Achieving LEAN Processing through Disposable Technology and Systems

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THE MARKET LEADER IN PHARMACEUTICAL CONSULTING

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 globally
- 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

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

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

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.

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.

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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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.

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.

Some Potential Drivers to Use Disposable/Single Use Systems

- Potential capital cost savings
- Reduction in equipment and facilities-both number pieces and sizes
- 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

Potential Savings Reviews

- 50% reduction in capital costs
- 35% reduction in floor space
- 67% elimination of ancillary corridors and air locks
- 30% reduction in loss of goods
  - 30% reduction in class 10.000 clean room space
  - 30% reduction in gowning loss
  - 30% reduction in manufacturing labor
  - 60-70% reduction in cleaning, sterilizing, maintenance and 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.

Operational Advantages

- Change-over times can be reduced by 75-80% over conventional approaches
- Process set-up/start up times can be 50% of conventional systems
- Both of these can be achieved within a single shift

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Possibility of Reduction in Failures Due to Technology Solutions

- Reduction in contamination
- 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!

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?

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?

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*

Advantages of 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

Opportunities for 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.

Opportunities for Single-use Systems

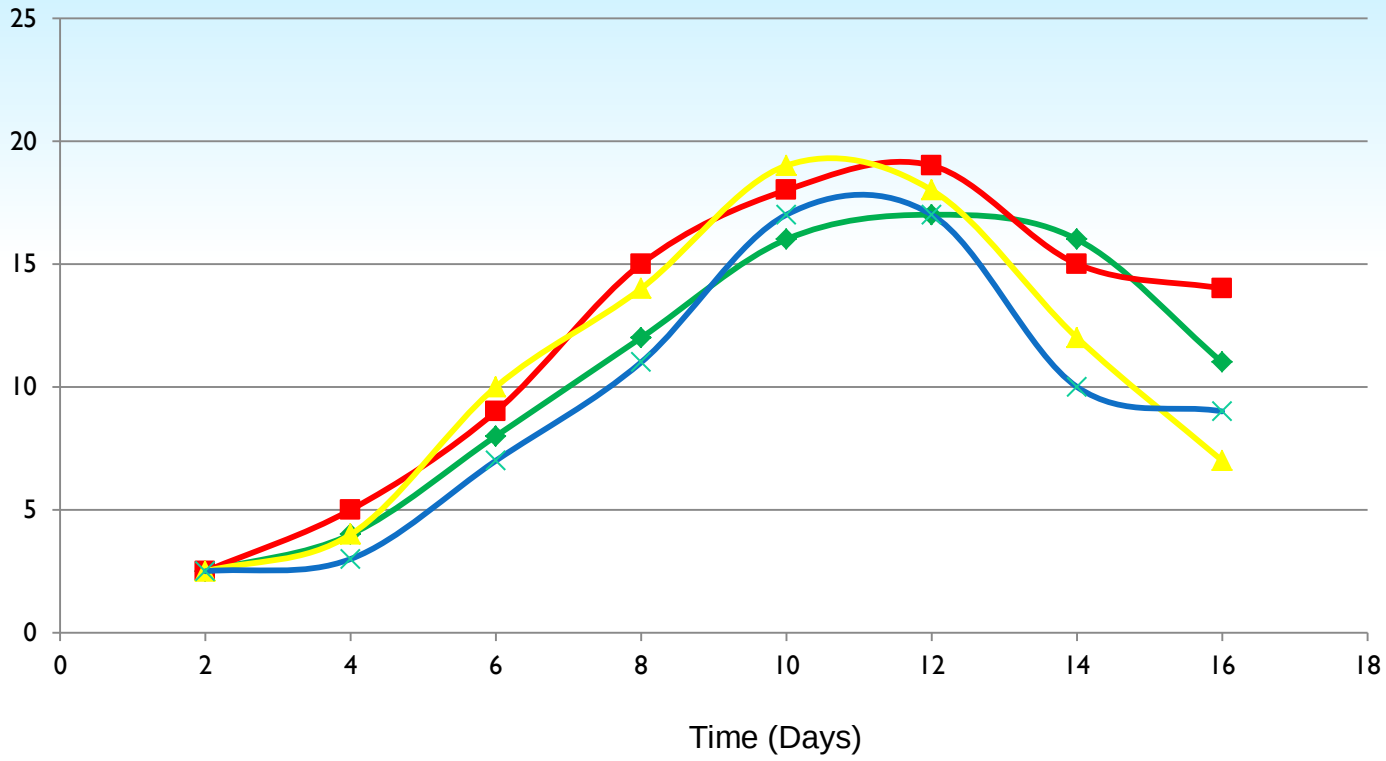
- Time to market is an important consideration—will become increasingly important.
- Cost of production will also become more important than in earlier decades.
- With conventional systems, we see long times for construction and validation. From "green field" to "turn key" might be 5 years. Several examples now show that this can be reduced by 50% for production plant start up. Deciding on when to build is often made before one has certainty about the drug's efficacy.

