Achieving LEAN Process Implementation through Disposable Technology

Disposable Solutions for Biomanufacturing
27-29 February 2012
Husa President Park Hotel
Brussels, Belgium

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Introduction

- You've got some great speakers this week that will talk about specifics of the aspects of disposable technology. So, I'm not going to cover that in detail in this workshop.
- Instead, what we'll cover is a review of ideas that will show you how the use of disposable technologies lend themselves to "LEAN" operation, which is going to be an increasingly important factor in bioprocessing as the business of making biological products continues to evolve.

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Thoughts

- After 30 years making biologicals we're now at a point where commodity principles are starting to play an important role in how we look at production and production processes.

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Why is this?

- Technology capability has been disseminated
- Yields are up in terms of per cell production or per liter production
- Patent expiration
- Products becoming available through generic routes (biosimilars)
- Production recovery is more efficient
- Labor costs are high in the West and lower globally
- New methods of production possible due to technology
- Reduction in costs of facilities due to simpler technology

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Why is this?

- Potential reduction in equipment costs
- Reduction in operating costs
- Market forces are driving flexibility due to needs for products/product candidates

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Market forces are driving flexibility due to the needs for products / product candidates

- More clinical candidates
- More frequent changeovers
- Requirements for rapid production
  - By CMOs
  - By multi-product companies
  - Pandemic vaccine production
  - Anti-terrorist countermeasure production

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Application of Mainstream Production Principles

- So, like we've done in bioprocessing for other molecules, such as enzymes, antibiotics and vaccines, we're at the point with rDNA products where biochemical engineering principles related to manufacturing really start to matter.
  - Cost of goods reduction
  - Streamlined processes to reduce cycle time
  - Better use of physical plant resources
  - Better use of labor resources
  - Integration of upstream/downstream processes
  - Simpler production layouts/configurations

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Disposable Solutions & LEAN

- Disposable systems provide an ideal opportunity to look at LEAN system implementation because the basic LEAN operating philosophy is underscored by the need to operate them in such as way to return value.

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What is LEAN?

- It's a holistic and sustainable approach that uses less of everything to produce more.
- It's a culture what emphasizes taking the waste out of every aspect of the operation:
  - Supply chain
  - Manufacturing
  - Laboratory
  - Distribution
  - Compliance
- It's a culture that is directly associated with the whole enterprise.

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Consider the Following Principles

- Process streamlining
- Cycle smoothing
- Cycle-time reduction
- Mistake proofing;:“poke yoke”
- Rapid changeover: SMED
- Lead time reduction
- Value stream mapping

These are all core parts of the LEAN toolbox and we will return to this later for our disposable analysis.

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Effective Risk Management Strategy

- Risk Management is a knowledge management program providing Decision Makers the power to make better Quality decisions.
- It involves identifying potential failure causing issues.
  - Ranking for criticality.
  - Mitigating the effects of these.
  - Where possible, eliminating these.
- Maintenance of sustainable compliance through oversight policy.
  - Determine areas needed.
  - Set out structure for levels required.
  - Execute oversight measures.
  - Review and make adjustments as necessary.

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Determine Criticality Through Quantitative/Qualitative Models

Example: Compliance Record

Compliance Actions	Historical Database of Compliance Issues				
	No issues	Few issues	Occasional issues	Many issues	Significant issues
FDA violations requiring attention	**Low**	**Medium**	**High**	**High**	**High**
FDA objections voluntary action	**Low**	**Low**	**Medium**	**High**	**High**
Periodic internal audit findings	**Low**	**Low**	**Low**	**Medium**	**High**

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Risk Analysis Related to Production

- Example:
  - Probability of plant contamination with a virus
  - Plant shut-down
  - Lost production
  - Regulatory action
- Genzyme / Genentech had viral contaminations of fixed place plants.

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Risk Reduction Potential

- If these had been disposable plants how would the remediation been affected?
- In a disposable facility it might have been possible to recover more quickly as all components would have been discarded.
- Something to consider!

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How to Get the Best Out of Your Disposable Approach

- Develop a high-level strategy in relation to how you'll employ various unit operation solutions to mitigate issues as the process is scaled.
- Where possible, the approach should be as seamless as possible to maximize flow and minimize points of obstruction or hold-up.
- Streamline the use of components so the possibility of incompatibilities is reduced.
- Barcode components to assure correct assembly and traceability.
- Prepare assembly area as a staging space like for other components/materials and pre-assemble key pieces.

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How to Get the Best Out of Your Disposable Approach

- Where possible, create operational modules to reduce waiting time between runs.
- Where possible, use the same company components for scale-up—"Uni-part".
- Note: tech transfer to larger scale can be severely affected if different components have to be sourced and used for the next scale.

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Some Potential Drivers to Use Disposable/Single Use Systems

- Potential capital cost
- Reduction in equipment and facilities
- Reduction in operating costs
- Market forces are driving flexibility due to needs:
  - More clinical candidates
  - More frequent changeovers
  - Requirement for rapid production
- Potential for shortened development timelines
- Reduction in cleaning and cleaning validation

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Some Potential Drivers to Use Disposable/Single Use Systems

- Faster set-up time
- Faster product changeover time
- Ancillary issues
  - Reduced documentation; SOPs and protocols
  - Reduced validation possibility
    - Utilities
    - Different qualifications for equipment
  - Simpler disaster recovery plan.

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Possibility of Reduction in Failures Due to Technology in Use

- Reduction in contaminations
- Enzyme turnover of product as a result of holding times
  - Example of ½ product lost in a centrifuge
- Error prevention
  - Poke Yoke – wrong valves opened and product lost
- Carryover of cleaning material residues or carryover of previous product
- In a contamination (disaster) situation, remediation can be much simpler and faster – it's a LINE CLEARANCE!

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Some Key Considerations When Contemplating a Single-use Disposable Approach

- How effectively the various unit of operations can be linked to provide an advantage.
  - Is it a "plug and play" scenario?
  - Is there significant re-engineering to make it work?
- Can the system provide the capacity to deliver the product in the right amounts?

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Some Key Considerations When Contemplating a Single-use Disposable Approach

- Will it work to deliver your product reliably?
  - Sufficient aeration
  - Sufficient agitation
  - Can it maintain temperature?
  - Can it provide sufficient in-process data for key operating parameters?
  - Does it meet any operating pressure requirements?
  - Can material be easily recovered?
- Will it work in the facility space you have available?

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Some Key Considerations When Contemplating a Single-use Disposable Approach

- Is it safe and can it meet health and environmental requirements?
- Can it meet disaster recovery requirements to maintain business continuity?
- *Note: This is very important and is frequently overlooked*

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Processes for Biologicals Determine the Product Specifications

- Folding pattern – cysteine residues
- Glycosylation
- pH
- Ionic conditions
- Temperature
- Specific nutrient availability
- Timing of any induction phase

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Processes for Biologicals Determine the Product Specifications

- Process development and scale-up for conventional bioreactors can prove difficult.
- Using high-yielding cell lines – Do we need high capacity?
  - In many cases – No!
- So, possibilities for bag-type technologies or other disposable solutions such as pre-formed bioreactor inserts.

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Single-use Components

- Faster set up of process equipment
- Less cleaning
- Less validation work for cleaning
- Validation / qualification of equipment can be simpler
- Higher flexibility
- Lower capital expenditures
- Lower risk of investment

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Single-use Components

- In process development and clinical production, products often made in parallel or one after another
- Needs higher flexibility
  - This is **challenging** for cleaning equipment
  - Also set up times can be lengthy
- When production yields are on the rise due to more productive cell lines, there are greater opportunities for medicines made in small quantities—personalized medicine.
- There may be opportunities for volume products in conventional bioreactor trains—blockbusters. But for smaller volume products, disposable production methods offer another alternative.

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Benefits of Single-use Systems
Upstream / Downstream

- Time to market is an important consideration—will become increasingly important.
- Cost of production will also become more important than in earlier decades.
- With conventional systems, we see long times for construction and validation. From "green field" to "turn key" might be 5 years. Deciding on when to build is often made before one has certainty about the drug's efficacy.

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Benefits of Single-use Systems
Upstream / Downstream

- Many companies have had significant drug failures at Phase II. For example:
  - Building before you have certainty may leave you with a "white elephant"—not needed facility. However, waiting for certainty will leave you stalled at the starting line with no facility ready to launch the product if initial clinical results are positive.

    So there's the dilemma!

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Benefits of Single-use Systems
Upstream / Downstream

- Using integrated platforms for the various unit operations brings the possibility to reduce waste (holding times, cycle time, extra tankage, etc) and streamline operations.

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Pros

- Simple designs – efficient process flows
- Reduced need for pre-engineering / revised engineering as process is systemized.
- Possibility for late stage decision making due to simplified conceptual process and facility needs
- Opportunity for streamlining process unit operations without altering product specifications
  - Reducing wasted hold times

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Pros

- Fast start-up opportunity
- Faster recovery and business continuity in case of disaster recovery*

  ** Note – Genzyme viral contamination in conventional systems (raw material) or Genentech (MVM–minute virus of mice) in medium component*
- Would recovery been faster with a disposable facility? ***Something to think about operationally***.

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Some Key Issues for Consideration as One Considers Single-use/Disposable Solutions

- Process compatibility
- Process efficacy
- Volume
- Filtration and discharge
- Agitation
- Temperature and pressure
- Maintenance of process valves
- Material handling /space requirements
- Environment / health and safety

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System Sizes

- Single-use ➔ 2500L
- Hybrid 500 ➔ 2000L
- Multi-use 1 ➔ 10,000L

- Distinguish
  - Clinical
  - Commercial

  } Manufacturing

- Media Prep – Used up to 3000L
- Single-use seed cultivation – rocking motion agitation
- Production size STR – often single-use

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System Sizes

- Harvesting up to 2000L use disposable depth filters
  - Some single-use centrifuges are becoming available.

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DSP – Clinical and Commercial

- UF is disposable up to 100L
- Protein A is reusable – will not change
- Polishing steps, filtration and mixing steps are now serviced by disposables (mid-scale production size)
  - Product volumes of purified products can be 10-fold less
  - Hold, transfer and storage are areas where disposables are in use. In clinical and mid-range commercial size.
- Connecting unit operations is always an issue—especially sterile connections. Many thermoplastic solutions now exist together with various other steam-through connections.

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DSP – Clinical and Commercial

- Large manufacturers use hybrid systems where some disposables are tried and tested.
  CMOs – clinical manufacturers often use these because they provide greater flexibility and turnaround options.
- Some constraints do exist, although disposable valves, pumps, heads and filling systems exist.
  Main issues – disposable valves, filling lines for rapid transfer.
  Sterile and closed containment is a big requirement.

