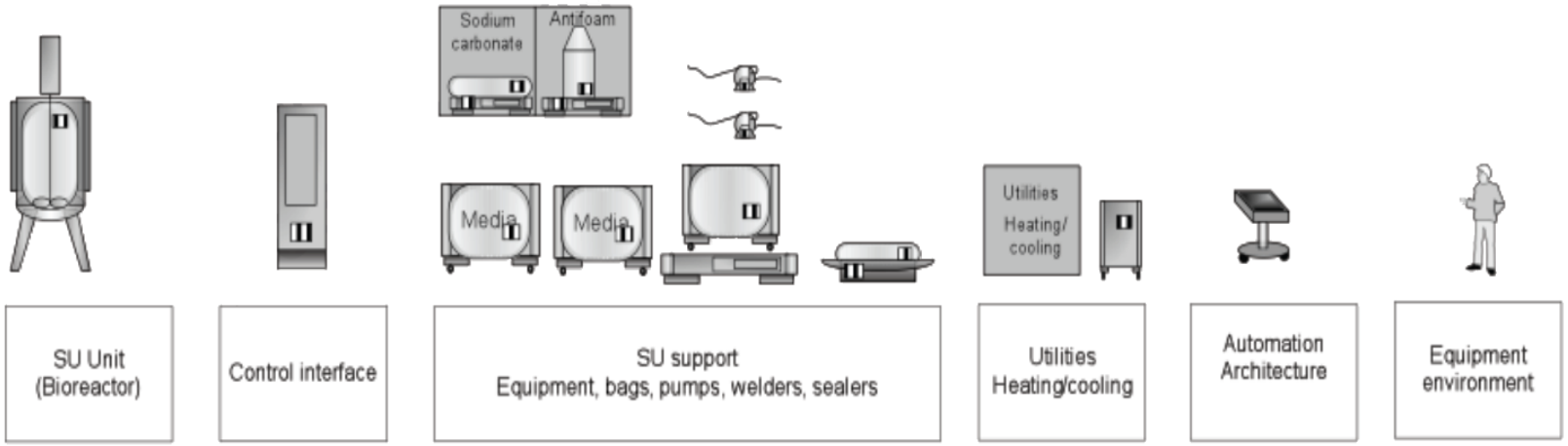
# Agenda

- Background
- Overview
- Why Single Use ?
- When Single Use ?
- Business Drivers for Adoption of SUS
- SUS Potential Opportunities
- Risk Management SUS Operation
- Other Salient Points to Consider
- Hybrid System Points to Consider
- Summary

# Background

- The central idea behind the usage of single-use bioprocessing technology is to **decrease the cost** and increase the **product time to market/patient**.

- This technology is used in a broad range of biopharmaceutical applications such as **filtration**, **mixing**, **purification**, **upstream expression**, **storage, and separations**




*Source PDA-2014TR66 Application of Single-Use systems in Pharmaceutical Manufacturing .pdf*

# Background

- Single-use equipment, particularly for **upstream manufacture** (e.g., bioreactors), now thoroughly **dominates pre- commercial**, i.e., small- to mid-scale R&D.

- The potential of disposable systems to reduce expensive infrastructure can help move toward **creating flexible facilities in Emergent Global Markets**

# Overview

**Pressure** on drugs **prices**,

- Cost per gram in the early years was 1,000$ per gram
- Advanced with technology reduced it to 100$-500$ per gram
- The cost now can be ranging from 50$-100$ per gram
- Purpose is to reach to 5$-10$ per gram

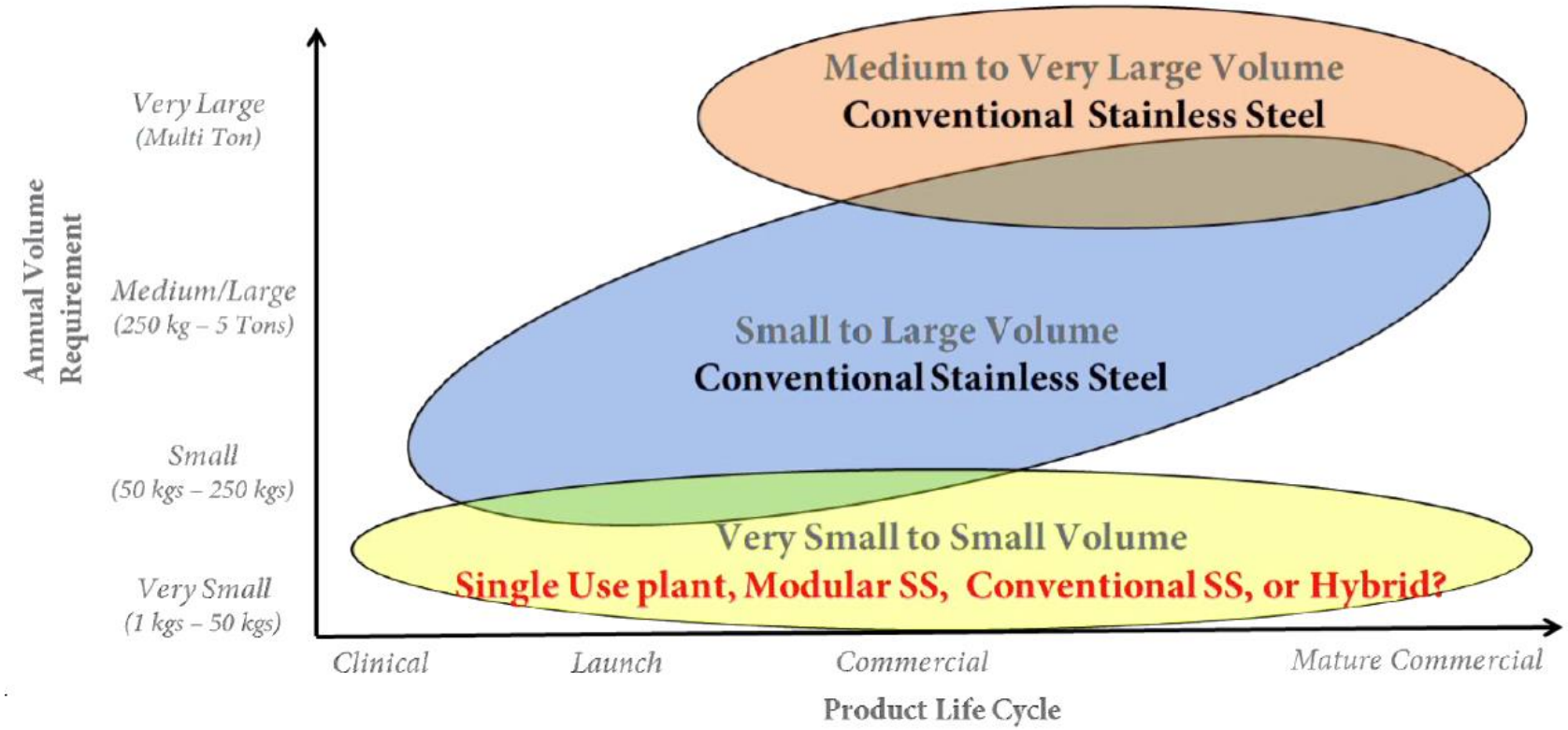
*Source (GE- 2017) : http://csdd.tufts.edu/files/uploads/Manufacturing-WP-2017.pdf*

# Why Single Use ?

- Low Capex
- Faster time to Market
- Flexible & agile multiproduct manufacturing / modular approach / Plug and Play
- Effective integration with continuous manufacturing
- Environment  friendly
- Space optimization
- Personalized medicines

