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Process Evolution from the Iron Age to the New Age – A Case Study

A Transition from Stainless Steel and Glass to a Fully Disposable Upstream Process During Clinical Development

BIO International
Chicago, 2013

Avid Bioservices – Substantial Experience in both Stainless Steel (SS) and Single Use Stirred-Tank Reactors (SUB)

- Considerable experience in cGMP production
  - Over 200 cGMP lots produced to date
  - Stainless Steel bioreactor production since 1997
  - 1st CMO in the west coast implementing SUB production in 2008
- 1,000 liter scale in both SS and SUB
- Significant experience in regulatory inspections with over 17 successful US FDA and European inspections
- Commercial production in SS reactors since 2005

Customer Perspective:

1. **Prefer Stainless Steel reactor based processes**
2. **Prefer SUB based processes**
3. **Flexible and have no preference**

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The Case for Single Use Technologies

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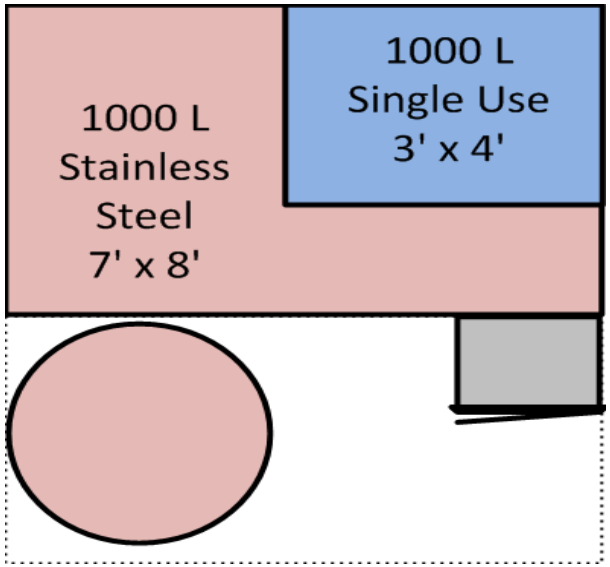
Disposables – Manufacturing Facility Perspective

Lower initial investment cost

- Less manufacturing infrastructure
- Ease of implementation
  - Easy to retrofit into existing facility without building modifications
  - Smaller footprint eases space restrictions
  - Expand capacity through multiple reactors



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Disposables – Process Perspective

- **More efficient production processes**
  - No cleaning validation reduces turnaround time
- **Multi-Product facility risk reduction**
  - Eliminate the potential for product cross contamination
  - Eliminates potential reservoirs for virus contaminations

Everything was going along fine until they discovered their HeLa cell line expressed Y chromosome markers.

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Disposables – Is Avid Just Drinking the Koolaid

- *57.1% of Biomanufacturing Firms to Focus on Scaling up Single Use Systems to Commercial Manufacturing in 2012*
  - *Survey conducted by* Pharma iQ

- The biomanufacturing community is focused on replacing traditional facilities with single-use systems to improve flexibility, efficiency, and savings.

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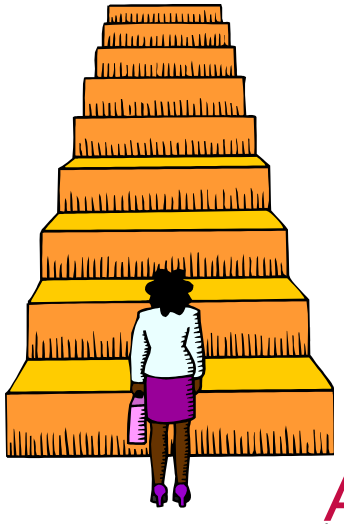
Disposables – OK its Not All a Bed of Roses

- Leachables and Extractables
- Must show process and product comparability when switching from Stainless Steel to Single-Use Bioreactors
- Robustness of plastic bag construction
- Difficulty of growing lipid dependent cell lines
- Dependency on vendors for single-use bioprocess containers
- Limitation in single-use bioreactor size
  - 2000 L largest available



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Solutions to Challenges

Challenges		Solutions
Leachable and Extractable	→	Leachable and Extractable testing performed by manufacturers or contract testing labs
Show process and product comparability when switching from Stainless Steel to Single-Use Bioreactors	→	Successfully demonstrated comparability between Single Use and Stainless Steel processes with the FDA
Robustness of plastic bag construction	→	Single-use bioreactor containers are pressure integrity tested by the manufacturer
Difficulty of growing lipid dependent cell lines	→	Recent data shows feasibility to grow lipid dependent cell lines in Disposable Vessels
Dependency in vendor single-use bioprocess containers	→	Integrated Supply Chain Materials Management System working closely with vendors to maintain inventory for production campaigns SUB = Stainless Steel Bioreactors
Limitation in single-use bioreactor size	→	Process improvement to increase yield; SUB manufacturers are continuing implementing larger vessels Ease of expanding capacity with same process and same SUB size