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Other Issues – Clinical and Commercial

- Better flexibility is required for some single-use systems—simplified operation and/or reduction in complexity
- Issues connected with sampling and final processing are an issue where systems are opened up. Require good HVAC (ISO 8 – Class C). However, with closed bay arrangements it may be possible to reduce HVAC issues—savings!
- For connection use barcoding to identify trace parts of system.

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Challenges to Future Single-use Implementation

- Conventional systems take +5 years to bring on-line
- New materials considered safe have brought disposables as an option.
- To derive the most benefit—need application specific solutions that integrate.
- Possibilities exist for combination use of conventional and disposable solutions—hybrid.
- Success of strategy requires vendor support throughout the cycle.

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Some Cons

- No high-level process automation
  - CIP SIP not an issue except for hybrids
    - Short and longer term
- Require stability studies for gamma irradiated systems
- Biocompatibility – testing
  - USP 87 biological tests in vitro
  - USP 88 biological tests in vivo
- Mechanical strength tests
  - Elongation, seals, air lead

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Some Cons

- Gas transmission
  - ASTM D3985; oxygen
  - ASTM F1249; water vapor
- USP 661 test for plastics
- E.P. 3.1.7; EVA for containers and tubing
- E.P. 5.2.8; on TSE – BSE
- TOC
- pH/conductivity

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Some Cons

- Extractables and leachables
- Chemical compatibility testing
- Endotoxin testing
- Gamma irradiation sterilization validation
- Bacterial ingress test

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Some Cons

- For PQ would use model solvents and simulate process variables—like TSB for filling lines
  - Within end user variables
- Filters need a biological challenge
- Product hold bays undergo an ingress challenge

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Pros

- Sensors built into application
  - pH, DO, conductivity
- Validation work
  - Much can be provided by vendors with help from clients
- Cleaning is main saver
- Cross-contamination is greatly reduced
- Disposability may save on detergent clean up and uses of vast quantities of **water** and **energy**

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Production Strategy for Biologicals

Imperatives

- Reliable production
  - Process capability
  - Ease of operation
- Shortest cycle times
- Integrated production; upstream/downstream

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Production Strategy for Biologicals

- Regulatory requirements
  - Purity
  - Run process at least 3x/year to maintain qualification
  - Process capability
  - Process control
  - In-process control
    - Sterility
    - Bioburden
    - Critical points
    - Test methods and analysis
    - Test requirements/batch/lot

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Unit Operations to Consider

- Media prep
- Buffer/additives preparation
- Culture production (fermentation/cell culture)
- Cell recovery/removal
- Liquor pooling and stabilization or cell paste stabilization – 80°C

Sterile filtration	OR	Cell paste rupture / separation
Product capture		Buffer exchange
Viral inactivation		Product capture
Viral clearance		Product concentration UF
UF/Diafiltration		Diafiltration
Freeze		Freeze

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Purification Steps

- By employing some standardized components it's possible to develop streamlined process flows that minimize downtime and lags between steps.
- In future, this should become easier as the industry accepts standards to harmonize components (note ISPE and ASME working groups)

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Technology Available for Integration of Up/Downstream Operations

- DSP
  - Millipore BioPak disposable UF system
  - Cuno CTG-Klean enclosed filtration system
  - GE Hollowfiber Filter part of their Ready To Process line
  - DSM Rhobust® expanded bed adsorption
- Purification
  - Sartorius Single Step
    - Improved resources of recovery of viruses 51% over ion exchange chromatography
  - PALL's Mustang Q Membrane Chromatography
    - Starter kit – 10 fold increase in performance over standard chromatography
  - Millipore OptiCap XL and XLT
    - Shows compatible capsule filter are designed for bioreactor up to 2000L

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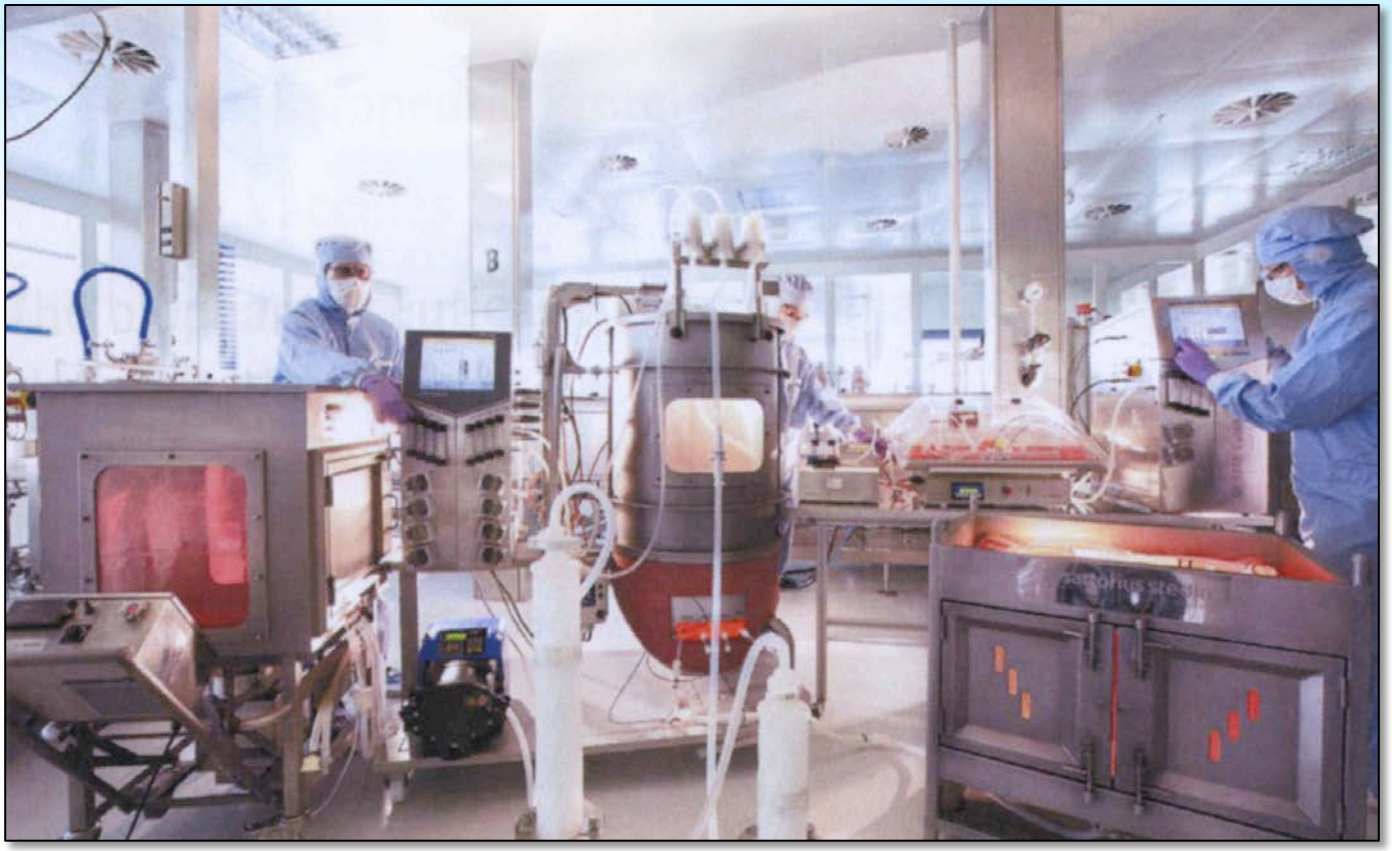
Courtesy of Sartorius Stedim

Modular Disposable Approaches



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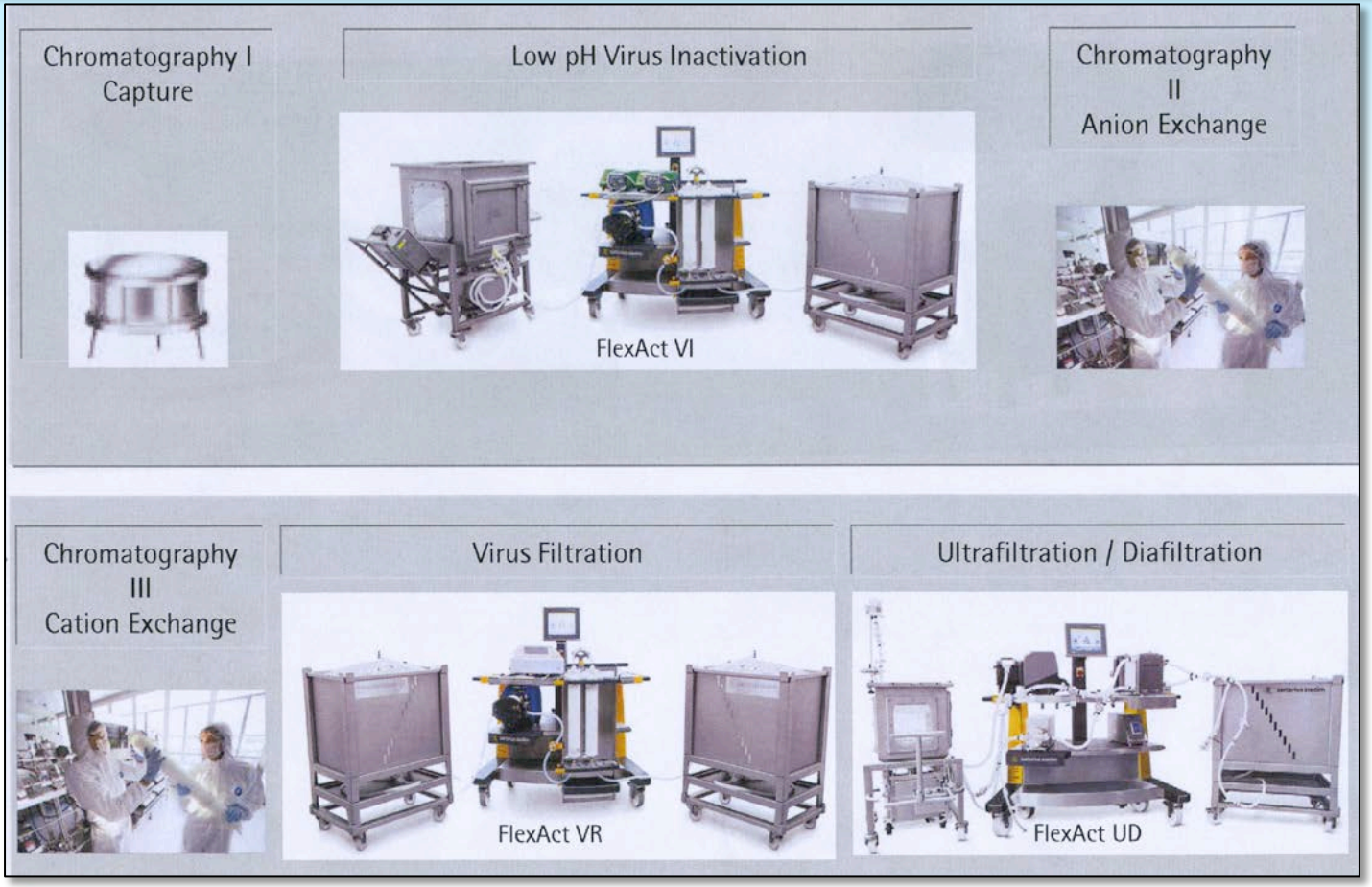
Downstream Equipment