# When Single Use ?

## In relatively small scale production

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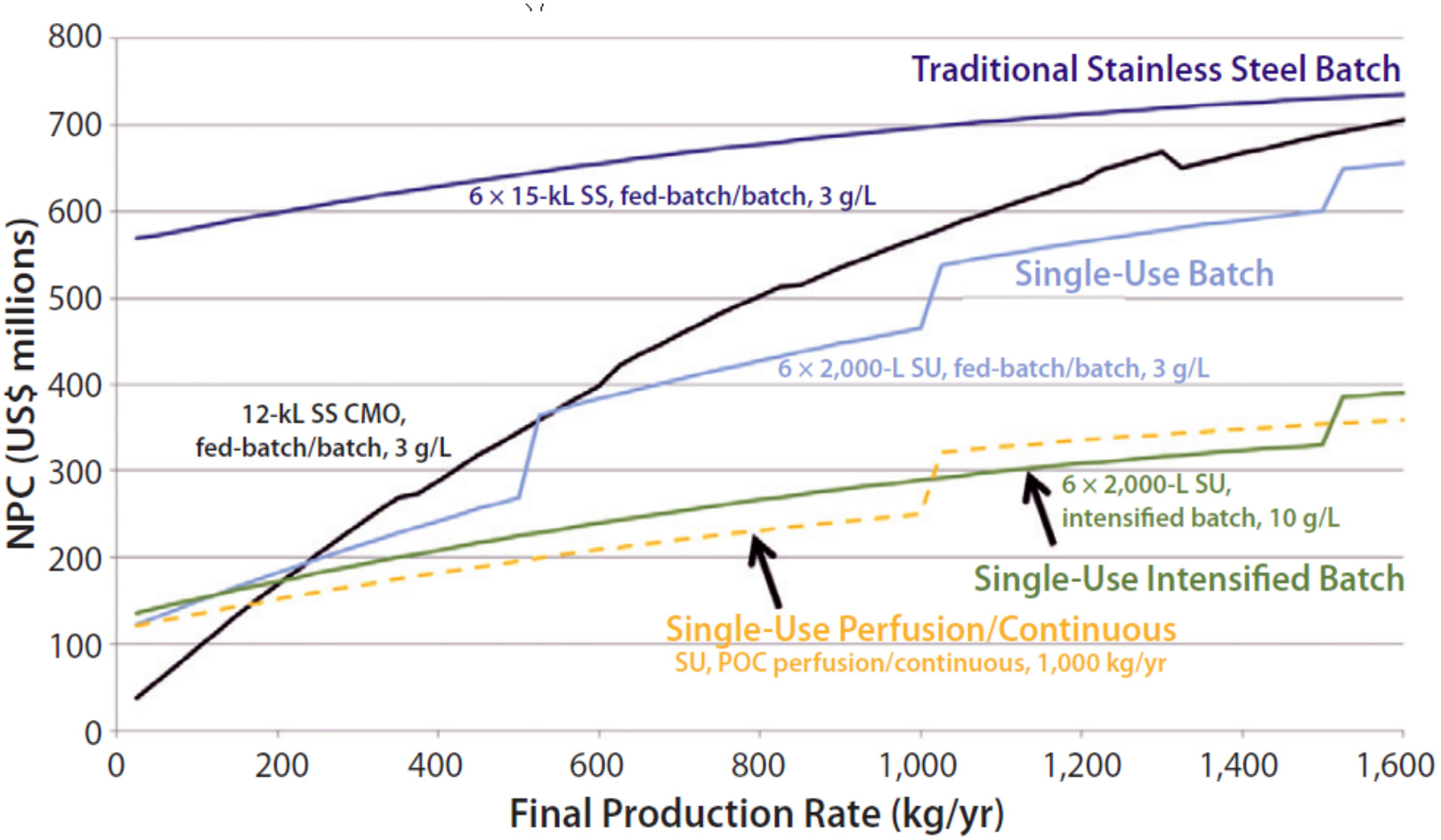
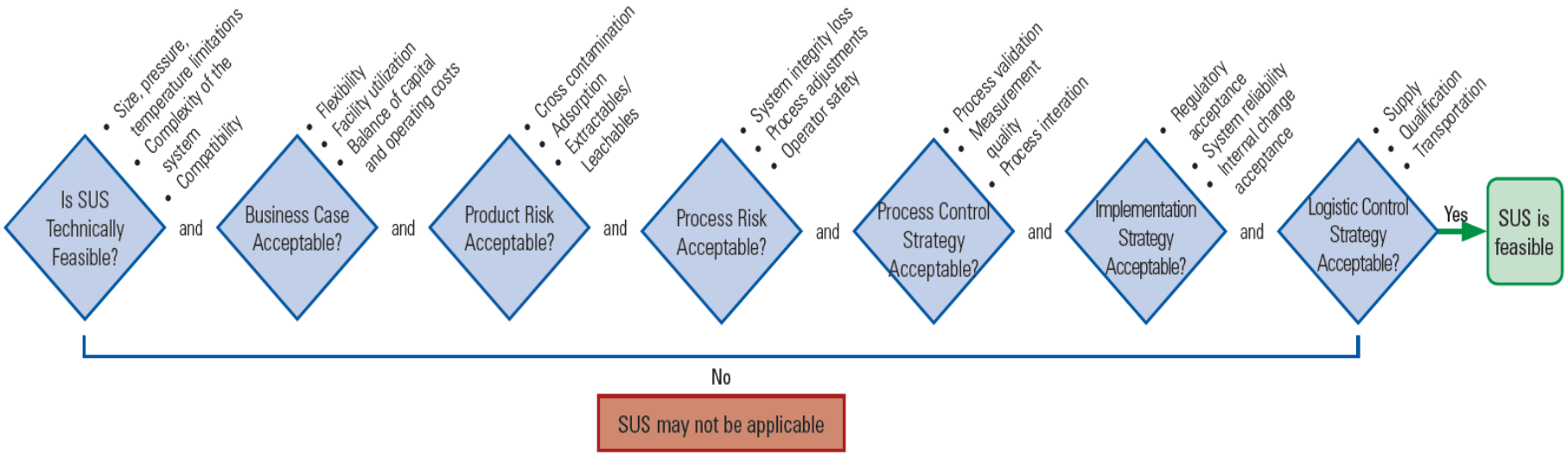
# When Single Use ?




