

Process Intensification with Disposables

Evaluating the ReadyToProcess™ Concept
The New Generation of Bio-Manufacturing

materials valley

Workshop Rote und Weiße
Biotechnologie

22. April 2010



imagination at work

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Outline

Introduction

Process Intensification in USP

Process Intensification in DSP

News & Outlook

Questions / Discussions



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Why going Disposable?

SECURITY!

- **Containment**
 - Working with toxic or pathogenic products
 - Contamination protection
- **Sterility**
 - Bioburden control
 - Sterile processing needed
- **Traceability**
 - Unique equipment
 - Avoid cross contamination

COST!

- Capital Investment
- Clean Room area / level
- Utility need
 - Clean Steam
 - WFI
 - CIP
- Working Hours



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FLEXIBILITY!

- Deployment of new manufacturing capacity
 - Delivery time of equipment
 - Cleaning / Sterilization validation
 - Last minute changes in process design
- Change over time
 - Installation and preparation
 - Cleaning and Sterilization
 - Verification and testing
 - Documentation
- Lot to Lot variation
 - Changes in volume, titer or contamination



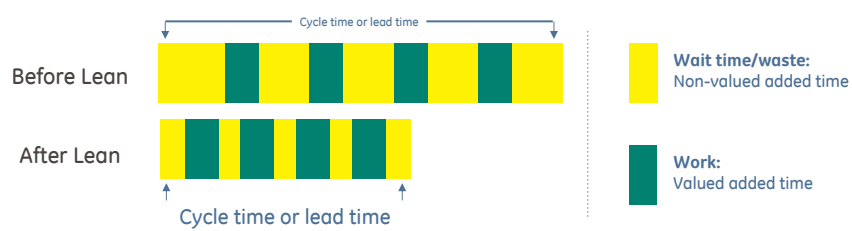
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Process Intensification?

Lean!

Lean is the relentless pursuit of the perfect process through waste elimination



LEAN helps achieve operational efficiencies by:

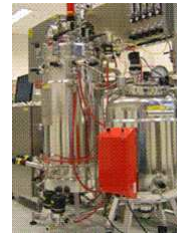
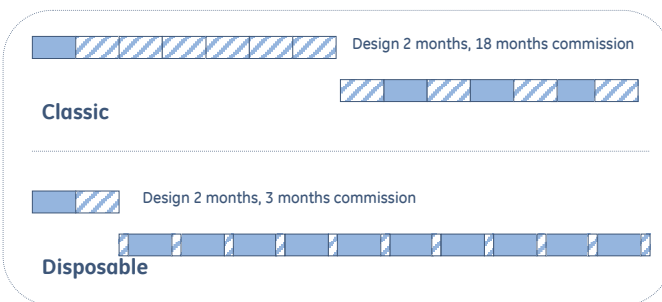
- ▶ Reducing change-over times
- ▶ Rapid transfer from lab to commercialization
- ▶ Reducing setup times and cycle times
- ▶ Improving work, people, and material flow
- ▶ Improving facility throughput

Process Intensification in USP



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Process Intensification in USP



Classic

Cost: equipment \$750k - \$1M

Time: 18-24 months to start, 1-2 weeks downtimes for cleaning

ReadyToProcess

Cost: equipment \$250k

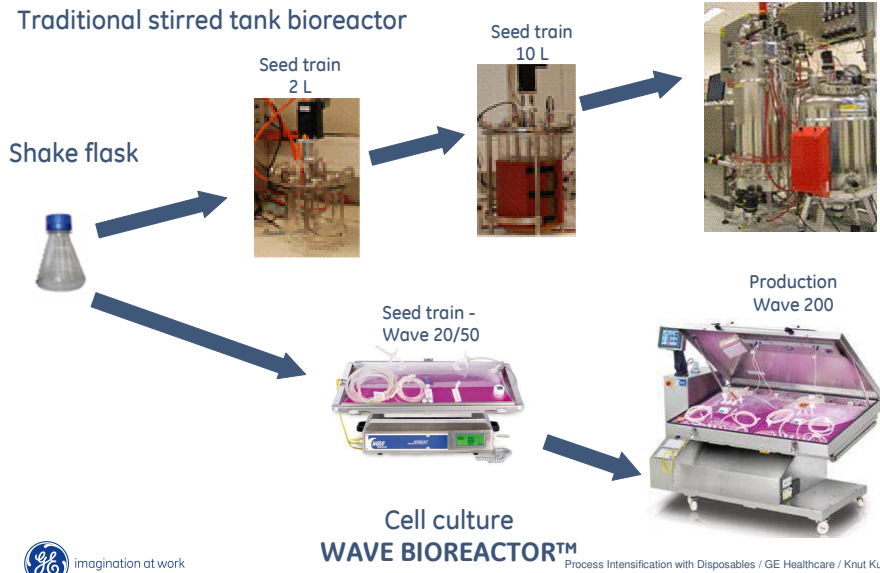
Time: 1-2 months to start, 1-2 hours downtime