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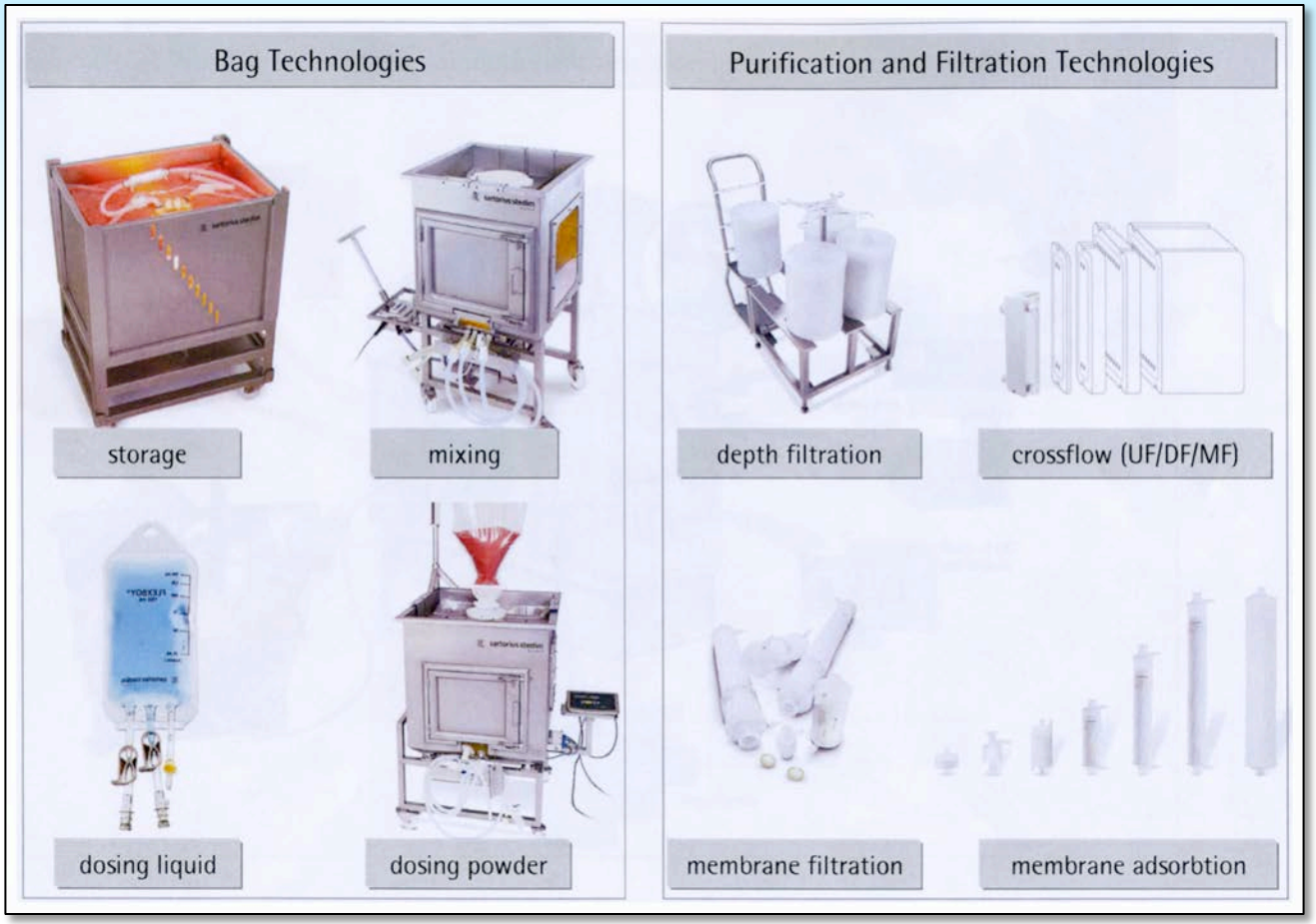
Single-use Technologies



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Downstream Processing and LEAN

- Mobius® Flexible Filtration (EMD Millipore) are designed to target the waste identified by LEAN process initiatives
  - Overproduction
  - Defects
  - Excess inventory
  - Overprocessing
  - Holding periods
  - Non-added value movement
  - Underused labor

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Some Considerations Using Disposables and the Modern Flexible Facilities They Operate In

Consider FlexFacility by Xcellerex

- Estimated 35% reduction in floor space
  - Possibilities to get rid of clean rooms
  - 67% reduction in airlock space required
- 30% reduction in COG
  - 30% reduction in Class 10,000 space
  - 30% reduction in gowning
  - 30% reduction in labor costs
- 10% more annual production

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Flex Facility Modular Systems

- Using this approach in an open modular facility permits the possibility for multiple manufacturing platforms.
  - Examples: Xcellerex XDR system which they claim can be up and running within a year
  - Wave bioreactor – GE
  - Hyclone's single-use bioreactor
- Turn-around and changeover is simplified over conventional approaches.
- This function reduces to the point of "LINE CLEARANCE" because you discard everything on the process line. Changeover time can therefore be reduced by >80%.

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Some Considerations Using Disposables and the Modern Flexible Facilities They Operate In

- As with all disposables, flow is smooth because it's lifted in and lead times can be made short
- Changeover occurs by module allowing each unit operation to proceed, so manufacturing can continue in all other limit operations while just one is turned around. Hence, flexibility, scheduling and logistics are enabled.
- Speed to GMP qualification; 70% faster than conventional validated space.

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Courtesy of Xcellerex

Xcellerex Flex System

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Some Issues Remaining to be Addressed for Single-use Systems

- Can't handle pressure > 1.0 psis
- Can't handle temperatures > 70° C
- Non-standardized connectors
- Reliance on vendor qualifications
- Due to DSP—scale is somewhat limited to 2,000L

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Questions

- Improve process flexibility
  - Due to probability for changeover
  - Removal of unnecessary holding steps
- Reduce production lead time
  - Show layout for inoculation, etc.
- Achieve shorter run turnaround times
  - Simple hook up; no cleaning
  - Could show as a line clearance type operation
- Successfully integrate upstream/downstream processes
  - Disposable filters
  - Fluidized beds

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Reduce Process Lead Time

- Address by using "hybrid" approach to minimize "waiting" time in production bioreactor.

Points to consider

- Hybrid uses bags to generate seed cultures in advanced state for production bioreactor.
- Conventional systems have limited potential for multiple seed culture development for production bioreactor inoculation.

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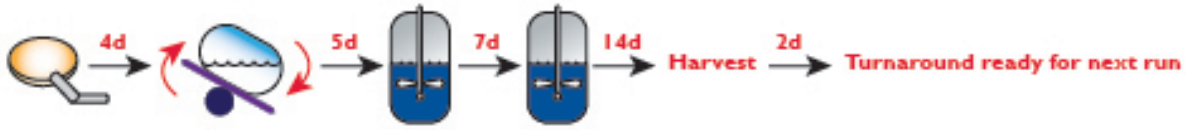
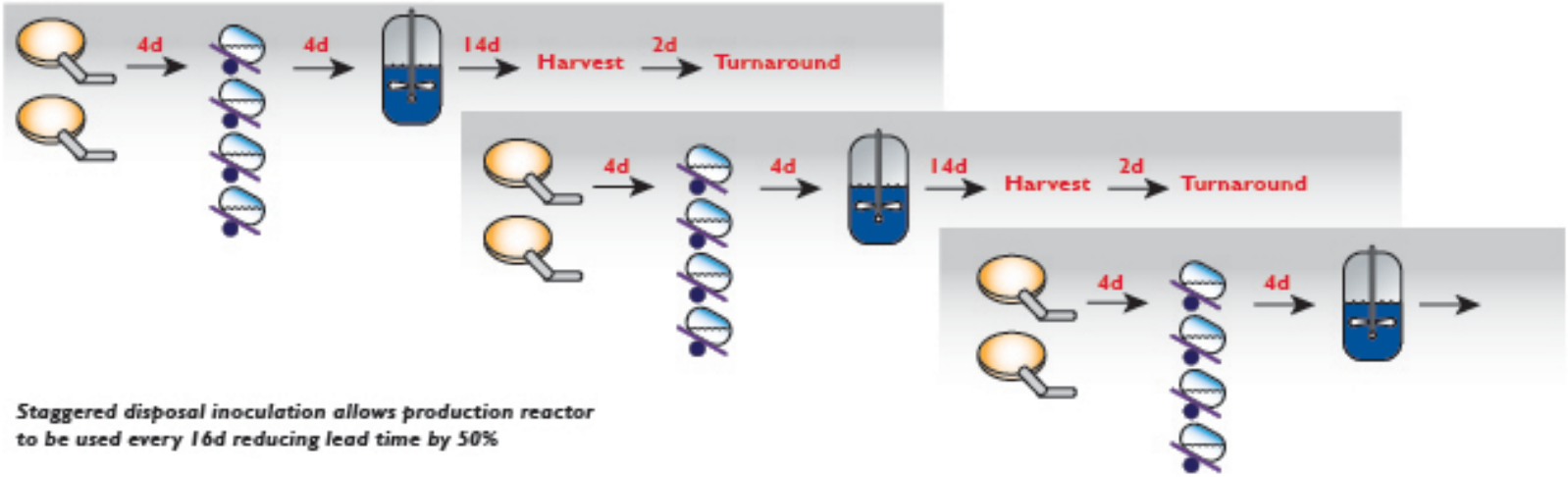
Consider Two Scenarios

Conventional System



Production based on 32d cycle; Production Reactor (idle for 16 days)

Disposable Hybrid



Staggered disposal inoculation allows production reactor to be used every 16d reducing lead time by 50%

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Experience: for Biodefense Application

Key issues

- Rapid response to attached by biological countermeasure
- Changeover and start up of new product takes time
  - Cleaning
  - Sterilize
  - Quality/validate systems
- Disposable systems reduce this from potentially a week to hours for changeover and setup

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Facilities Design

- Modular in design
- Open layout with little or no fixed plant assets
- Portable units – pre-sterilized critical components.
- Multi-stream possibilities
  - Self-contained units
- Utilities
  - Clean steam
  - WFI can be bought
  - Basic plant steam – biowaste decontamination
  - Water USP purified: outsource; buy buffers; buy media

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Facilities Design

- Other
  - Solid waste disposal
    - Regional
  - Liquid waste disposal
    - pH; local regulations

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Possibilities for Reducing Process Time

- Modular manifold units to allow interchangeability and redundancy
- Robotic bag filling to prevent unwanted interventions—bags, etc.
- Common component standards including bags
- Universal quick connect standards for technology to allow interchangeability and hook up of in-line processing assemblies/modules under sterile conditions.
- Results should provide for faster, reliable, easy, efficient, secure changeover that impact cycle-time and resource use.