*Source (2016): http://www.bioprocessintl.com/business/economics/standardized-economic-cost-modeling-next-generation-mab-production/*

# When Single Use ?

## *Proposed SUS Decision Pathway*

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# Business drivers for adoption of SUS

- CAPEX 25%-30% ↓ OPEX 0% - 30% ↑
- Time to market 30% - 50% ↓

| Criteria | Technology | |
|---|---|---|
| | Stainless steel /conventional | Single-Use/'Disposables" |
| **Implementation** | | |
| Investment (CAPEX) | 100% | ≈ 70 % - 75 % |
| Operational cost (OPEX) | Standard | impact of single-use components only at higher batch numbers |
| Construction time | | |
| *Greenfield* | | |
| *MC* | 20-24 months | 15 - 18 months |
| *IQ / OQ, commissioning* | 4 - 8 months | 3 - 4 months |
| *Validation* | 9 - 12 months | 6 - 8 months |
| *existing building shell* | | |
| *MC* | 12 - 18 months | 6 - 8 months<br>defined by lead time of supplied material and components |
| *IQ / OQ, commissioning* | 3 - 6 months | 2 - 3 months |
| *Validation* | 6 - 9 months | 4 - 6 months |

*Source sanofi_aventis_peter_kraemer.pdf*

# Business drivers for adoption of SUS

- Capital design
  - Capital investment
  - Equipment costs
  - Utilities costs
  - Facility floor space (cleanroom versus lower classification, production area versus warehouse)
  - Commissioning, Qualification and Validation

# Business drivers for adoption of SUS

- Operating Costs: Day-to-Day Variable Costs
  - Labor
  - Utilities and Energy
  - Waste management
  - Sterilization
  - Cleaning
  - SUS run cost and inventory
  - Changeover time, Multiproduct or single-use
  - Value-added activities, preventive maintenance

# Business drivers for adoption of SUS

- Drug development and process assessment
  - Time-to-market and constraints
  - Number of batches per year
  - Number of product per year
  - Workforce skill level
  - HSE
  - Process complexity

# Business drivers for adoption of SUS

- Green manufacturing
  - Environmental concerns for manufacturing process
  - SUS waste generation
  - Resources for waste management
  - Design for sustainability

# Business drivers for adoption of SUS

- Value added activities
  - Cost of quality and cost of failure
  - Outsourced activities, make versus buy SUS
  - Quality compliance, validation, calibration, operations
  - Expedited transfer of manufacturing site to new location, reducing the time required to accommodate demand for addition product

# SUS Potential Opportunities

## Environment friendly

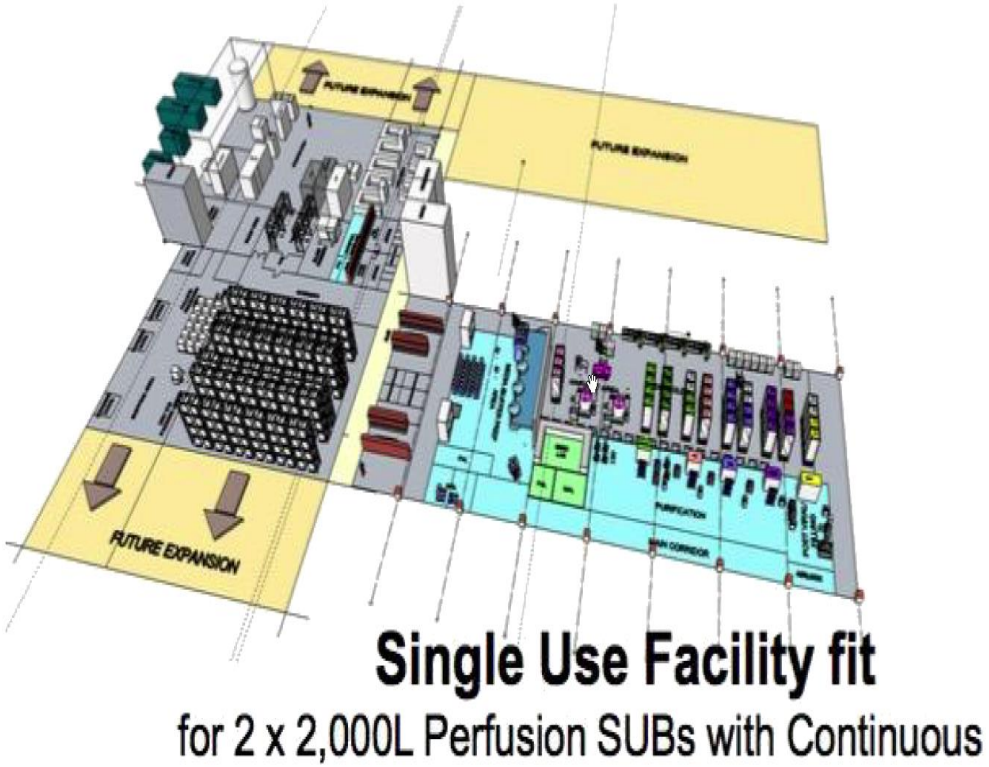
- SUTs bring both **advantages** and **disadvantages** when it comes to environmental impact
- Disposables are made from a combination of non recyclable plastics
- Single-use operations result in a great deal of waste
- SU manufacturing is considered environmentally friendly because it **reduces energy consumption**

*Source PDA-2014TR66 Application of Single-Use systems in Pharmaceutical Manufacturing .pdf*

# SUS Potential Opportunities

## Effective integration Continuous processing with SUS

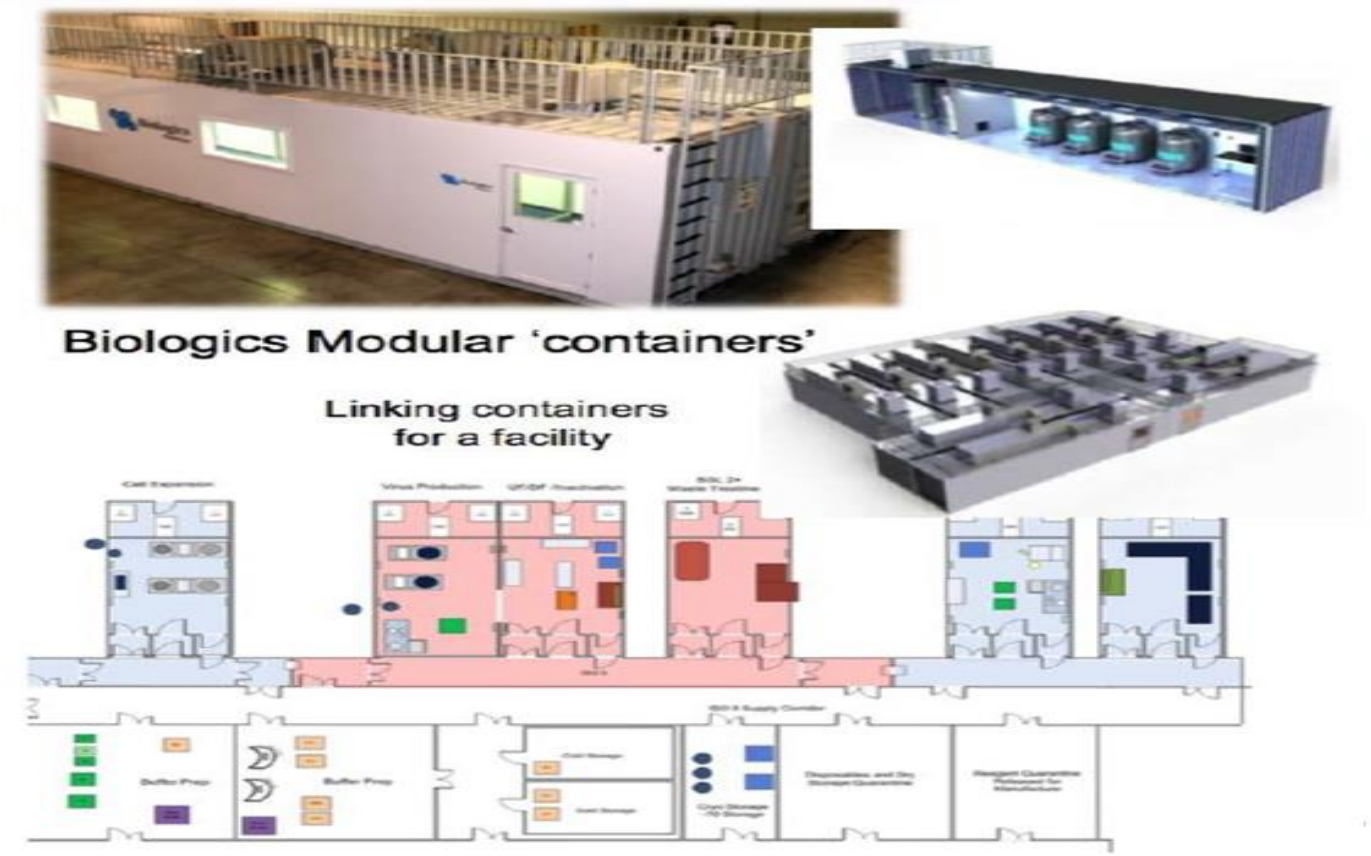
- SU based platform up to 2,000L scale
- Provide most significant cost reduction
- Perfusion with consistent harvest titer