- Value adding work
- Non-value adding work

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Process Intensification in USP



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Process Intensification in USP

Comparison 2 Liter Batch

Working & waiting time	Glass Bioreactor	WAVE
Setup	0.5	0.5
Sterilization	3.0	0.0
Sterility test	12	0.0
Decontamination	3.0	0.0
Cleaning	0.5	0.0
Σ per Batch	19.0h	0.5h

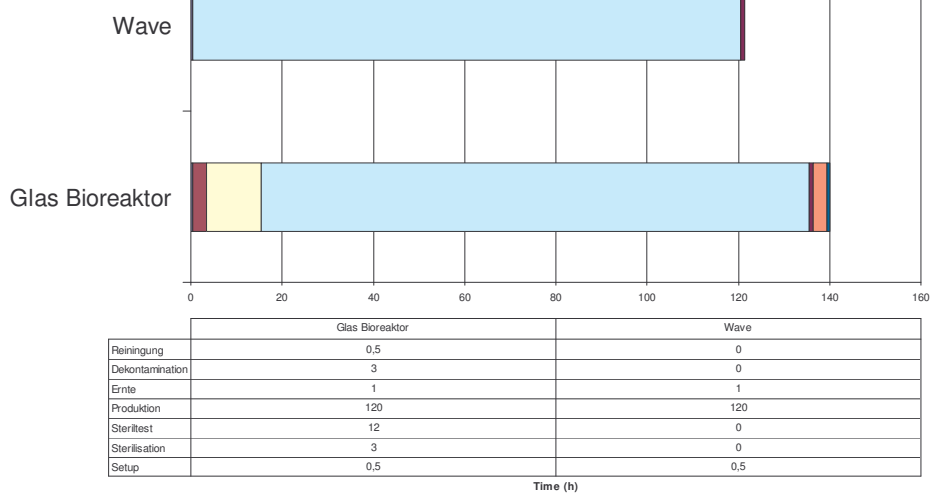
Difference per Batch: 18,5h

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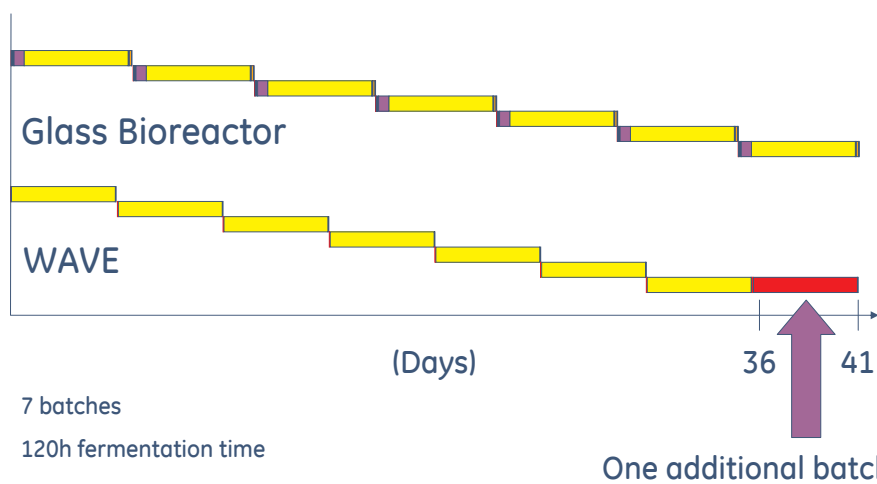