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Case Study: Client That Required Multiple Process Changes During Clinical Development

- **Phase 1 Clinical Trials (20-100 patient trials)**
  - *Need to move quickly resulting in limited process development*
  - *Result was sub-optimal yields yet adequate to support early development*
- **Phase 2 Clinical Trials (70-250 patient trials)**
  - *Implemented new cell line to improve yields and process potential*
  - *Must maintain product comparability to Phase 1 material*
- **Phase 3 Clinical Trials (500+ patients trials)**
  - *Larger trials require up to multiple kg yields*
  - *Process with improved performance that can be well characterized and validated during phase 3*
  - *Must maintain product comparability to Phase 1/Phase 2 material*

Our Case Study

Process Evolution

- Iron Age
  - Original process – sub-optimal yield (<200 mg/L)
  - Early Iron Age at 300 L
  - Late Iron Age at 1000 L Stainless Steel
- Middle Age
  - Cell line change – Mid Yield (<600 mg/L)
  - Non-disposable inoculum
  - 1000 L Stainless Steel or Single Use Bioreactors
- New Age
  - Optimized medium & process (>2g/liter)
  - Upstream process with new media and feeds
  - Completely disposable inoculum train
  - 1000 L Single Use Bioreactors

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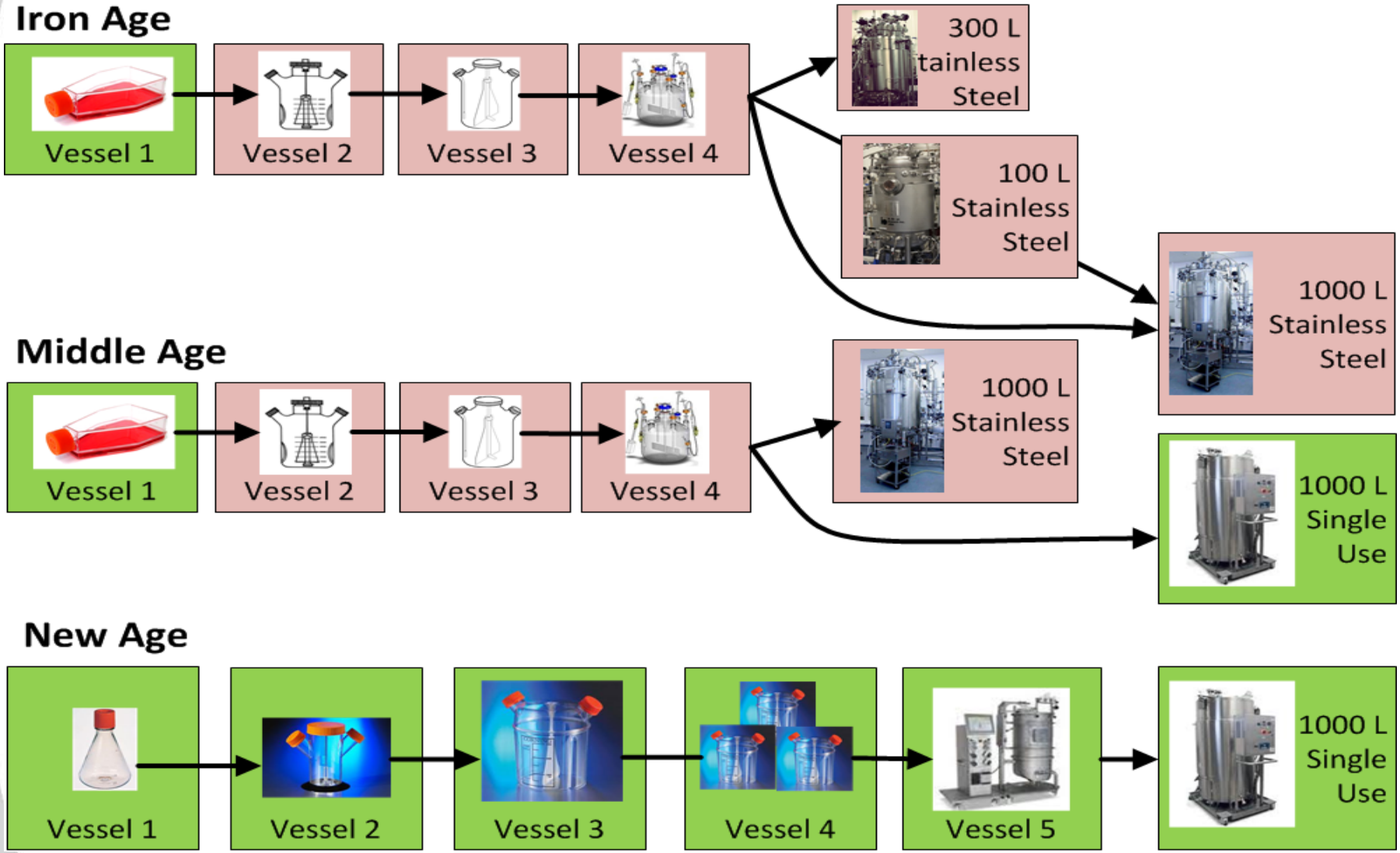
Upstream Process Successfully Transitioned to Completely Disposable Process