*Source (Merck- 2018) : Continuous Biomanufacturing: Innovative Technologies and Methods*

# SUS Potential Opportunities

## Flexible and agile multiproduct manufacturing / modular approach / Plug and Play

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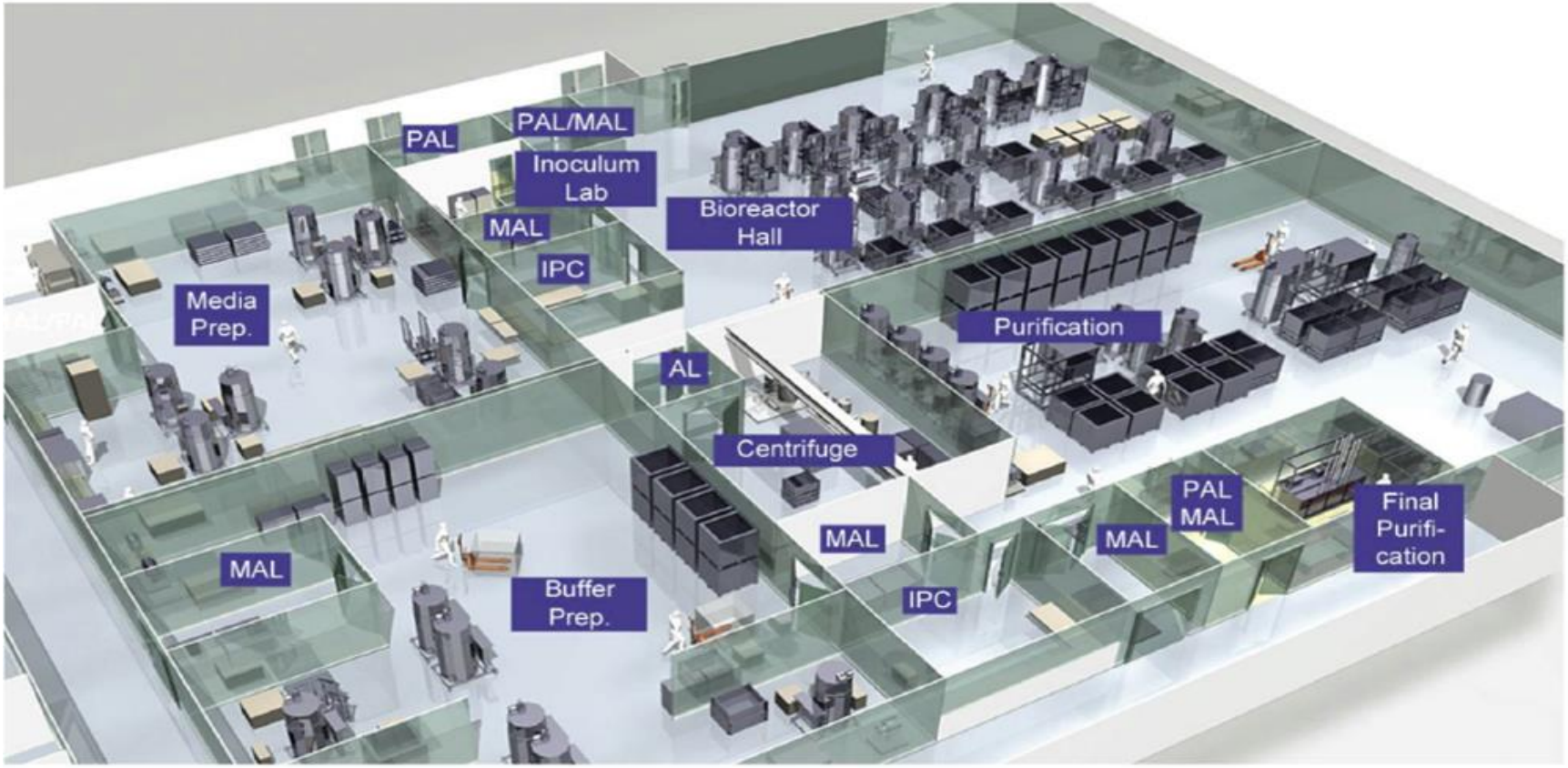
# SUS Potential Opportunities

A modular facility design uses a set of **standardized parts as building blocks**

- Enhanced **quality control**
- **Transferring labor hours** away from the construction site
- Can **reduce the construction** schedule for the facility project **by 50 %**
- **Simplified site logistics**
- **Reduces risk and overall cost for the facility** construction project

# SUS Potential Opportunities

Ballroom Concept, Large area with mobile equipment and minimal segregation due to closed systems use.

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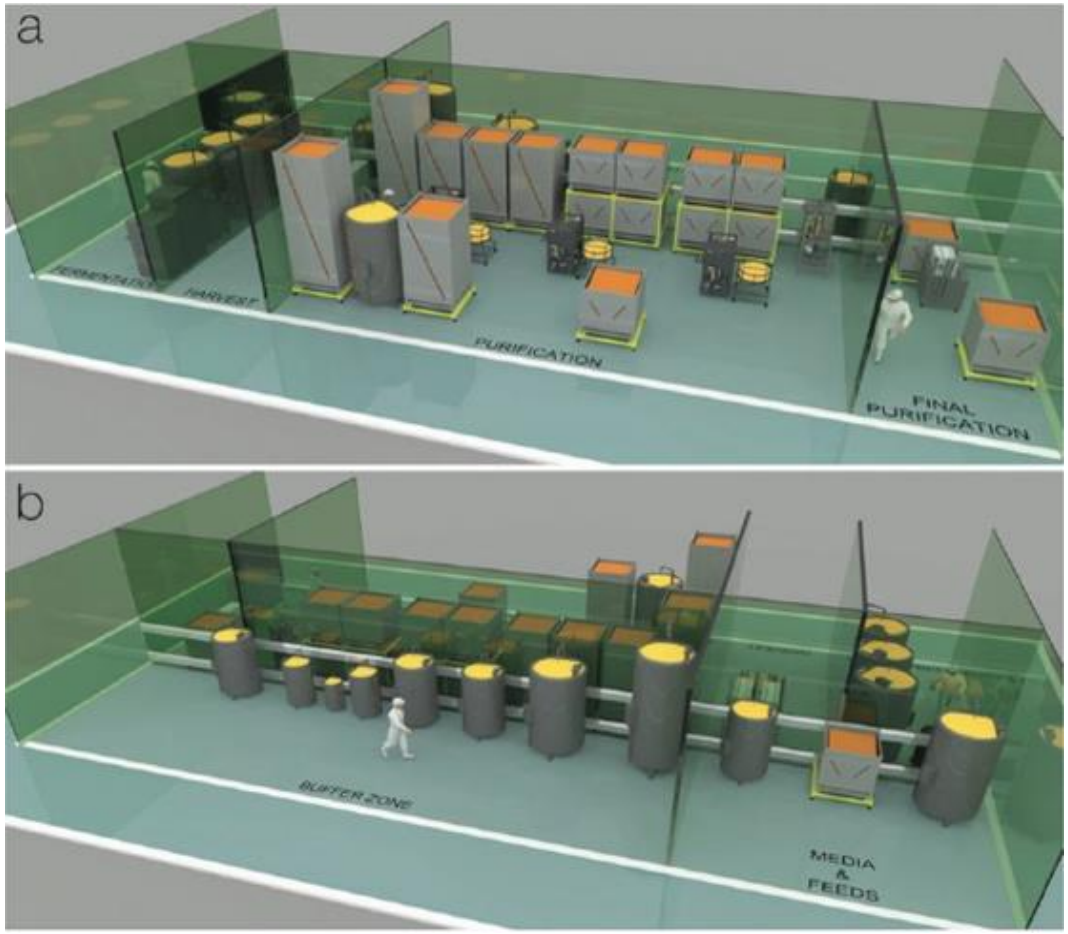
# SUS Potential Opportunities