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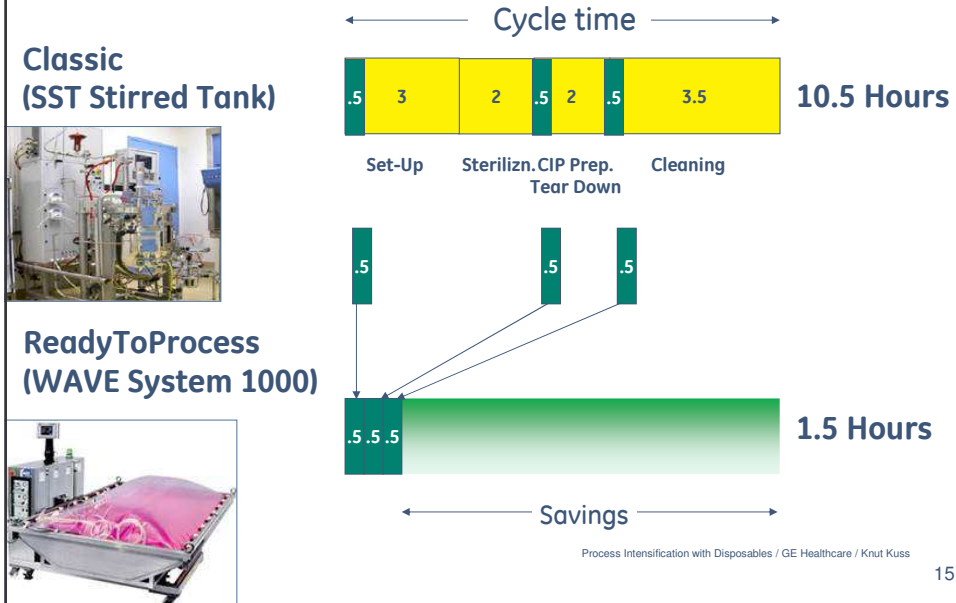


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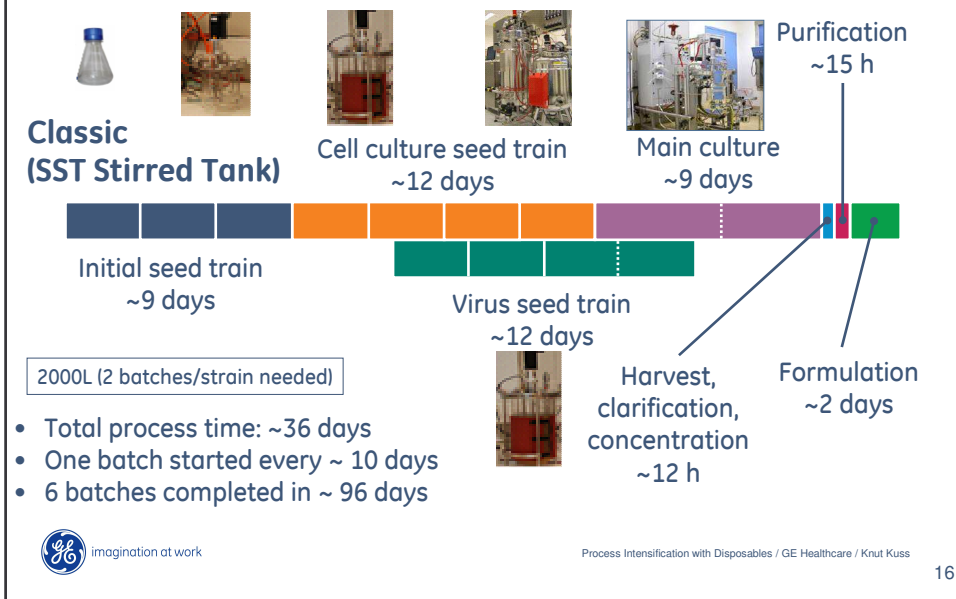
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Process Intensification in USP