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Process Evolution – Regulatory Approach

Iron Age

- Sub-optimal yield
- Early Iron Age (300 L SS)
- Late Iron Age (1000 L SS)

Regulatory Filings

Demonstrate Process Comparability

Demonstrate Product Comparability through Analytical Characterization

Middle Age

- Change of cell line resulted in mid Yield (<600mg/l)
- Non-disposable inoculum
- 1000 L Stainless Steel or Single Use Bioreactors

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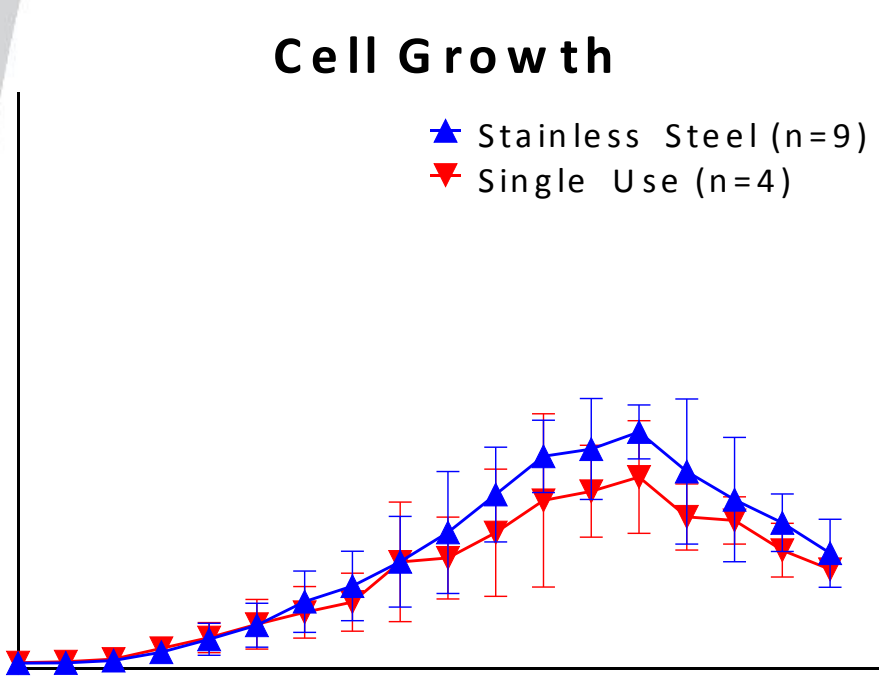
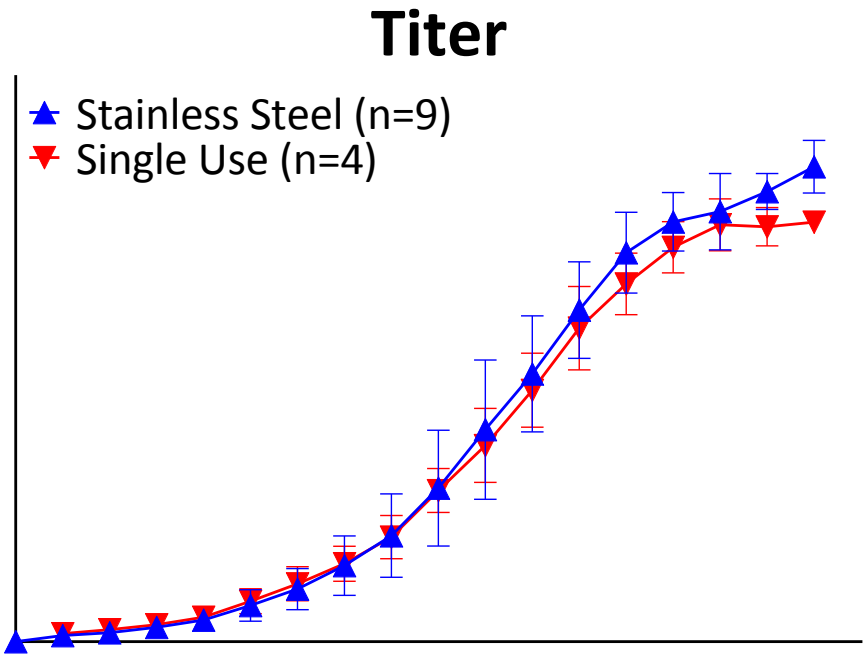
Comparable Upstream Process between 1,000 L SS vs. 1,000 L SUB