## Dance floor concept

(a) 3x2,000L bioreactor suite
(b) Buffer/media preparation areas

- **Leaner**: minimal movement of totes
- Smaller: only space provided for ergonomic access, vertical height utilized

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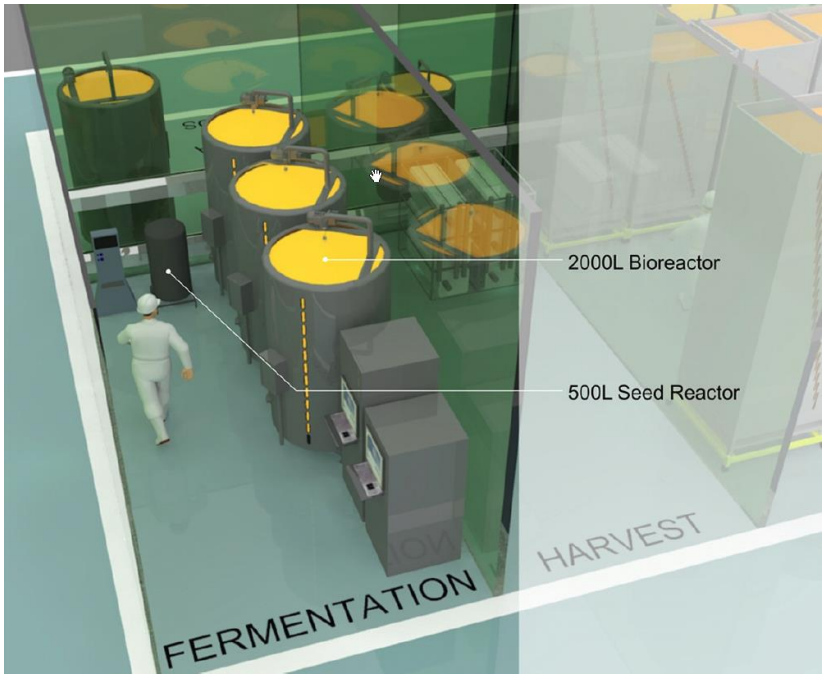
# SUS Potential Opportunities

## Space Optimization

- SUT can reduce footprint by 30 – 40 %
- 2,000L single-use bioreactor very similar footprint with 500L
- Reserving space opportunity to add extra bioreactors

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# SUS Potential Opportunities

## Personalized medicines

As the drive towards more targeted therapies with smaller niche populations

- Manufacturers will need to produce a **larger number** of **products** in the **same facilities**
- The future biotech drugs are likely to be targeted to **smaller patient populations**

# *Risk Management SUS operation*

Quality risk management (QRM), benefit on the **manufacturer**, **patients**, **quality auditors** and **regulators**

Correlation system complexity and process risks.

| Directional Risk Profile | | Complexity of SUS Items | | |
|---|---|---|---|---|
| | | **Low** | **Moderate Low** | **High** |
| Risk of SUS Application | Low | Tubing & Connectors | Sampling Systems: Not a direct impact | Clarification/ Concentration |
| | Moderate | Manifolds: Externally sourced | Storage using SUS: raw materials, media, supplements, buffers, drug intermediates, product | Drug product formulation |
| | High | Manifolds: Self-assembled | Sterile connectors | Cell & virus culture |

*Source PDA-2014TR66 Application of Single-Use systems in Pharmaceutical Manufacturing .pdf*

# *Risk Management SUS Operation*

## Product risk

## SUS potential impact on the **product quality**

- **Sterility**
- Technical limitations of the SUS, which could lead to suboptimal processing, **poor cell growth**, **low yields**, or impact to product-critical quality attribute (e.g., limitation of **temperature control**, **mixing** etc...)
- Impact on **system integrity**

# *Risk Management SUS Operation*

## Product Risk

**Key operating parameters** assessment at **different process** steps should include the following considerations,

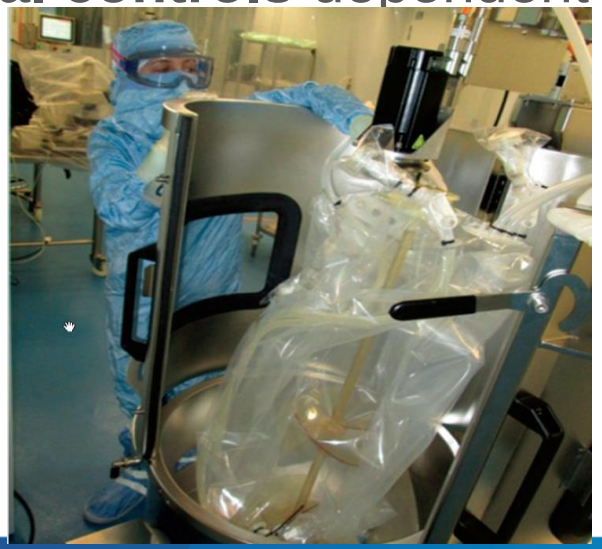
- Estimation of risk of **equipment** or system **failure** for both **SUS** and **MUS**, including downtime for correcting potential failures
- **Size limitation** of an **SUS** as compared to an **MUS**
- **Productivity** impacts when using **SUS** as compared to an **MUS** approach

# Risk Management SUS operation

## Process Risk

The monitoring capability of **SUS** and **MUS** may differ,

- **Balance** the **cost per batch** to generate the **desired data**
- **Control** of **sensor calibration**, **cleaning validation** and probe **accuracy & reliability**.
- SUS's typically include **more manual controls** dependent on operator training and execution.