Opportunities for Single-use Systems

- 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!

Comparison if Disposable and Conventional Bioreactor Mab Producing CHO Growth Profiles



Red=Disposable Run 1
Yellow=Disposable Run 2
Green= Disposable Run 3
Blue= Conventional Bioreactor

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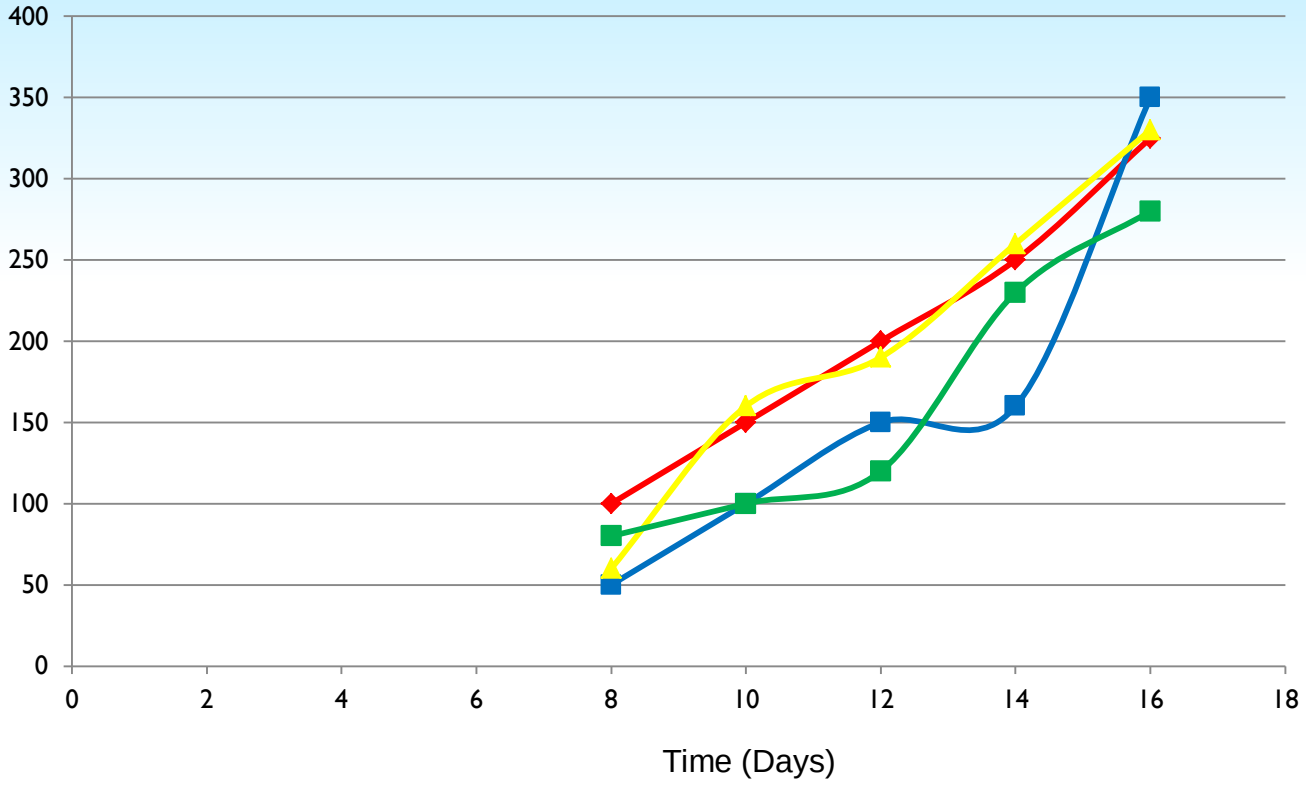
Comparison of Disposable and Conventional Bioreactor Titers for Mab Producing CHO Cells