- No significant difference in **cell growth or titer**

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Product Comparability Demonstrated

Lot Release		Additional Characterization
✓ Antigen Binding	✓ Peptide Mapping	✓ Analytical Ultracentrifuge
✓ Bioburden	✓ pH	✓ C-terminal Sequencing
✓ Carbohydrate Analysis	✓ Potency	✓ Monosaccharide Composition
✓ Concentration	✓ Residual DNA	✓ Neutral Sugar Assay
✓ Endotoxin	✓ Residual Host Cell Proteins	✓ N-terminal Sequencing
✓ Iso-Electric Focusing		✓ Non-Clinical Pharmacokinetics in Rats
✓ Ion Exchange Chromatography	✓ Residual Protein A	
	✓ SDS-PAGE	
✓ Monomer Content	✓ Visual Inspection	

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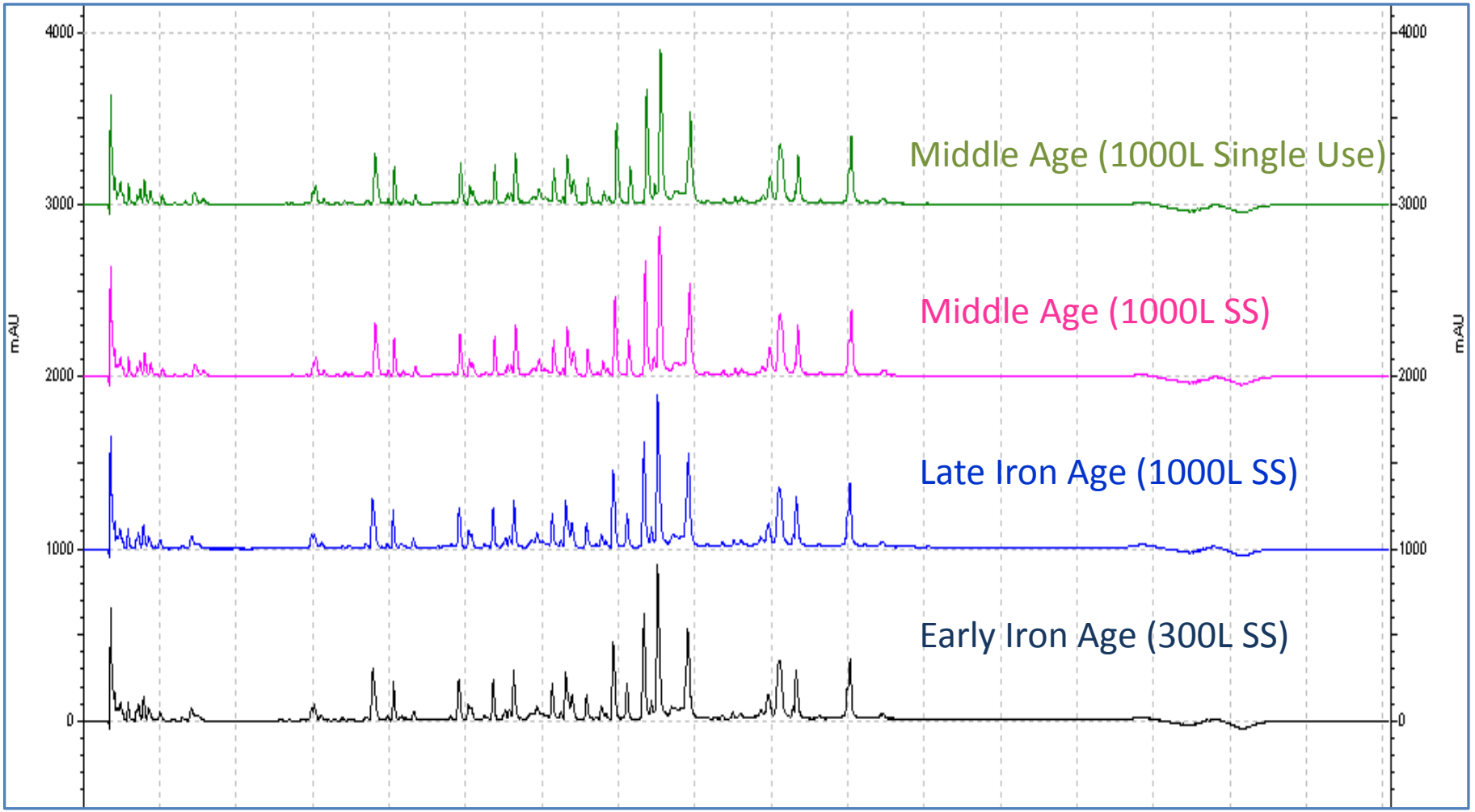
Iron Age to Middle Age: Comparable Product Peptide Map