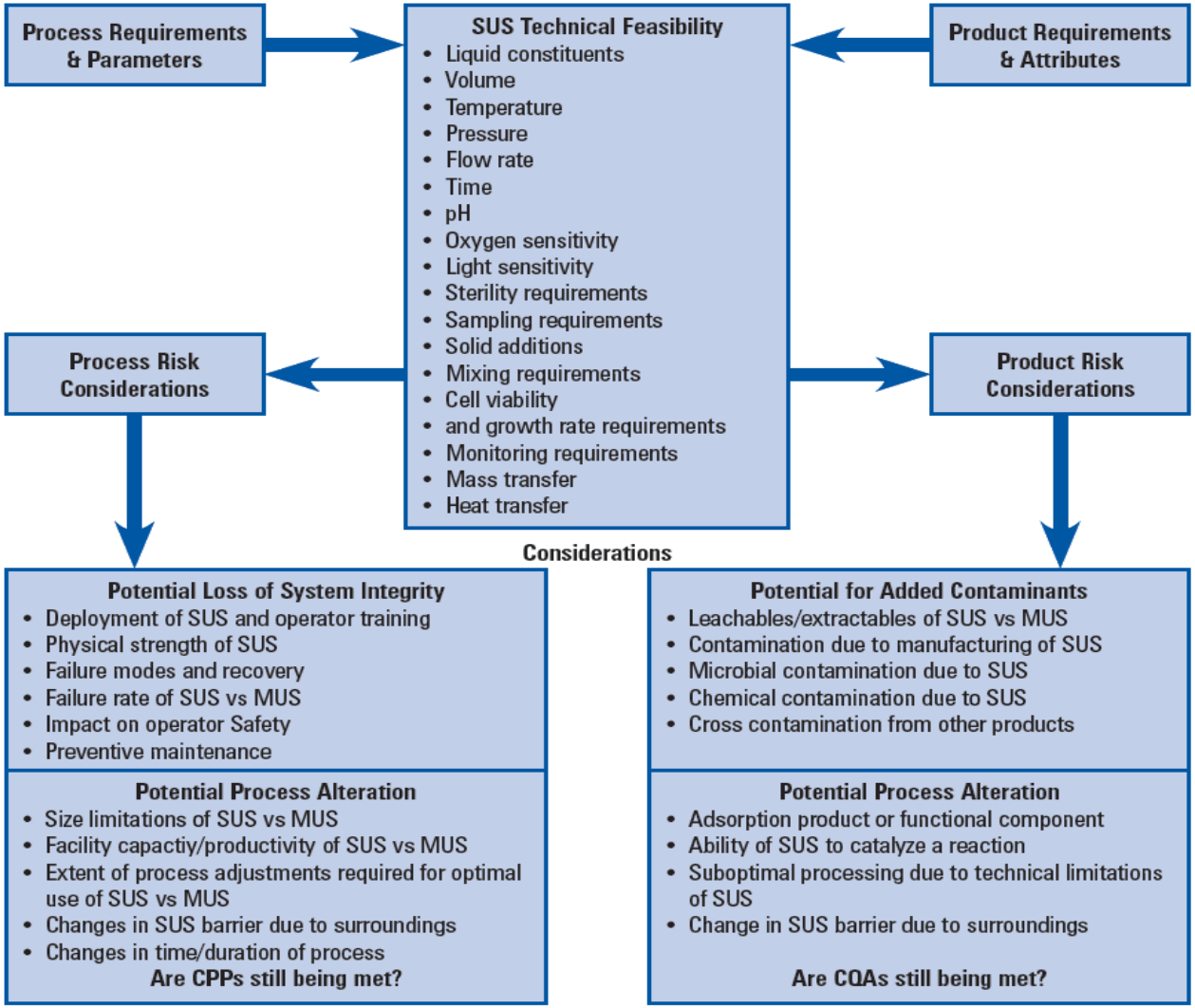


# Risk Management SUS Operation

## Process Risk

- **Adjusting pH, adding solids, foam control** *in some cases these adjustments may not be possible with SUS*
- **Qualifying and calibrating probes** and the measurement system before use may be **more complicated** or not possible if a single-use probe
- Evaluate **dependency on the supplier's and vendor's** quality system and qualification activities
- **Account for the possibility** of **smaller batch sizes** with increased frequency or sub-batch or **batch pooling** due to smaller container volumes

# Risk Management SUS Operation

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# *Other Salient Points to Consider*

Sustainability

In general, SUS's are **more sustainable**

The SUS strategy should define a policy that includes,

- Fossil fuel depletion
- Energy use
- Urban land occupation
- Pollution, green-house gas emission and ozone depletion
- Water depletion and so on

# *Other Salient Points to Consider*

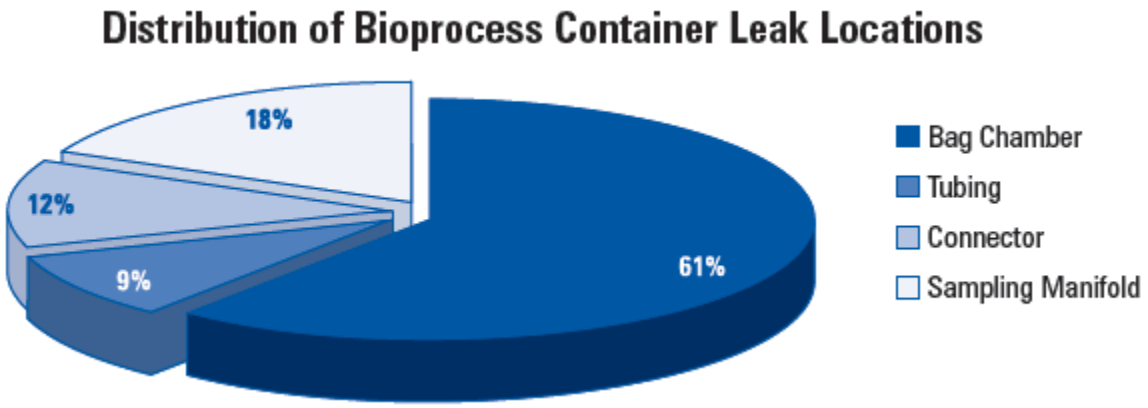
## Supplier Selection,

- The **selection of appropriate SUS** suppliers can often be an arduous task that can be made less cumbersome with a **risk-management approach**.
- For a successful SUS implementation, it is essential to have a **detailed and transparent relationship between suppliers, vendors and the end user**.
- One way to mitigate that risk is to have **multiple vendors** with **standard adaptors, connections, components** and **equipment's**

# Other Salient Points to Consider

## Health and Safety Issues Related to SUS

- SUS's often consist of plastic components that have **low resistance** to **physical stress, pressure, and temperature extremes**
- A typical setup includes a range of **support equipment** (e.g., pumps, agitators, scales) that requires **manual transportation, installation, and dismantling**.

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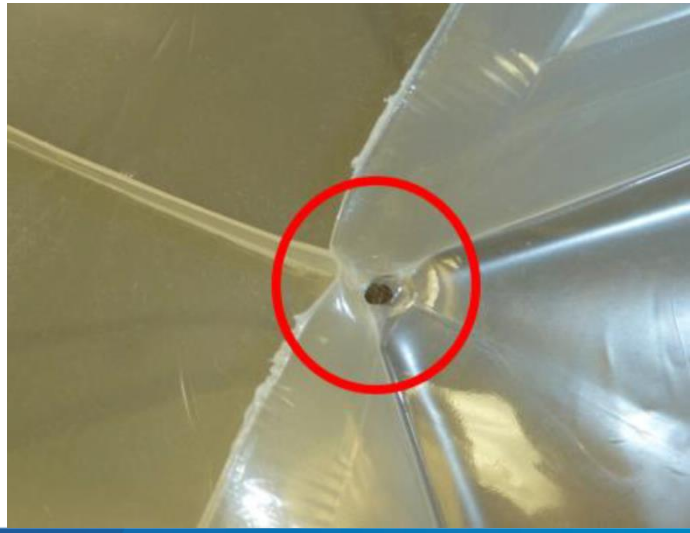
# Other Salient Points to Consider