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Workshop

So, let's look at two mechanisms for producing a biological to see what our options might be…

One conventional bioreactor system

One using a disposable arrangement

- We'll take an hour to construct these models and then review the findings and discuss the outcomes.
- As a working exercise, we'll take a mAb process being made at 500L in a conventional bioreactor; 350-400L culture volume.

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LEAN Manufacturing Methodology

Five important processes

- People
  - The ability of the organization to adapt
- Support systems – TPM
- Flexible manpower systems – optimized labor use
- Autonomation
  - Principle of stopping production to address defects
- Just In Time (JIT)
    - The right parts and elements in the right place at time with the shortest lead time

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Muda, Muda, Muda – 7 Forms of Waste

- Transport
- Waiting
- Overproduction
- Defect
- Inventory
- Motion
- Extra processing

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In order to produce LEAN benefit, single-use/disposables should deliver several key benefits.

- Reduce the possibility of deviations
- Provide stream-lined processing saving time while maintaining compliance
- Through leveled processing provide a consistent product specification
- Reduce cycle time and improve process efficacy
- Reduce waste in all its forms

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So let's analyze where we can save and be LEAN using single-use/disposables.

- Transport
  - Using modular platforms the potential for damage resulting in loss can be reduced.
- Waiting
  - Set up is a big piece of an operational run; using a modular filtration assembly can reduce this by >50% providing greater flexibility.
- Overproduction
  - Correct sizing of modular single-use components prevent overproduction and controls processing time

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So let's analyze where we can save and be LEAN using single-use/disposables.

- Defects
  - Poke yoke application of parts to assure correct assembly and uses operation prevents error and encourages standardized work flow.
- Inventory
  - Modular-based single-use filtration system can reduce the number of parts needed and prevent mix-ups together with resulting in a reduction in storage space.

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So let's analyze where we can save and be LEAN using single-use/disposables.

- Motion
  - Non-configured single-use assemblies can result in wasted material associated with pre-assembly. Arranging these into modular units can save time and reduce motion muda.
- Extra processing
  - With an integrated platform the possibility for possible product damage is reduced.

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Some LEAN tools we'll use in our exercise

- Value stream mapping
  - Lead time
  - Take time
- Spaghetti diagrams
- Flow smoothing
- 5S: Sort, Straighten, Scrub, Systematize, Standardize
- Create work cells
- Kaizen – continuous improvement

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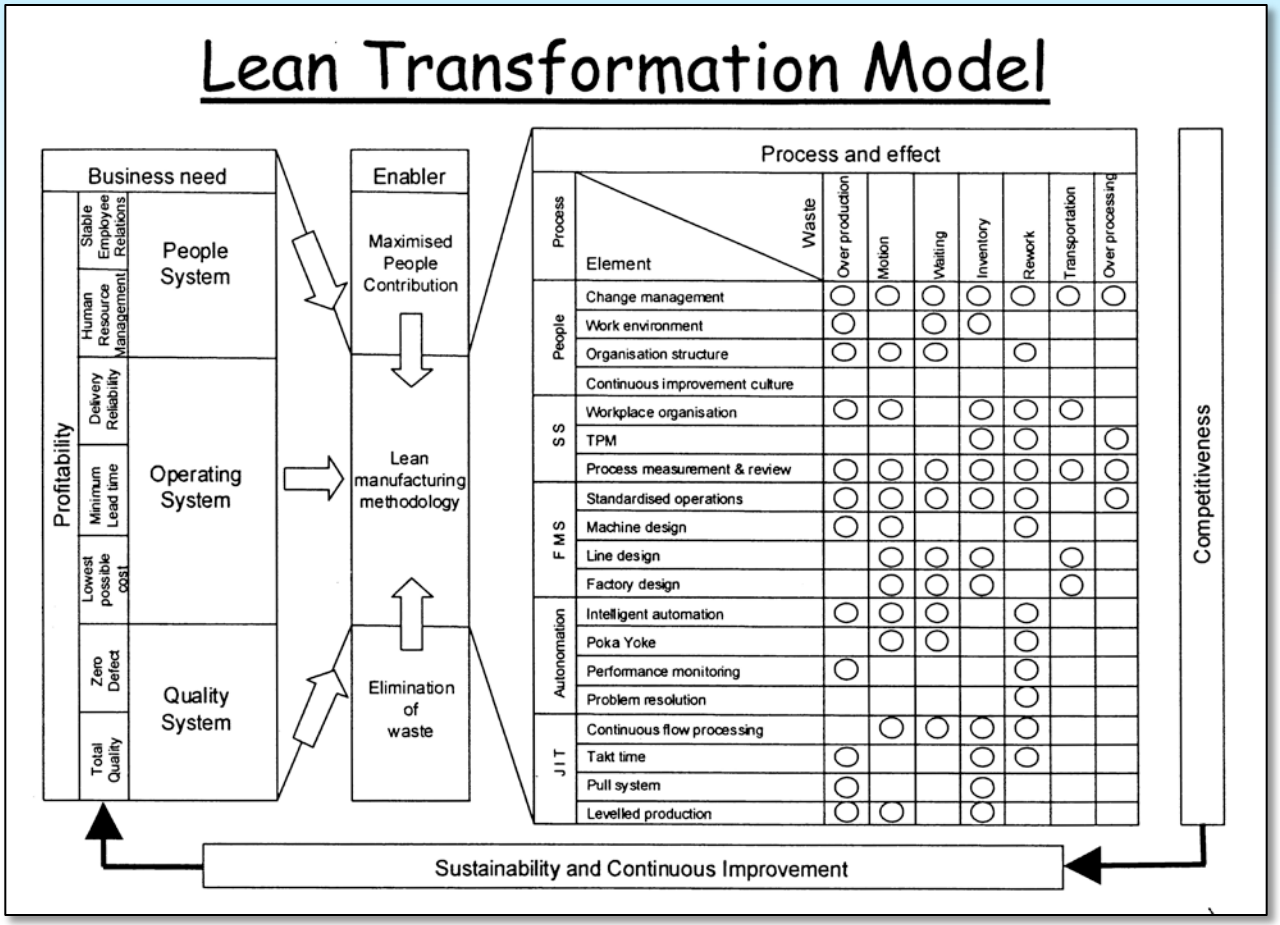

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Workshop

Things to consider

- Documents
- Cleaning; equipment; facility
- Product changeover; batch/batch
- Scaleability
- Validation
- Cleaning validation
- Facility
  - Size
  - Type
  - Separations needed (why?)

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Workshop

- Waste disposal
  - Material
  - Biowaste
- Flexibility
  - What value from JIT and rapid response; changeover
- Disaster recovery/business continuity
- Risk – risk mitigation

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Workshop

- How much Process Development Time
  - Methods development to support
    - Products
    - Cleaning
      - Residuals
      - Products
- Scale-up time – how many transfers

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Workshop

- What does the facility need?
  - WFI
  - USP purified water
  - Deionized H_2O
  - Clean air
  - Mixed gases
    - Cleaning: walls, floor ceiling
- Transfer technology—samples
  - In-process samples
- System validation
  - Bioreactors
  - Utilities
  - Addition vessels

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Plan

See the Current State

- Study the process to gain a DEEP UNDERSTANDING of:
  - Activities performed
  - Resources required and where they come from
  - Flow of people, materials, and information
- Take photos of current state—as in process development
- Use any data available to help gather details of what ***is*** vs. what ***should be***

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Plan

See the Current State (Details, Details, Details)

Process Path:	Date:	Observer:

Kaizen Observation Checklist

Are there unsafe conditions in the work area?	Is the work area clean?	Is it well marked?	Are there andons?

What decisions do associates have to make?	How do they know the answer?	How often are they wrong?	How do they get help?

What materials, supplies, tools do they need to do their job?	How available are they?	Is the quantity too high or too low?	What condition are they in?

What do associates have to wait for?	Who do they wait for?	What do they wait for?	How often or for how long?

Do they know their performance for safety?	Quality?	Productivity?	Overall department?