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Iron Age to Middle Age Comparison

- No significant difference in **Product Quality Attributes**
- **Received FDA approval for:**
  - ***Manufactured product interchangeably in Stainless Steel and Single Use Bioreactor***
  - Post process changes (ie. cell line and downstream process)
- **Provided adequate drug product for several Phase II clinical studies**

Iron Age to Middle Age: Labor comparison

- Turnaround time:
  - Stainless Steel is ~10 days
    - Break down and CIP: 3 days
    - Quality Control testing: 3 days
    - Release for use of next product: 2 days
    - SIP: 1 day
  - Single Use is 1 day
    - None of the above required
- Stainless Steel has considerably higher associated labor costs

Process Evolution – Regulatory Approach

Middle Age

- Change of cell line resulted in mid Yield (<600mg/l)
- Non-disposable inoculum
- 1000 L Stainless Steel or Single Use Bioreactors

Regulatory Filing

Demonstrate Product Comparability

- New Age
  - Optimized medium & process
  - Upstream process with new media and feeds
  - Completely disposable inoculum train
  - 1000 L Single Use Bioreactors

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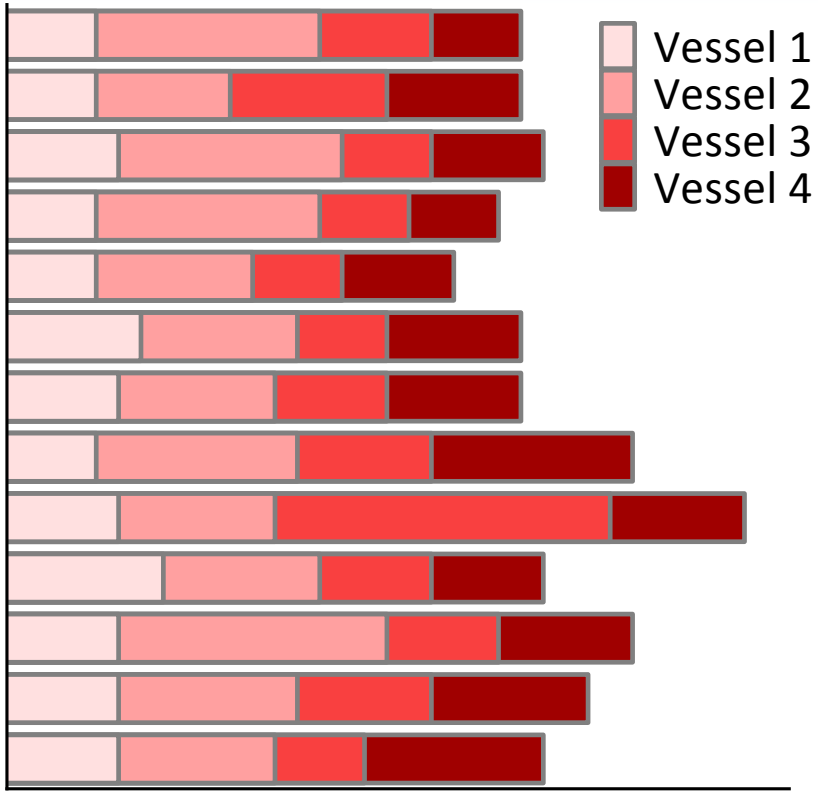
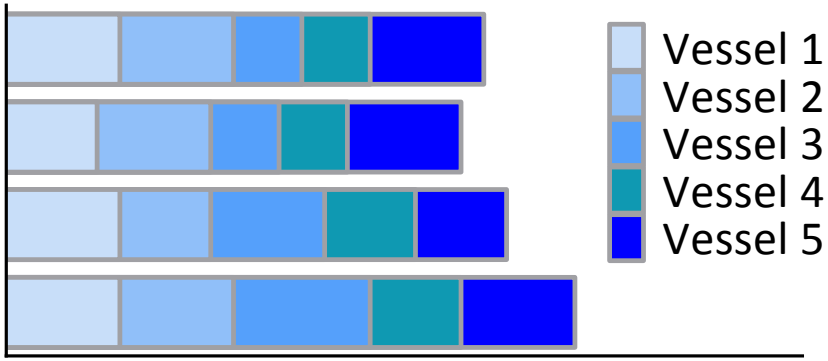
Inoculum Expansion Comparison