## Health and Safety Issues Related to SUS

- **Safety** - Tubing ruptures/Bag ruptures at eye level, Spills and slippage, emergency stops/restart for moving parts, tubing on floor that may result tripping
- **Health** - Ergonomics for installation, removal of SUS components, handling bags that contain liquid, Lifting heavy or cumbersome objects, Insufficient work space and surfaces

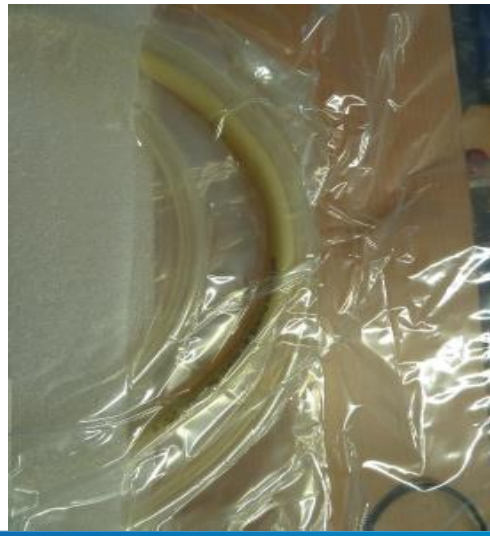


# Other Salient Points to Consider

## Logistics and Storage

The storage and warehouse facilities required efficient operation of the SUS.

- High risk consumables Vs Standard consumables
- Storage policy
- Environmental storage conditions monitoring and control
- Pallet space



# *Other Salient Points to Consider*

## *Waste*

The SUS strategy and PEP should address waste management as an important part of SUS implementation

- Handling and elimination/Inactivate of process fluids before disposal
- Waste collection and storage
- Feasibility of recycling SUS components
- Transport routes, Frequency of pickup, training, safety
- Impact of local, national or regional regulation

# *Hybrid system design*

## Points to consider

- Scale out instead of scale up (Up to 6 bioreactors lines)
- Eliminate/Minimize cleaning and sterility time
- Chrom & TFF skids, buffer and media prep system usually have high temperature and pressure requirements – that challenge implementation of SUS
- Check option to store Chrom & TFF skids with caustic and self cleaning for the buffer & media prep

# *Hybrid system design*

## Points to consider

- Eliminate/Minimize the use of CIP facility Skid and SIP
- Use bags for buffers and intermediate product storage
- Consider using depth filtration instead of centrifuge
- Use disposable filter skids
- Reduce room classification requirements when close system are in use

# Summary

Single-use technology has the potential to transform pharmaceutical manufacturing by offering tremendous opportunities to **reduce cost**, **improve flexibility**, and **shorten the time** needed to build a manufacturing process,

Successful SUS implementation needs a **comprehensive** approach balancing the **product** and **process** goals achieved

An effective evaluation will have a balanced viewpoint, with input from **engineering**, **regulatory**, **quality and project management**.

SUS increase **Complex** and **critical manual operation** and as a result risk for failure and contamination.

SUS's have a **yield limitation** and **increase operational cost** with the increasing of the amount of batches

# Summary

SUS **increase** the amount of **production SOP's** and **reduced automation records** & **control**

Encouraging an **open science** and **risk based dialogue** during supplier audits and evaluation of SUS supply chains

Pharmaceutical manufacturers and single-use technology **suppliers** have become **partners**, success is dependent on the control strategies implemented

SUS suppliers provide equipment that includes the **outsourced value added** activities that the end user no longer performs.

Only a **formal partnership** with SUS supplier can ensure that quality is as good as or better than what is achieved with traditional system.

# Backup slides

## Assessment of process Compatibility

| Factor | Design Considerations |
|---|---|
| Construction materials | Chemical compatibility with the product and process fluids (liquid and solid), cleaning and sanitizing agents; biocompatibility; animal-derived components; extractable and leachable profiles; and nonspecific adsorption. Note that films may be permeable to some chemical agents (e.g., those used for wipe-down), which could have an impact on the process or product. |
| Physical properties | Attributes such as film or tube thickness, durometer, brittleness, surface smoothness, elongation, modulus, and impact and tear resistance will contribute to the ruggedness of the system and its resistance to breach of system integrity. |
| Microbial control methods | Ability to withstand gamma irradiation and/or other means of sanitization or sterilization |
| Time | Contact time (e.g., short passage in fluid conduit versus storage over an extended period of time), processing time (e.g., mixing time) |
| Volume | Size and scale of operation, holdup or residual volume (relative to drainage), dead volume |
| Temperature | Ability to withstand variations in temperature. Freezing applications require specialized systems to retain system integrity. The requirement for controlled addition of heat (e.g., to facilitate the flow of highly viscous fluids), and time for adjustment of temperature |
| Gas barrier | The loss of water vapor and moisture; oxygen, carbon dioxide, and nitrogen ingress and egress. (Barrier properties are temperature and relative humidity dependent.) |
| pH | Limitations in high or low pH; fixed versus variable pH over time or imposed profiles |
| Pressure | Limitations in absolute or differential pressure of the system and individual components (e.g., bags, which do not carry an absolute pressure rating; tubing burst pressure; and vacuum resistance ratings). Applications allowing for pressurized filling and draining of bags in enclosed rigid outer containers are possible following Good Engineering Practices) |
| Optical | Limitations in the visual process-monitoring capability (e.g., polymeric materials are often classified as transparent, translucent, or opaque) |
| Light | Sensitivity to light (including exposure time). The transparency of cell culture bags to light may or may not be a desirable feature. |
| Flow rate | Tubing ID, bag porting size, gravity drain versus pump capability |
| Particulates | Limitations due to normal particulate content or shedding as a result of abrasion and spallation |
| Mixing | Viscosity, inadequate mixing, and the generation of particles in cases where there is no terminal filtration. The ability to keep a solution homogeneous in applications involving suspensions. Make sure the design of the container allows for low-volume dispensing and mixing. |
| Sterilizing filtration | Location of the filter to ensure optimum product drainage; filtration inside sterile core or outside; venting or draining of filters during operation; pre-use flushing and integrity testing and post-use integrity testing; redundant sterilizing filters or need for prefiltration, filter sizing |

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# Backup slides

## Specific Considerations for Fermenters or Bioreactors

| Factor | Consideration |
|---|---|
| Process control | SU sensors and the mating control systems may have different capabilities from a traditional MUS. |
| Process limitations | Compared to MUS, SU fermenters and bioreactors may be limited in the regulation of temperature, pressure, and oxygenation rates. |
| Polymer-specific effects | Make sure that the components neither adsorb nor produce reactive leachables, which could have adverse effects on cell viability, productivity, and the quality of the molecule of interest. |
| Design attributes | Investigate the quality of mixing and the magnitude of induced shear during the evaluation of specific, user-application requirements for the SUS bioreactor. |
| Light sensitivity | Determine the impact of exposure to ambient light on cells cultured in a transparent fermenter or bioreactor bag. |
| Mass transfer | Determine the capability of SUS to achieve desired power input, KLa*, and oxygen transfer rate. |
| Heat transfer | Determine the capability of SUS to transfer heat to and from the culture. |
| Cell viability and growth rate | Determine the capability of SU bioreactor to support cell viability and growth rate. |
| Sensors | Compare requirements for process sensors (e.g., temperature, pH, and dissolved oxygen) to the sensor technology used, effects on the sterile boundary, level of SUS integration, and sensor accuracy, robustness, and calibration. |