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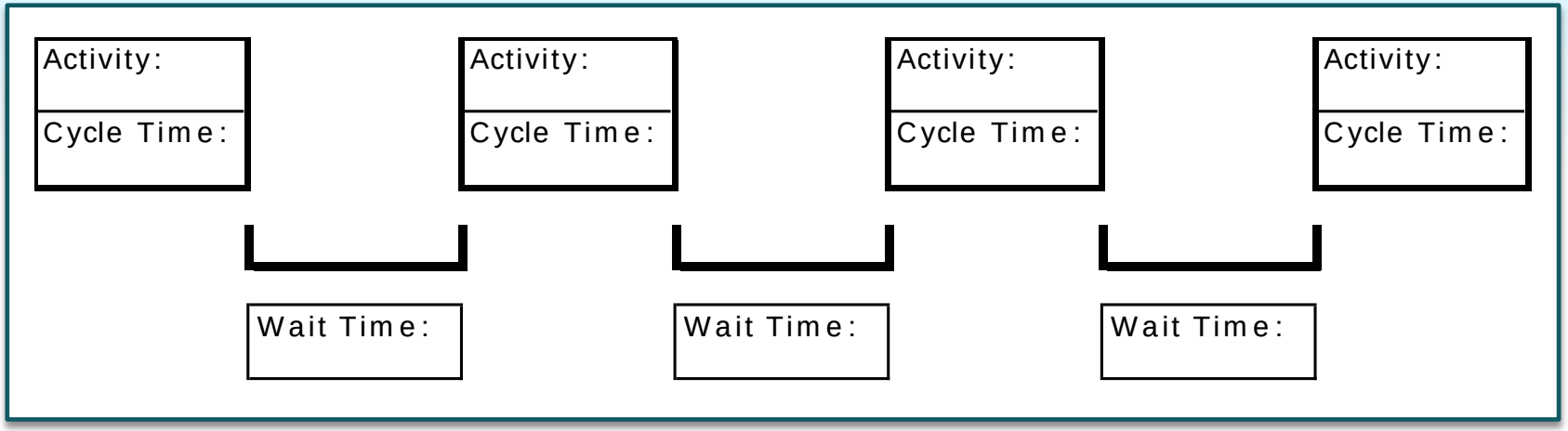
Plan

See the Current State

- Create a Value Stream Map of the process



- Initial version is done with post-it notes
- Measurements done on shop floor

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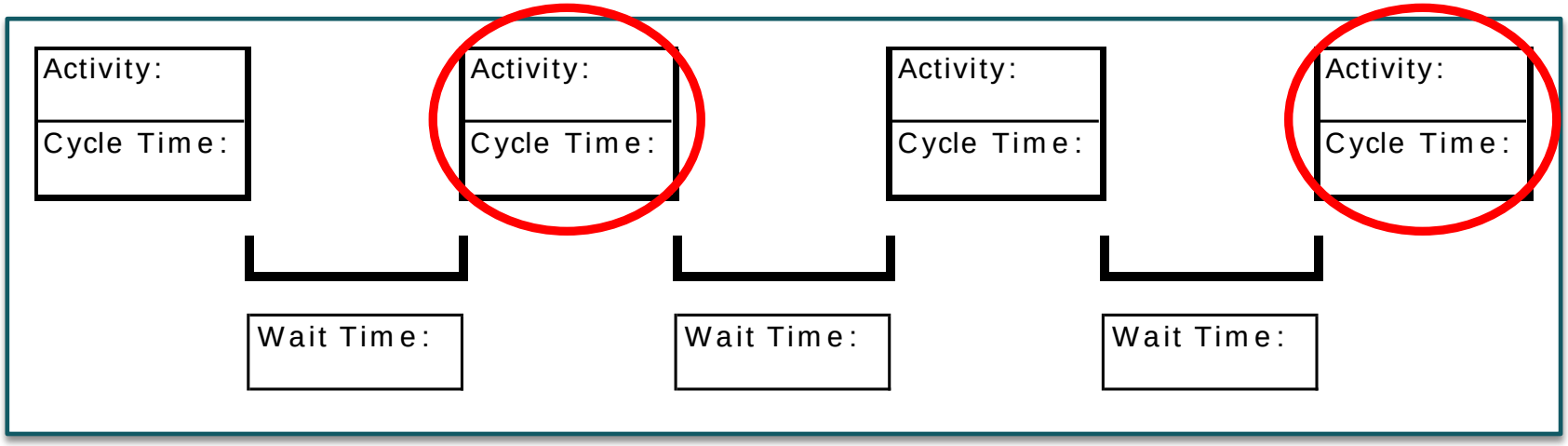
Plan

See the Current State

- Circle Value-Added steps
  - The customer must be willing to pay for the activity
  - The activity must change the form, fit, or function of the product, making it closer to the end product that the customer wants and will pay for
  - The activity must be done right the first time



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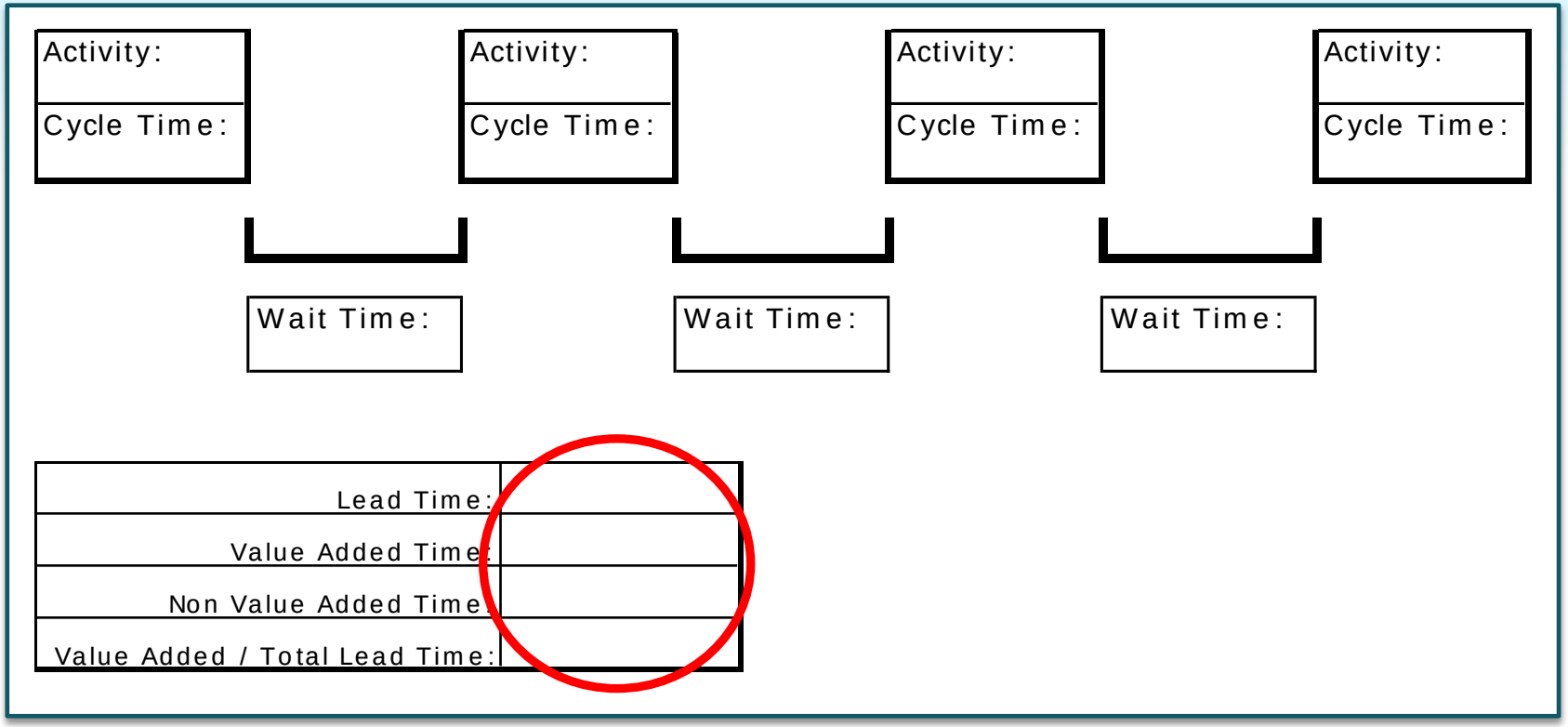
Plan

See the Current State

- Calculate timing of process



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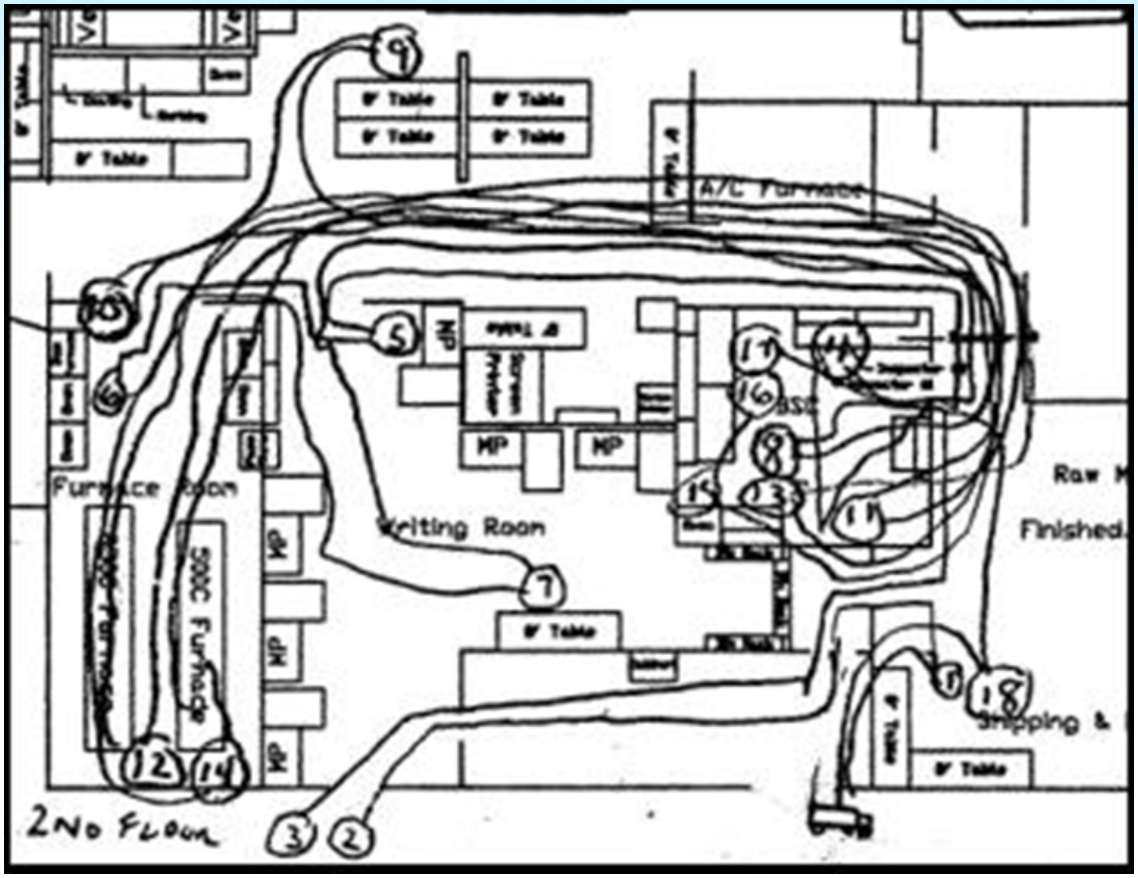
Plan

See the Current State

- If motion or transportation seem excessive, a ***spaghetti diagram*** is a useful tool to help see the current state (this can also be used for flow of materials or information)



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Plan

See the Current State – Identify Waste

- One primary purpose of LEAN Manufacturing principles is to eliminate waste. But, what do we mean when we talk about waste?
- Waste, also known as ***muda*** in the LEAN environment, takes place in 7 forms…

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Plan

See the Current State – Identify Waste

- Waste of ***Transportation*** (of data and things)
- Waste of ***Inventory*** (poorly managed stock)
- Waste of ***Motion*** (people)
- Waste of ***Waiting*** (delays and backlogs)
- Waste of ***Overproduction*** (making too much)
- Waste of ***Overprocessing*** (unnecessary handling)
- Waste of ***Defects*** (not doing things right first time)
- "***TIMWOOD***" is a useful acronym to remember the 7 classifications.