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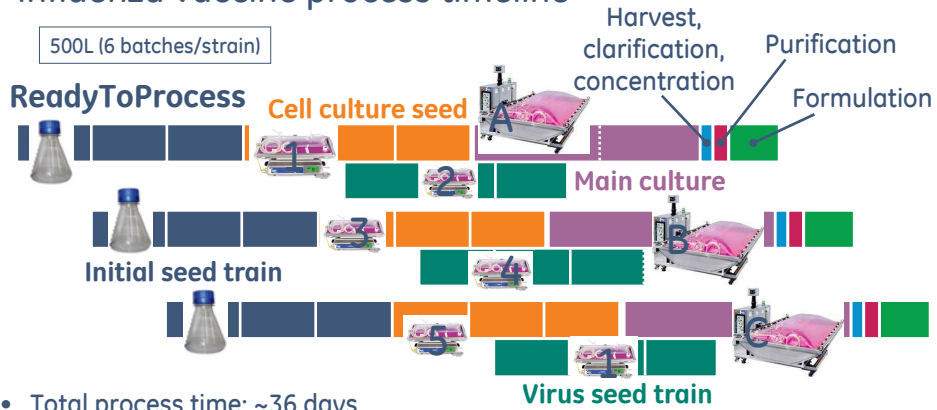
Process Intensification in USP



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Process Intensification in USP

Influenza vaccine process timeline



- Total process time: ~36 days
- One batch started every ~ 3 days
- 18 batches completed in ~ 90 days



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Process Intensification in DSP




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Process Intensification in DSP


ÄKTApilot




AxiChrom columns

ÄKTAReady system

Exchangeable Flow path



Pre-packed Pre-qualified Pre-sanitized
ReadyToProcess columns
1 L, 2.5 L, 10 L and 20 L

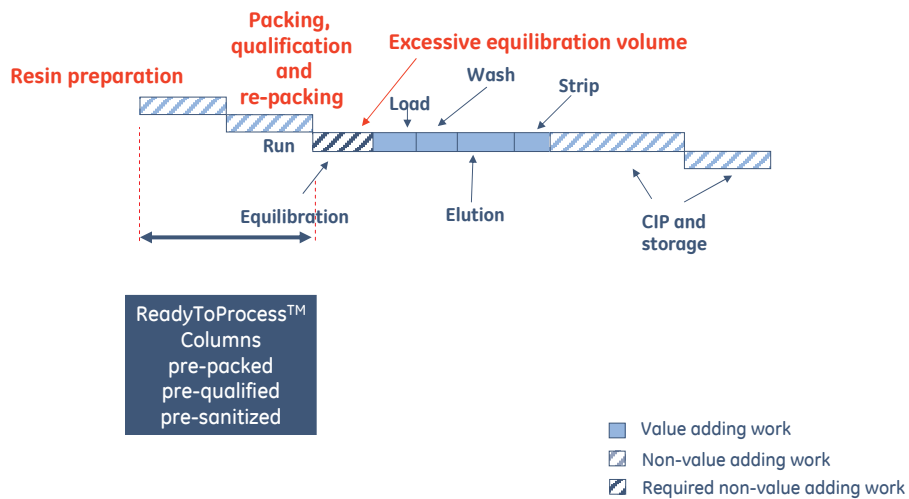


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Process Intensification in DSP



Setup of conventional vs. ready-to-use chromatography columns and system

Preparing and cleaning a system. For conventional equipment, the total time needed to clean a system is 6-7 man days.

Timing	Activity	Estimated time needed	Comment	Step eliminated in a single use process
Before use of new equipment	Produce cleaning protocol	1 day		✓
Before start of a campaign	Campaign equipment rationale	0.5 day	Includes QA review	✗
Before start of a campaign	Equipment set up	0.5 day		✗
Before start of a campaign	Cleaning before use	0.5 day	Includes preparation of CIP solutions	✓
During a campaign	Cleaning in between lots	1 day		✗
After a campaign	Preparation of sampling	1-2 hours	Training in protocol, wash of sampling glasses	✓
After a campaign	Cleaning after use	0.5 day		✓
After a campaign	Rinse sampling, drain of system and swab sampling	1 day	Includes preparation of CIP solutions	✓
After a campaign	QC assays	0.5-1 day	Two persons half a day	✓
After a campaign	Cleaning report	1 hour	Includes review	✓

The equipment is not ready for use in another production campaign until the results from the post-campaign cleaning are approved, which is at least 5 facility days after CIP and sampling is done.