Middle Age with Non-Disposable Vessels



New Age with Disposable Vessels



Time in Vessels

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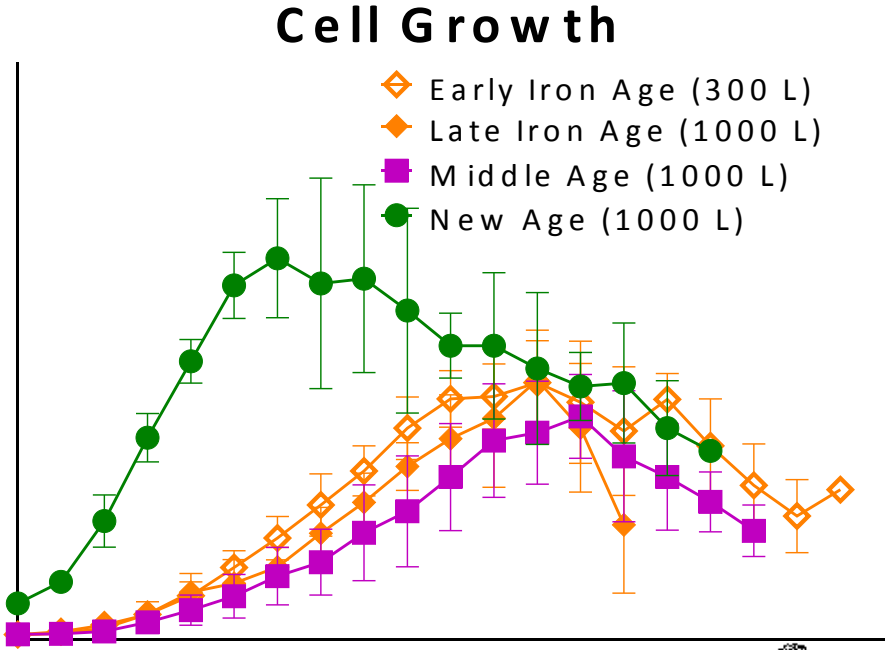
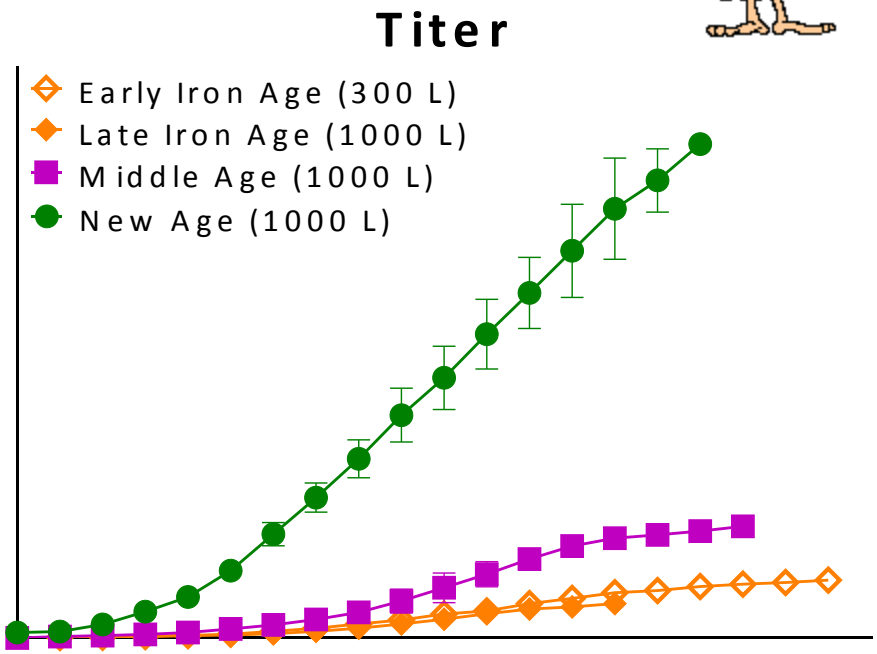
Iron Age to New Age