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Plan

Group team's notes together on the waste they observed and prioritize

- Waste of ***Transportation*** (of data and things)
- Waste of ***Inventory*** (poorly managed stock)
- Waste of ***Motion*** (people)
- Waste of ***Waiting*** (delays and backlogs)
- Waste of ***Overproduction*** (making too much)
- Waste of ***Overprocessing*** (unnecessary handling)
- Waste of ***Defects*** (not doing things right first time)

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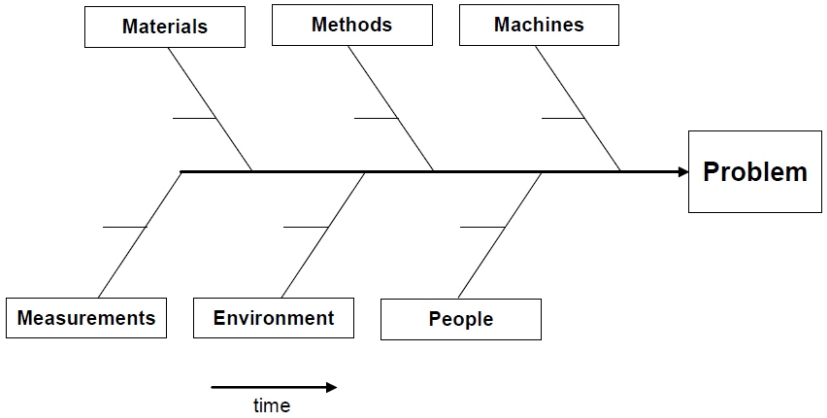
Plan

Identify Root Cause of Waste

- Ask "5 Whys"

Defect	Reasons
Why-1: Why did THE DEFECT occur?	
Why-2: Why did THAT occur?	
Why-3: Why did THAT occur?	
Why-4: Why did THAT occur?	
Why-5: Why did THAT occur?	
Why-6: Why did THAT occur?	

- Perform Fishbone or "Ishikawa" Exercise



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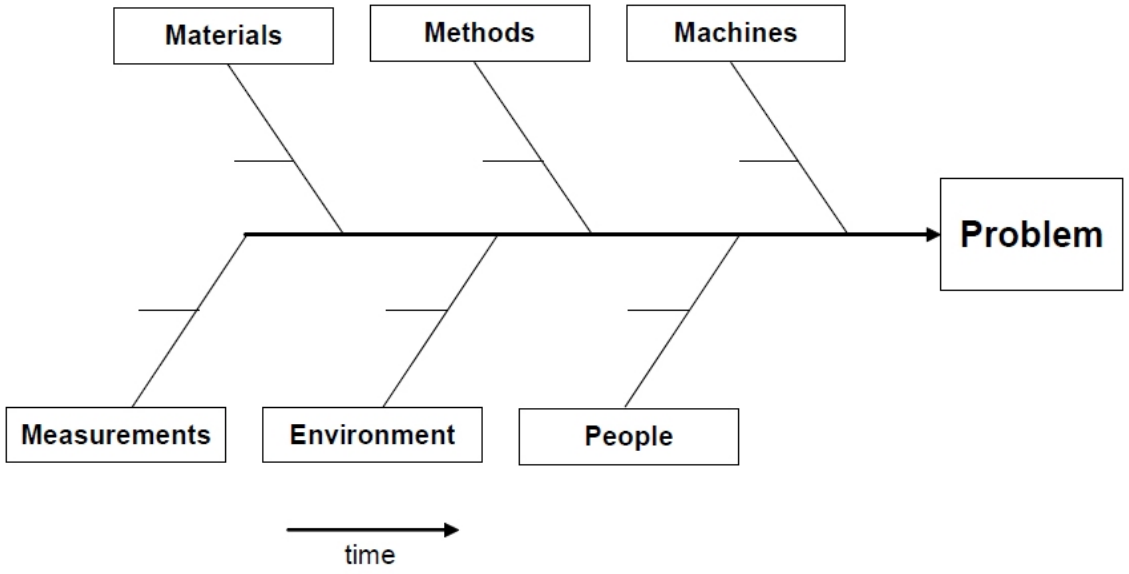
Plan

Fishbone Exercise

- Team agrees on problem statement (the head of the fish)
- Team brainstorms major categories that root causes may be grouped into (below diagram is a guideline, but other categories can always be used)



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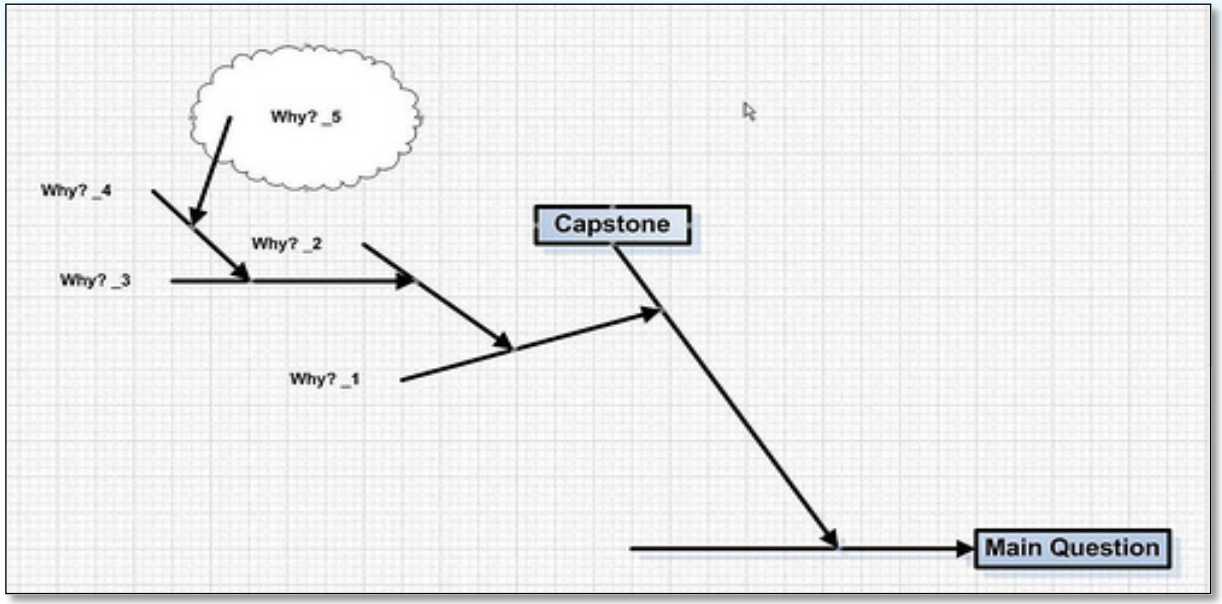
Plan

Fishbone Exercise

- Ask "5 Why's" on each potential root cause and add "bones" to the fish
- Identify potential root causes by drawing "clouds" around them.



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Plan

Define the "Ideal State"

We have spent a lot of time in the "Plan" phase of the kaizen event. And there is one last step to go. In this step, we will challenge the status quo to **find the safest, most value added and cost-effective process** that we can muster. Be careful not to get caught up in constraints and why "we can't do that, because…" This is pie in the sky and leads us on the path to incremental improvement.

- Refer to your Value Stream Map to see which non value-added steps can be removed
- Identify barriers between present state and ideal state.
- Choose which barriers can realistically be removed or changed

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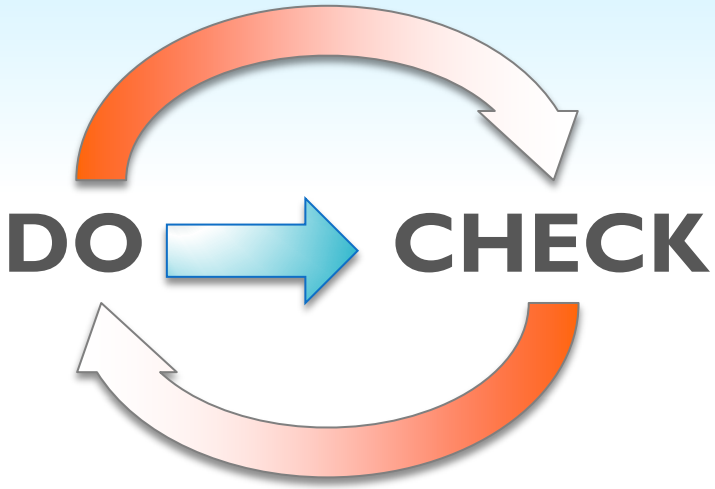
"Trystorming" Solutions

- Trystorming is "hands-on" brainstorming
- Creating new processes
- Changing workstations
- Altering, removing, or combining process steps
- Changing layouts
- Adding add-ons and poke-yokes



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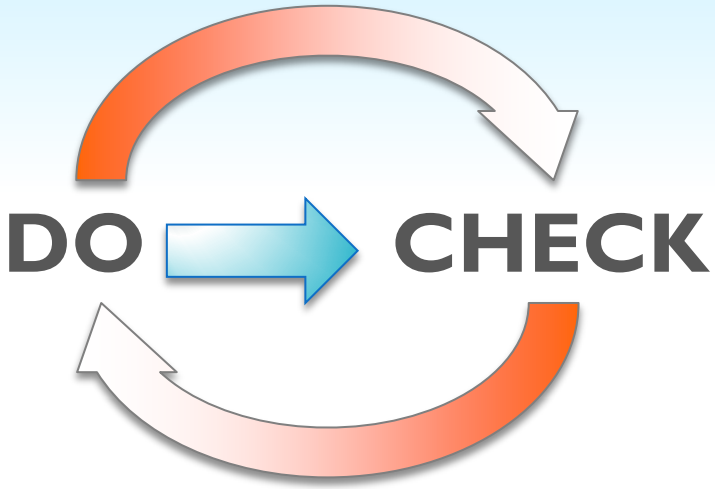
Solutions Must

- Be safe
- Be in our customer's best interest
- Stay within the scope of the kaizen
- Be communicated to all related associates
- Have all related training materials in place
- Follow "5S" principles



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5S

"A place for everything and everything in its place"

- **Sort** - Identify items not needed in the workspace and get rid of them.
- **Straighten** - Place things close to where the work happens in an orderly manner.
- **Shine** - Clean the workspace
- **Standardize** - All similar workstations or processes within the workspace are identical.
- **Sustain** - Strict adherence to maintaining the workspace in the prescribed condition (this is the hardest step).