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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

Questions to be Addressed in Deciding a Single-use Production Strategy

- 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

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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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.

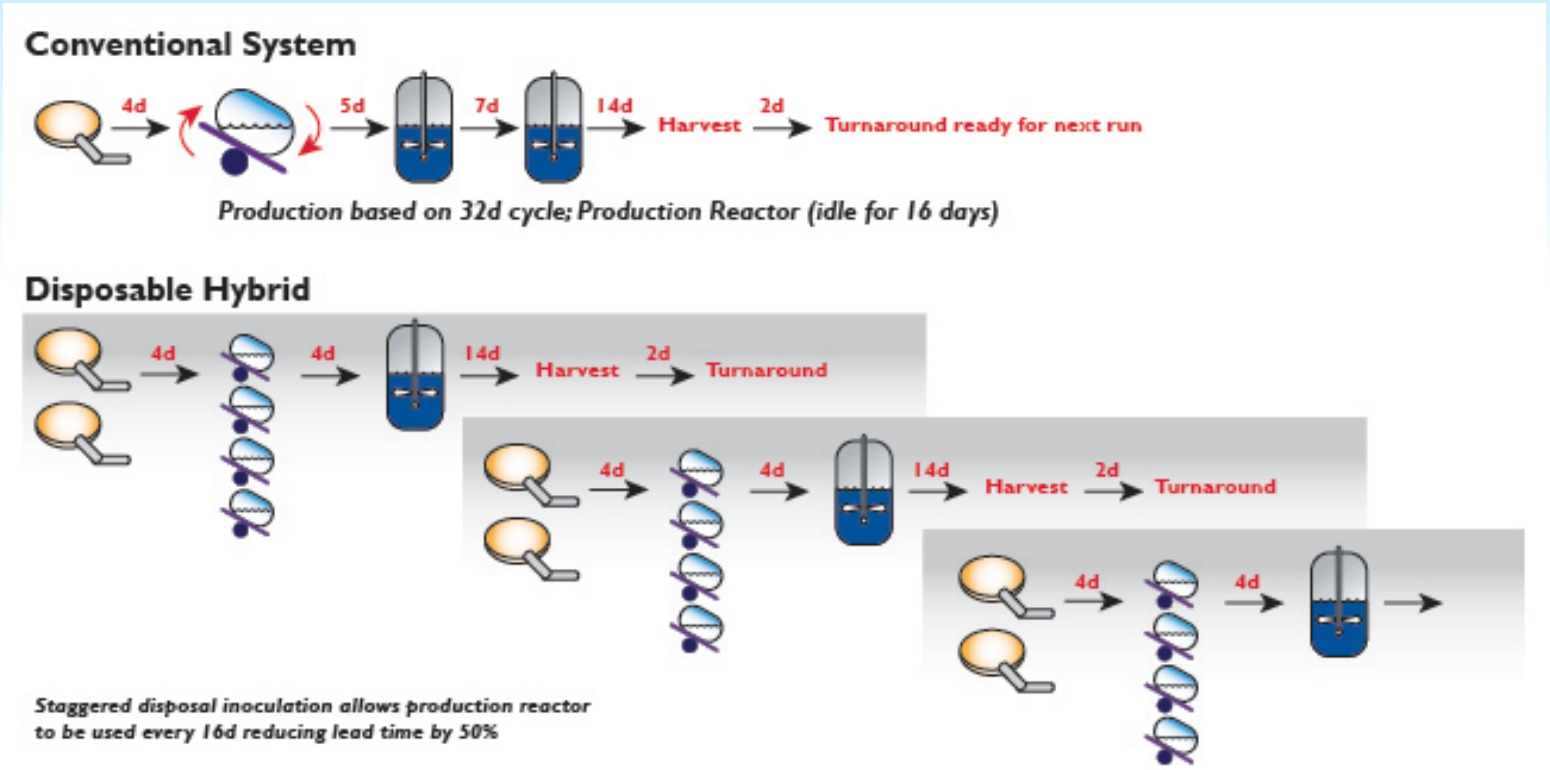
Reduce Process Lead Time

- 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.

Consider Two Scenarios



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Muda, Muda, Muda – 7 Forms of Waste

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

Benefits of the Single –use System for Waste Reduction Upstream/Downstream

- Using integrated platforms for the various unit operations brings the possibility to reduce waste (holding times, cycle time, extra tankage, etc)
  - Over processing waste- unnecessary handling and unit operation activity
  - Transportation waste- raw materials, WIP, product kept to minimum
  - Waiting Holding waste- potential for 50% reduction in start up
  - Motion waste- reduced operator travel
  - Over-resourcing waste- streamlined use of personnel through standardized work flows

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Benefits of the Single-use Systems

- 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
- A disposable strategy may save on detergent clean up and uses connected with high usage of WFI and energy
- 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

Current Sizes and Limitations

- Single-use systems work well up to 250L
- Hybrid systems work well in the 500-2000L
- Media Prep – Used up to 3000L
- Single-use seed cultivation – rocking motion agitation
- Production size STR – often single-use
- Harvesting up to 2000L use disposable depth filters
  - Some single-use centrifuges are becoming available.

DSP – Clinical and Commercial

- UF is disposable up to 100L
- Fluidized bed absorption is a new technology that allows clarification/ capture in a single unit operation
- 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.

DSP – Clinical and Commercial

- Disposable purification is now a reality eg. the OPUS multipurpose system founded by Replies
- 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 in filling 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.

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 bar-coding to identify /trace parts of system.