- **Better cell growth** with New Age Process
- Significantly **increased titer** with New Age Process
- **No impact on Product Quality Attributes**





Product Comparability Demonstrated

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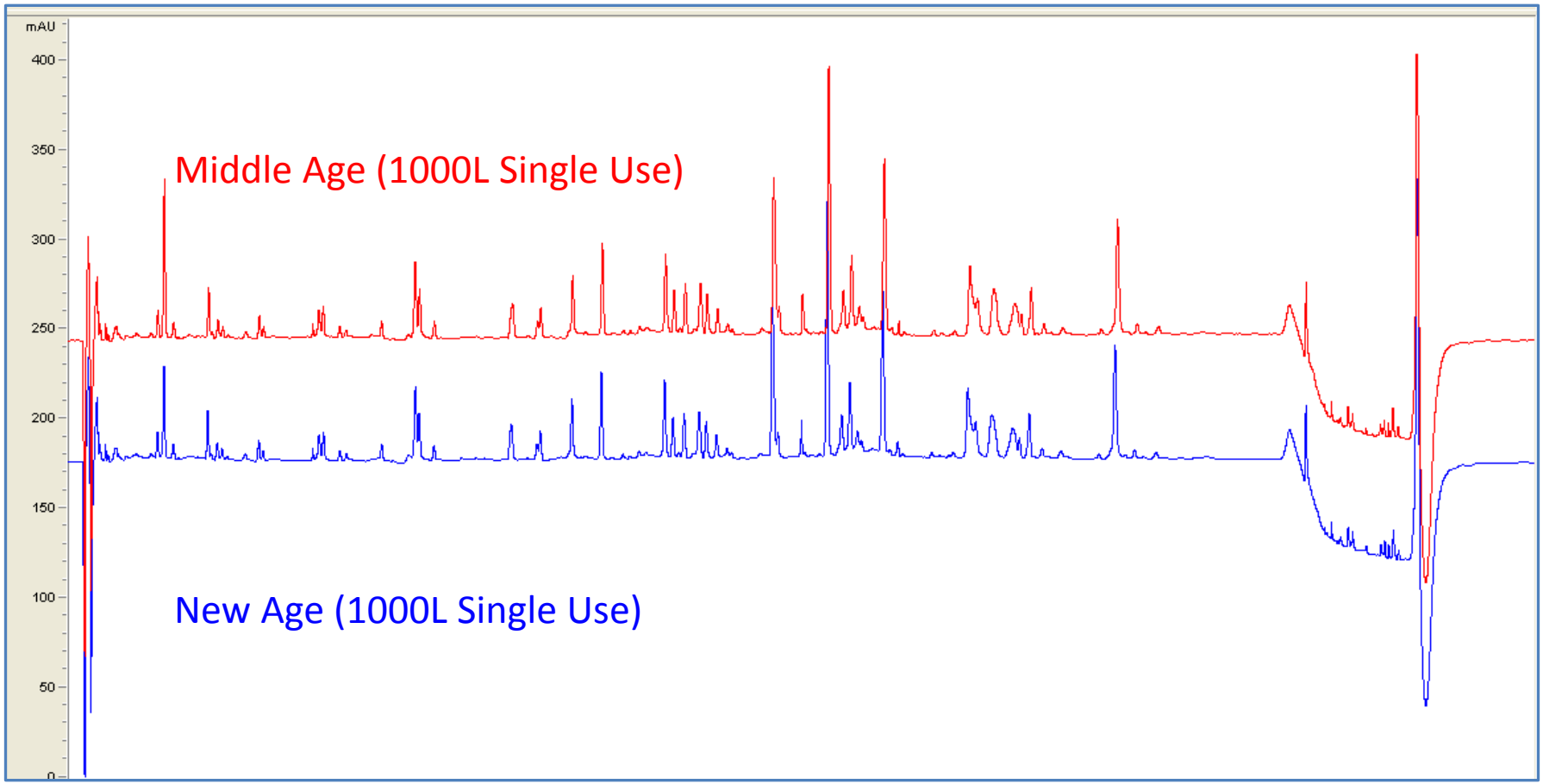
Middle Age to New Age
Product Comparability Peptide Map