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5S

"A place for everything and everything in its place"

- **Sort**

  Identify items not needed in the workspace and get rid of them.
  - Be critical. Do not allow "hoarding" of supplies just for security's sake.
  - Pay particular attention to cabinets, shelves and drawers
  - As you check for waste, also ensure everything is available to successfully do the job
  - Get rid of anything not directly related to doing the job. Unnecessary supplies will go to a quarantine area and either disposed of our repurposed within 4 weeks.
  - Tag items for removal if they require help from maintenance.

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5S

"A place for everything and everything in its place"

- **Straighten**
  Place things close to where the work happens in an orderly manner.
  - Create a functional layout of essential materials.
    - Include quantities needed
    - Use visual cues for min/max of materials
    - Label everything
  - Use a **shadow board** if helpful:
    - (Can you spot the missing tool?)

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5S

"A place for everything and everything in its place"

- **Shine**

  Clean the workspace.
  - Determine a schedule for cleaning
  - Ensure cleaning supplies are available
  - Regularly audit
  - This is also the point where machine operators should be enabled to maintain their own equipment, if it is safe to do so. The people that actually ***run*** the equipment are the best ones to ***maintain*** it.

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5S

"A place for everything and everything in its place"

- **Standardize**
  All similar workstations or processes within the workspace are identical.
  - Allows anyone to quickly spot an abnormality (missing supplies, defects in area, etc.)
  - Workstations my be slightly different only to accommodate different height associates, if applicable.
  - Ensure all associates are trained on maintaining the standard. This is particularly important for new shifts that have not yet seen the standard.
  - Regularly audit

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5S

"A place for everything and everything in its place"

- **Sustain (the hardest step)**
  Strict adherence to maintaining the workspace in the prescribed condition.
  - Post visible signage, visual aids, and training materials
  - Determine who should audit for compliance
  - Determine what should be audited and how often
  - Report results and make them important to the team
  - *Not only is this the hardest step in 5S, it is also the most important. We just spent a lot of effort in this improvement and letting it "slip" sends the wrong message. It tells our associates that we don't care about their ideas and they will soon stop giving them to us.*

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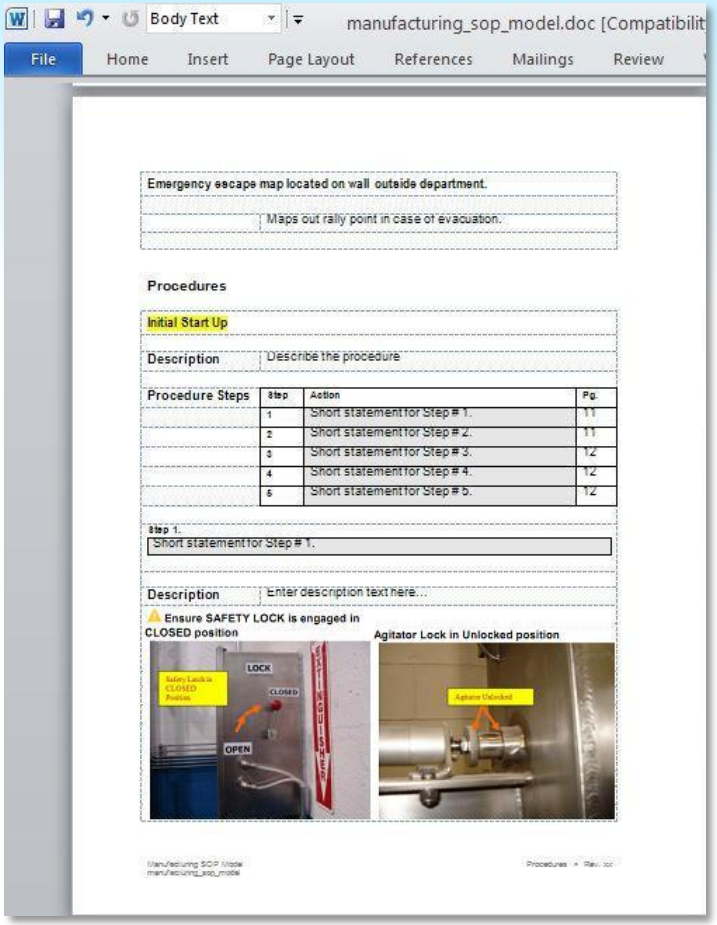
Act

Create "Visual SOPs"

- Easy to follow Standard Operating Procedure to help train everyone on the new process, along with future associates.
- Use photos and screenshots to illustrate steps in the job
- Post at workstations and in training binders



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Act

- Measure and validate
  - Return to the Target Sheet and post newly measured results. Validate with finance where applicable.
- Standardize
  - If results improved the defined process, standardize wherever it makes sense—whether in another department or building.
- Sustain
  - Maintain results within entire department on all shifts. Have tracking and audit mechanisms to do so.
- Share
  - Celebrate with the team! Share with the workforce and "show off" the results. Associates will be proud of the improvements they made…no matter how incremental.

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Consider 2 Scenarios

How do your analyses match up?

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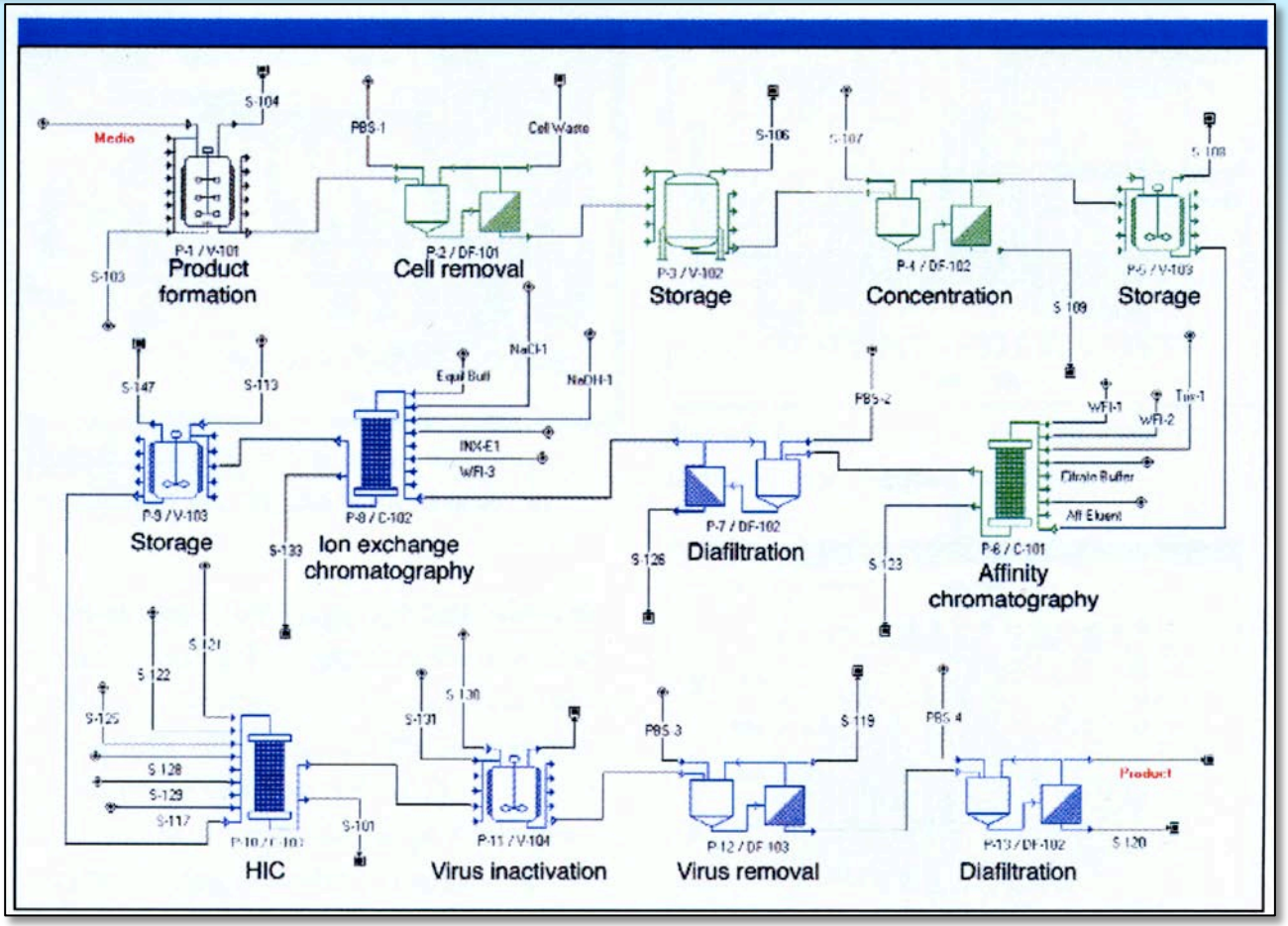
Courtesy of Demetri Petrides, Intelligen

Conventional Bioreactor Train for mAb Production

Monoclonal antibody production flowsheet
s = stream
p = procedure
v = vessel
df = diafilter
c = column