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# Backup slides

## Plastics Commonly Used in SUS

| Family | Chemical Abbreviation | Chemical Name | Brand Name* | Applications | Reasons to Use | Comments |
|---|---|---|---|---|---|---|
| Fluoropolymers | PTFE | Poly(tetrafluoroethylene) | Teflon®<br>Fluon® | Filters, tubing | Biologically inert<br>Chemically resistant<br>Extreme cold or hot temperature resistance<br>Low extractables and leachables | Cannot be sterilized using gamma irradiation<br>Limited mechanical properties |
| | PVDF | Poly(vinylidenefluoride)<br>Poly(vinylidene fluoride-co-hexafluoropropylene) | Kynar®<br>Kynar Flex® | Filters, fittings, tubing, bags | Biologically inert<br>Greater strength and wear resistance than PTFE<br>Broad temperature and chemical compatibility<br>Low extractables and leachables<br>Easily worked, molded, and sealed | Sterilizable by irradiation, steam, or chemical<br>Some strong solvents can solubilize the material |
| Polycarbonate | PC | Polycarbonate | Lexan®<br>Makrolon® | Fittings | Easily worked, molded, and thermoformed<br>Excellent durability<br>Temperature and impact resistant<br>Autoclavable<br>Clear, lightweight | Limited chemical compatibility range<br>Some grades may leach bisphenol A (BPA), which has been implicated in a variety of adverse effects in some studies |
| Polyester | PET, PETE<br>PBT | Poly(ethylene terephthalate)<br>Poly(butylene terephthalate) | Rynite®<br>Crastin® | Bottles,<br>filter capsules | Semirigid to rigid<br>Very lightweight<br>Good gas barrier<br>Naturally colorless with high transparency<br>High strength<br>Excellent stain resistance<br>Good wear resistance<br>Excellent dimensional stability | Radiation sterilizable<br>Fair moisture barrier<br>Naturally hygroscopic—must be dried before heat molding<br>Copolymer variations include PETG (cyclohexane dimethanol co-polymer) |

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|---|---|---|---|---|---|---|
| Polyolefin (polyalkene) | PP | Polypropylene | Moplen®<br>Pro-fax® | Filters, housings, piping, fittings | Good chemical resistance<br>Tough, impact resistant<br>Good processing properties<br>Higher temperature or chemical resistance over PE<br>Rigidity, hardness<br>Autoclavable<br>Irradiatable (stabilized formulations only) | Nonstabilized formulations cannot be sterilized by gamma irradiation (reduces shelf life, elevates extractables)<br>High thermal expansion<br>Poor impact strength at low temperature |
| | PE | Polyethylene | Dowlex®<br>Engage® | Bags, fittings | Good processing properties<br>Impact resistant<br>Good toughness<br>High stress cracking resistance<br>Lower extractables than EVA<br>Cold temperature performance | Properties vary by density (high, low, ultralow, linear low)<br>High thermal expansion<br>Cannot be autoclaved |
| Copolymers | EVOH | Ethylene vinyl alcohols | Eval®<br>Soranol® | Barrier layer in films | Superior gas barrier properties<br>Good chemical resistance<br>Very good clarity<br>Can be coextruded with many different polymers | Hygroscopic, gas barrier properties diminished with moisture<br>Moisture barrier properties lower than other polymers |
| | EVA | Ethylene vinyl acetate | Evatane®<br>Elvax® | Bags, tubing | Soft and flexible<br>Good clarity and gloss<br>Good barrier properties<br>Little or no odor<br>Excellent cold temperature properties<br>Better tear resistance than LDPE<br>Excellent resistance to environmental stress cracking | Gamma-irradiated EVA can lower pH of contents<br>Extractables may be undesirable<br>Poor heat resistance<br>Reduced barrier properties compared to LDPE<br>Attacked by polar solvents, hydrocarbons, oxidants, and strong acids<br>Reduced creep resistance compared to LDPE |

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# Backup slides

## Plastics Commonly Used in SUS

| Family | Chemical Abbreviation | Chemical Name | Brand Name* | Applications | Reasons to Use | Comments |
|---|---|---|---|---|---|---|
| Polyamides (nylons) | PA6,6 | Polyamide 6,6 or nylon 6,6 | Zytel® Ultramid®6,6 | Films, filters | High melt point (autoclavable)<br>Lower extractables than PA6<br>Moldable and extrudeable<br>Good mechanical properties and wear resistance | Susceptible to degradation by strong acids, bases, and oxidizing agents |
| | PA6 | Polyamide 6 or nylon 6 | Zytel® | Films, tubes | Tough, higher impact resistance<br>High-temperature resistant<br>Easier to process<br>Lower mold shrinkage<br>Good fatigue resistance<br>Greater elasticity and elastic recovery | Higher extractables<br>Susceptible to degradation by strong acids, bases, and oxidizing agents<br>Highest rate of water absorption and equilibrium water content |
| | PA11 | Polyamide 11 or nylon 11 | Rilsan® 11<br>Alamid® 11<br>Zytel® | Films, tubes | Improved chemical resistance versus other polyamides<br>Some are bio-based<br>Low water adsorption | More expensive than other PA<br>Lower impact strength<br>Minimal heat resistance (not autoclavable) |
| | PVC | Polyvinyl chloride Poly(chloroethanediyl) | | Pipes, films, tubes | Tough, strong<br>Inexpensive raw material and low processing temperature<br>Good combination of stiffness and impact strength (rigid formulation), toughness, extensibility<br>High ratio of strength to weight (flexible formulations) | Not autoclavable<br>High levels of extractants<br>Must be free of DEHP for fluid contact applications<br>Low cost<br>Disposal issues (generates dioxin on incineration) |
| Vinyl | CPVC | Chlorinated polyvinyl chloride | | Pipes | Good resistance to acids and bases Inexpensive<br>Improved chemical resistance over PVC<br>More flexible than PVC | Not autoclavable<br>Disposal issues (generates dioxin on incineration) |

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## Plastics Commonly Used in SUS

| Family | Chemical Abbreviation | Chemical Name | Brand Name* | Applications | Reasons to Use | Comments |
|---|---|---|---|---|---|---|
| Silicone elastomers | Silicone elastomer | Poly(dimethylsiloxane)<br>(May contain other silicone monomers) | Silastic® | Tubing, fitting, overmolding | Flexible, elastic<br>Broad temperature resistance<br>High tensile strength<br>Elongation and tear resistant<br>Low compression set at elevated and reduced temperatures compared to many organic rubbers | Not sealable or weldable<br>Peroxide-cured types can have higher extractables than platinum-cured types<br>Elevated silicone leachables can depress bubble point of downstream membranes |
| Thermoplastic elastomer | TPU | Thermoplastic polyurethane | Ellastolan®<br>Irogran® | Tubing | Flexible—can be stretched to moderate elongations and return to close to original shape<br>Processable as a melt at elevated temperature<br>Absence of significant creep<br>Autoclavable | TPUs have a large variety of chemical structures<br>Critical to specify manufacturer and grade of TPU resins |
| Thermoplastic elastmomer blends | SEBS-PP | Styrene-ethylene-butyl-styrene + polypropylene | C-Flex®<br>Kraton® | Tubing, fittings, overmolding | Flexible—can be stretched to moderate elongations and return to close to original shape<br>Processable as a melt at elevated temperature<br>Absence of significant creep<br>Weldable | Autoclave conditions may cause tubing to deform—tubing should be evaluated on a case-by-case basis. |

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