Received FDA Approval for Late Stage Development

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Labor: Non-Disposable vs. Disposable Process

Iron Age to Middle Age

- Labor & Overhead Costs for an entire production run at same scale and same process costs ~ ***25-30 % less*** with disposable process

Middle Age to New Age

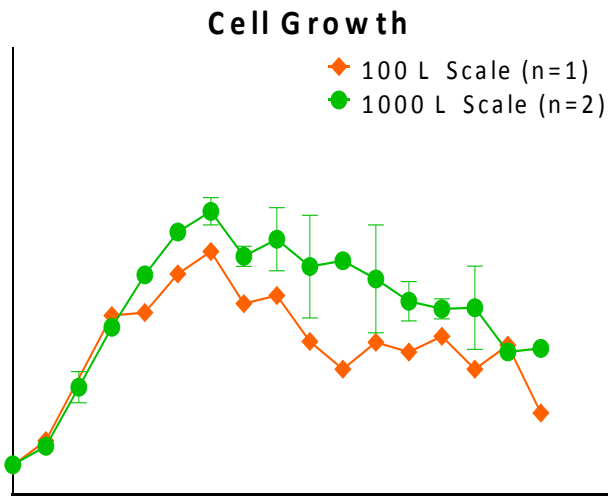
- ***Requires ~35 hours*** for Non-Disposable Inoculum Process
  - Process (clean and autoclave) all spinner flasks for one production run
  - Clean, perform cleaning verification (including testing), assembly, process, and post-use clean
  - Documentation and review of all paperwork

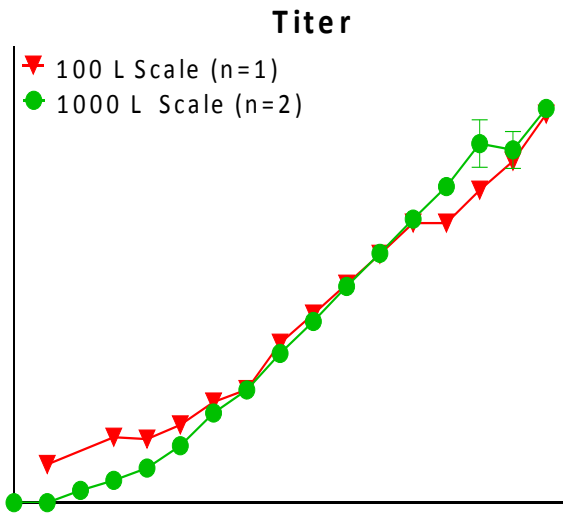
- 3-5 hours of prep time for completely disposable process

Scale-up from Process Development to Full Scale Production: No Problem!

- Aspect ratios and bioreactor parameters are kept constant for all size reactors making scale down verification prior to process transfer makes it easy and representative

Parameter	50L	100L	250L	500L	1000L
Fluid Geometry @ Working Volume (height/diameter) Ratio	1.5	Same	Same	Same	Same
Overall Reactor Geometry (height/diameter) Ratio	1.9	Same	Same	Same	Same
Impeller (quantity X blade count)	1 x 3	Same	Same	Same	Same
Impeller Scaling (impeller diameter/tank diameter)	1/3	Same	Same	Same	Same
Impeller Blade Pitch (angle)	45°	Same	Same	Same	Same
Impeller - Calculated Power Number (N)	2.1	Same	Same	Same	Same
Nominal Agitation Rating - Power/Volume Ratio	0.1 hp/1000 gal (19.7 W/1000 liter)	Same	Same	Same	Same
Agitation Shaft Resolved Angle	19.6°	Same	Same	Same	Same





Summary and Conclusions

- ✓ Single-use processes are transforming Bio-manufacturing and Avid has embraced this new technology early on

- ✓ Avid Bioservices Inc. is leading the way
  - ➢ Through extensive experience and expertise
  - ➢ Active role in making single-use product improvements
  - ➢ In constant communication with manufacturers for up-to-date progress in single-use container characterization and robustness

- ✓ We're setting the trend
  - ➢ Flexible manufacturing scale solutions for all project types
  - ➢ Single-Use fleet consists of 1000 L, 200 L, 100 L and 50 L
  - ➢ Avid has successfully demonstrated comparability between Single Use and Stainless Steel Bioreactors with the FDA

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