Other 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

Flex Facility Modular Systems

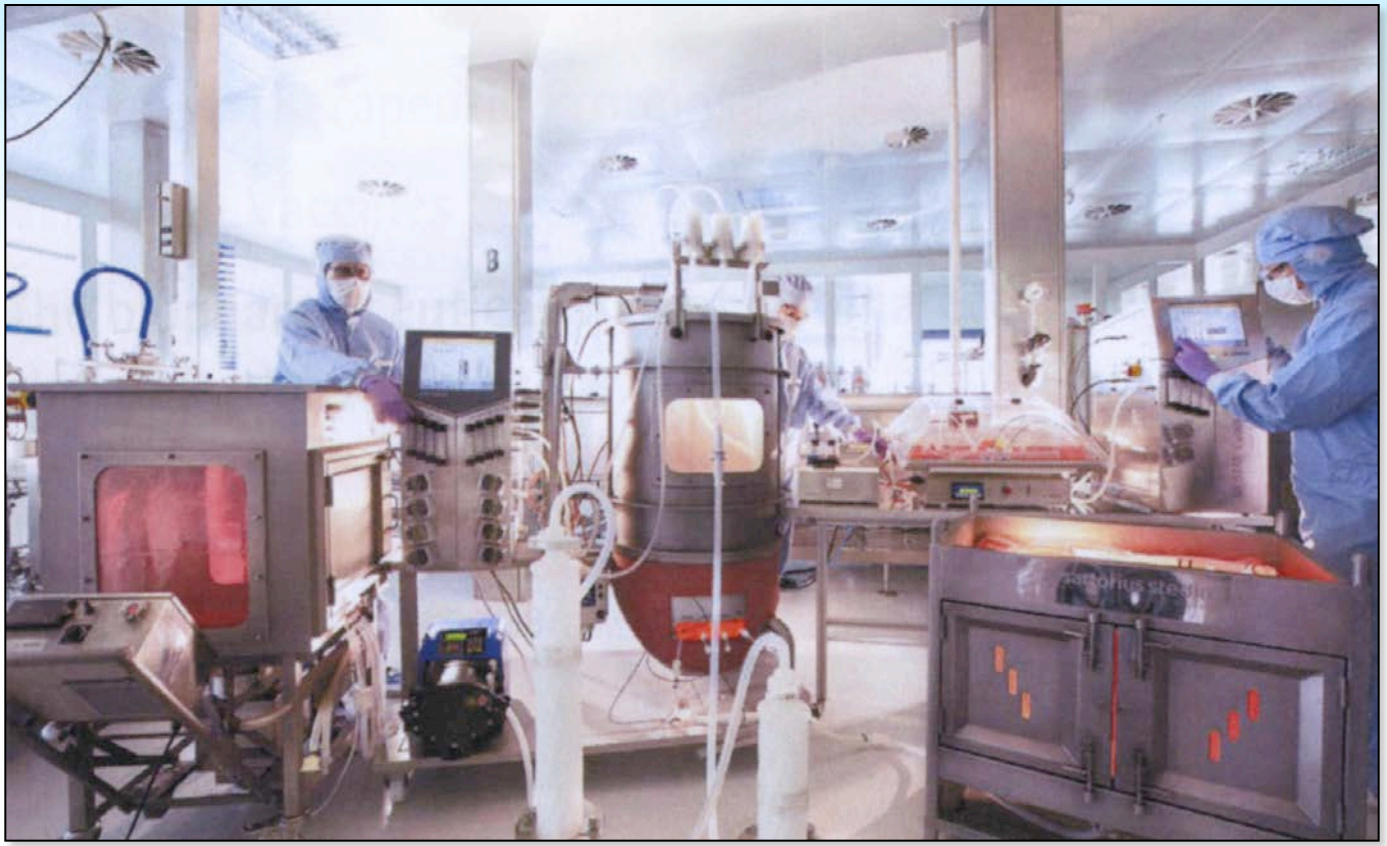
- Using this approach in an open modular facility permits the possibility for multiple manufacturing platforms.
  - Examples: Xcellerex XDR system which they claim can be up and running within a year
  - Wave bioreactor – GE
  - Hyclone's single-use bioreactor
- Turn-around and changeover is simplified 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%.

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; up to 70% faster than conventional validated space.