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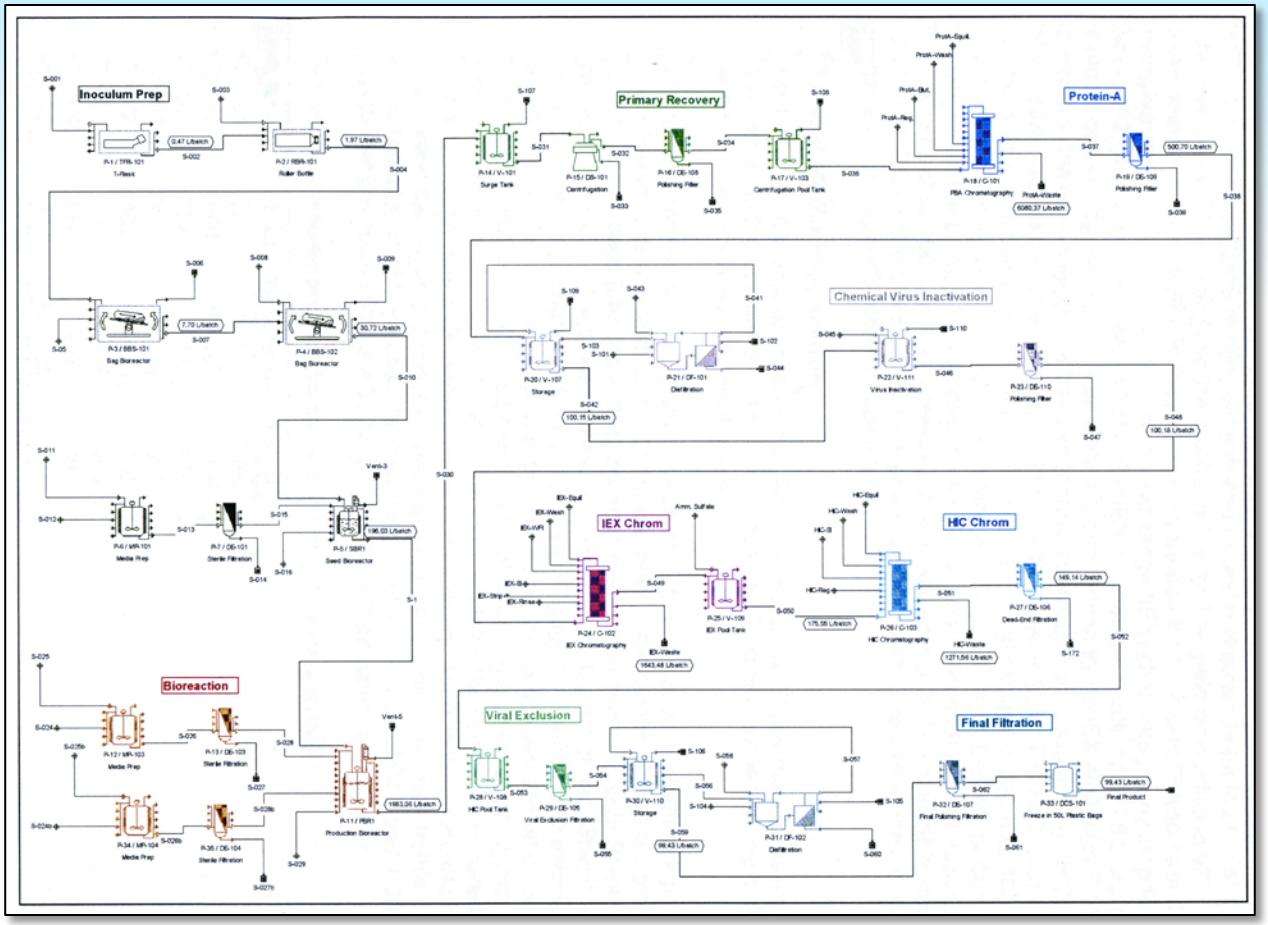
Monoclonal Antibody Production



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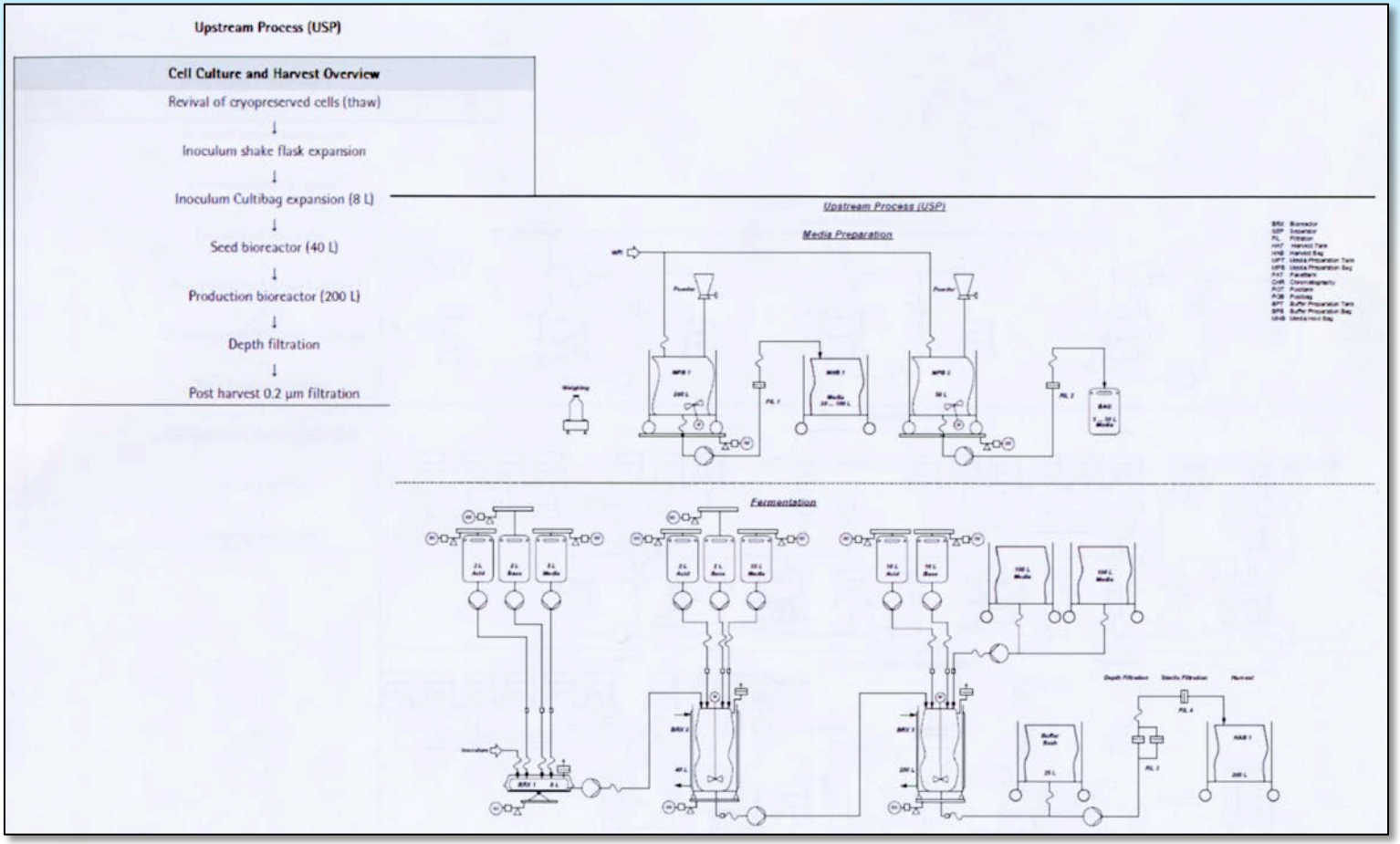
Courtesy of Sartorius Stedim

Single-use Processing – Upstream mAb Production



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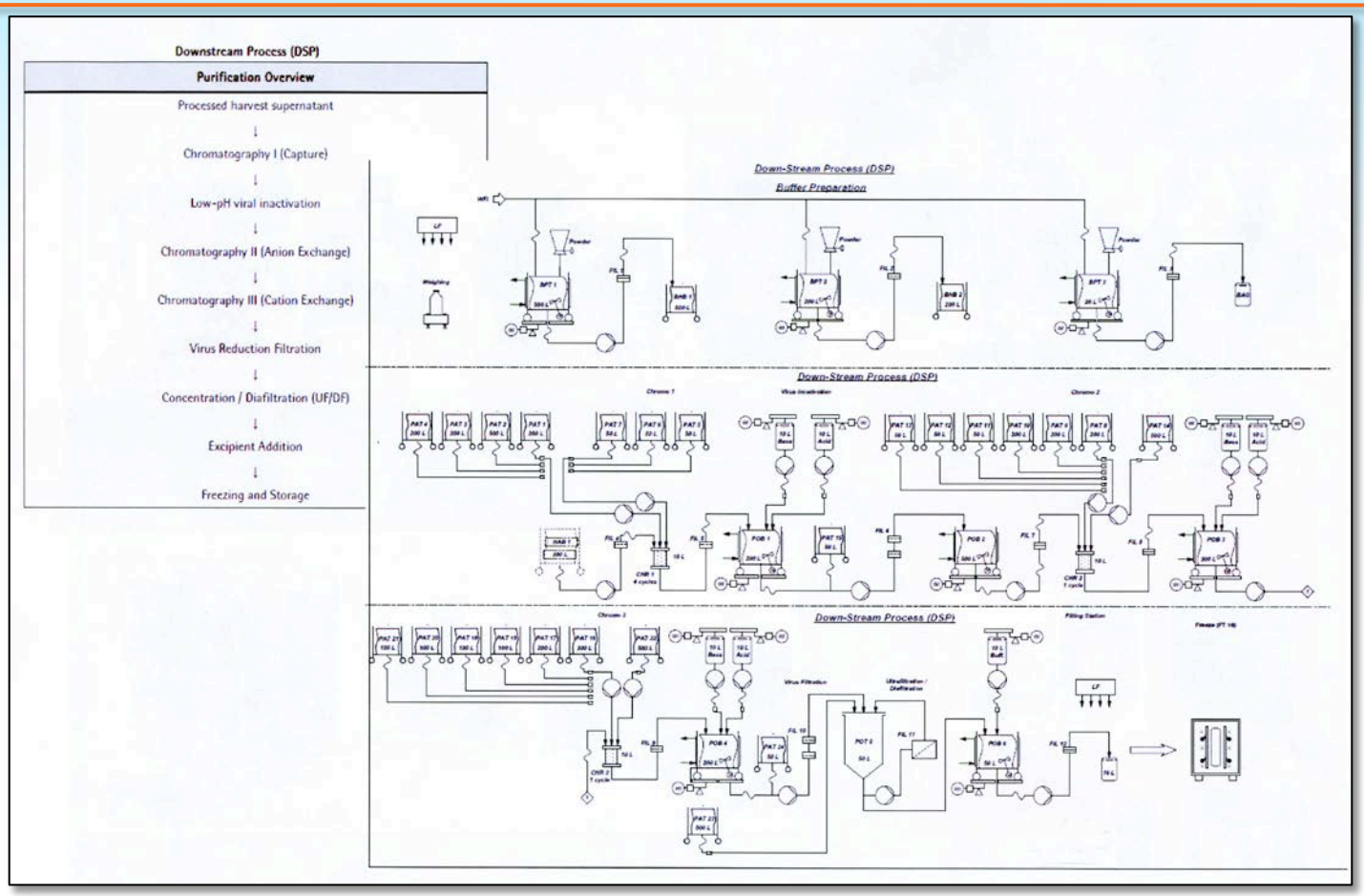
Single-use Processing – Downstream mAb Production



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