Preparing and cleaning a column. For conventional, the total time needed to clean a column is 5-6 man days

Timing	Activity	Estimated time needed	Comment	Step eliminated in a single use process
Before use of new equipment	Produce cleaning protocol	1 day	Only for new equipment. The cleaning protocol is reused	✓
Before start of a campaign	Campaign equipment rationale	0.5 day	Includes QA review	✗
Before start of a campaign	Equipment set up	0.5 day		✓
Before start of a campaign	Cleaning before use	0.5 day	Includes preparation of CIP solutions	✓
Before start of a campaign	Column packing and HETP test	1 day	Includes preparation of packing and HETP solutions	✓
During a campaign	Cleaning in between lots	0.5 day		✗
After a campaign	Preparation of sampling	1-2 hours		✓
After a campaign	Column unpacking, exchange of spare parts etc.	1 day	Two persons half a day	✓
After a campaign	Cleaning after use and sampling after use	1 day	Two persons half a day, includes preparation of CIP solutions	✗ (Column can be cleaned and stored until batch release)
After a campaign	QC assays	0.5-1 day	Actual depends on if assays for several instruments are run at the same time	✓
After a campaign	Cleaning report	1 hour	Includes review	✓

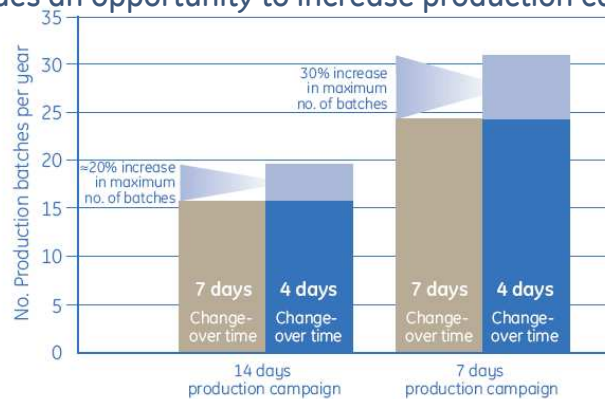
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Note: in this study specific time and costs for preparation of CIP solutions are considered negligible in relation to facility costs.

Process Intensification in DSP

Removing time-consuming steps with single-use products provides an opportunity to increase production capacity.

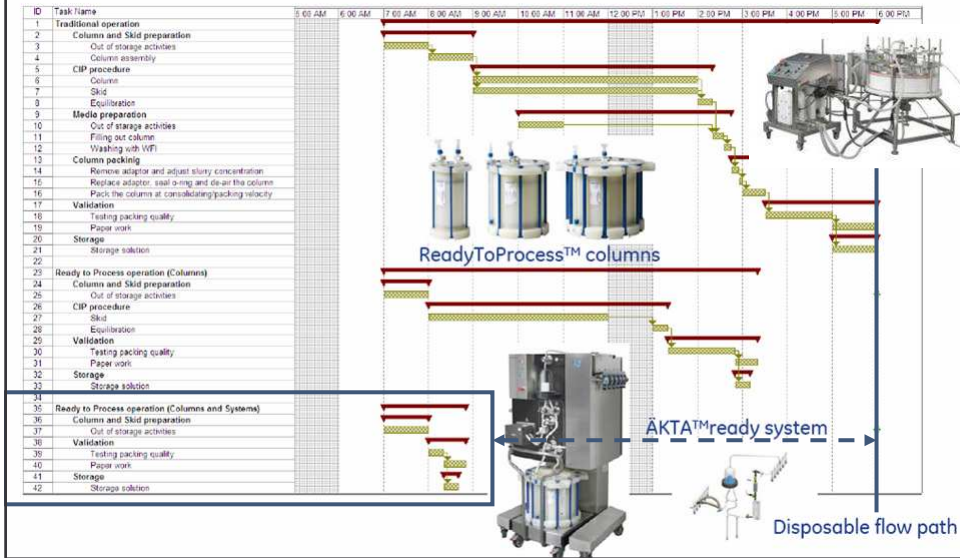


Estimated increase in the number of batches in a 14-day and 7-day production campaign schedule with single-use products for a facility with a 49-week production schedule (3 weeks allocated to maintenance and calibration).