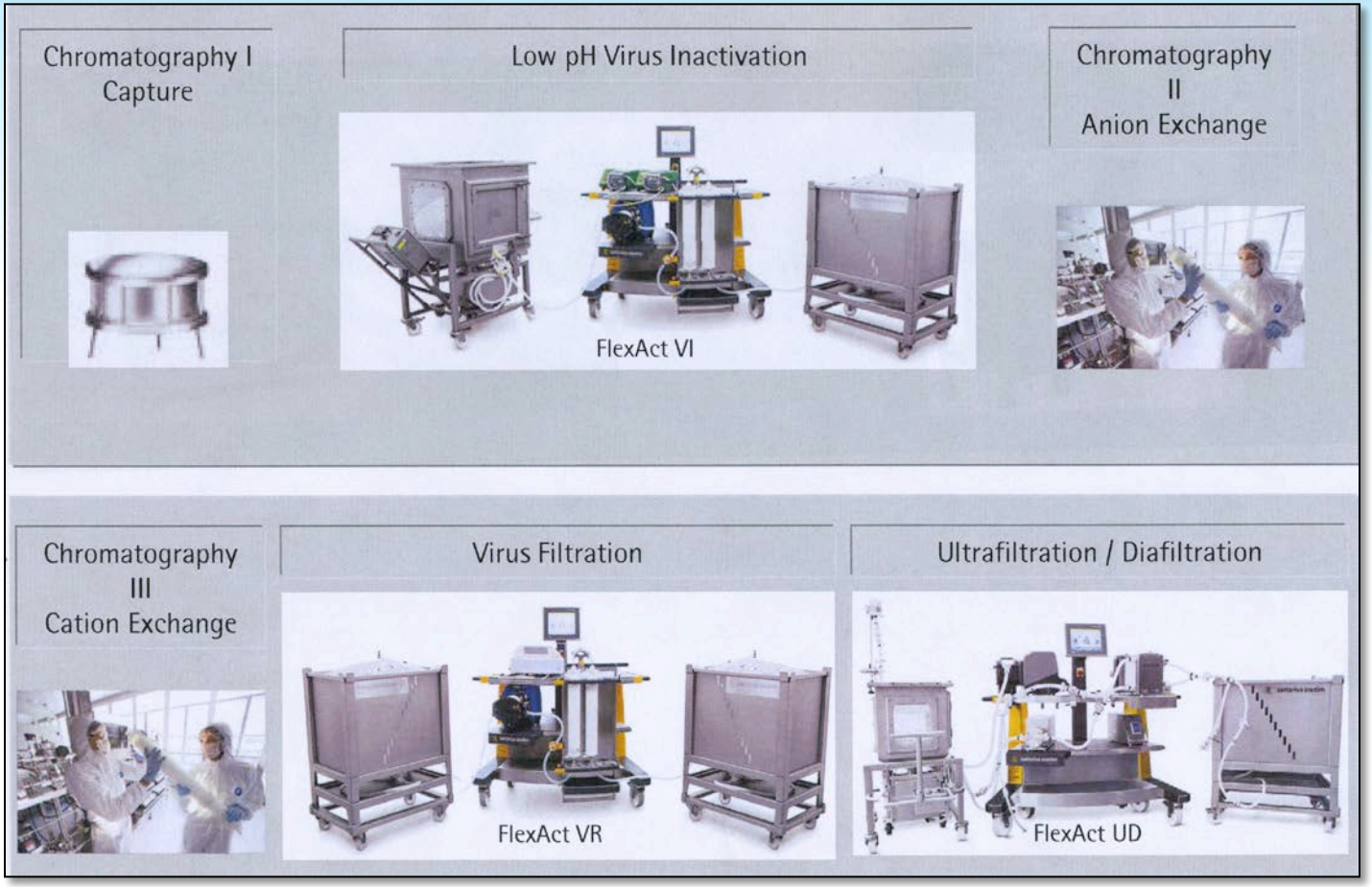
Courtesy of Sartorius Stedim

Modular Disposable Approaches



Courtesy of Sartorius Stedim

Downstream Equipment



Courtesy of Xcellerex

Xcellerex Flex System

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A Few Limitations of Single-use Disposable Systems

- Often there is no high-level process automation
- Require stability studies for gamma irradiated systems and sterilization validation
- Require a Risk Analysis and mitigation strategy prior to cGMP use
- Biocompatibility – testing for leachables and extractables
- For example:
  - USP 87 biological tests in vitro
  - USP 88 biological tests in vivo
  - Bacterial ingress testing
  - Endoloxin testing
  - Chemical compatibility testing
- Mechanical strength tests
  - Elongation, seals, air lead

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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

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.

Thank you for this opportunity to present our ideas.

Questions?

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