Process Intensification in DSP

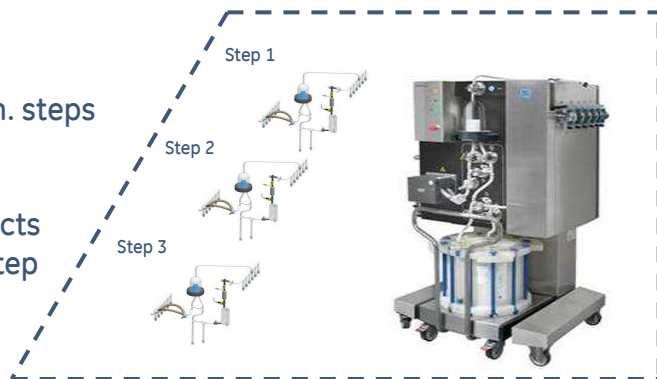
6-Fold Reduction in Set-up Time with ReadyToProcess Chromatography



Process Intensification in DSP

Number of chromatography systems can be reduced with ReadyToProcess!

One system:
different chrom. steps
same product
or
different products
same chrom. step



Process Intensification in DSP

UF/DF Cross Flow Filtration

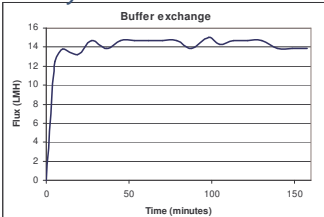
FILTER	SIZE	VOL TO AREA	Lpm
R	1200 - 2000	RATIO (L/SqM)	2000-12000
P	2800 - 4800	50 - 80	2.1 - 12.0
WPU (PUMP)	Process Intensity		
(RPM MAX)	TUBE ID x WALL	Lpm MAX	PSIG MAX
P20 (P25)	1/2" x 1/8"	11	20
P20 (P20)	1/2" x 3/16"	13	25

LARGE SYSTEM - CONC/CLARIF ONLY
 10L OFF RESERVOIR - SIZE 5 OR 6 FILTER
 MM 650 PUMP - 1/2" ID PUMP TUBING (1/8" WALL)
 1/2" ID PUMP TUBING (1/8" WALL)
 TC (PERMEATE WASTE) - 1/2" HIGH PR
 PRESSURE SENSORS (2) - 1/2"
 JUMPER (1" OR 3") - 1/2" HIGH PR VENT

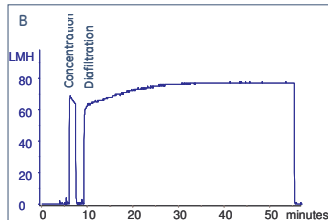
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Process Intensification in DSP

ReadyToProcess HF



Kvick Lab



Membrane format	ReadyToProcess HF	Cassette
Diafiltration factor	6	6.5
dP (bar)	1.0	1.6
TMP (bar)	1.0	0.8
Permeate capacity (L/m ²)	48	55
Load (g/m ²)	116	275
Yield (%)	98	98
Average flux (LMH)	14	73
Filtration time (minutes)	160	50
Start aggregate level (%)	10	12
End aggregate level (%)	10	12

Kvick Lab Cassette 3 * 0.11 m², 30 kDa
 ReadyToProcess Hollow Fiber
 0.48 m², 30 kDa, 60 cm length, 0.5 mm lumen id

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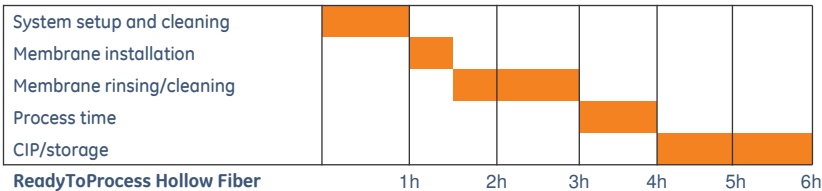
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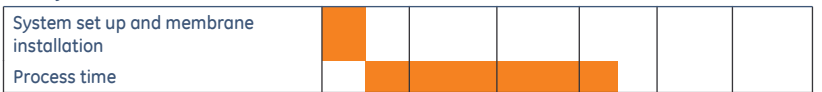
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Buffer exchange cassettes vs. ReadyToProcess HF

Traditional cassettes



ReadyToProcess Hollow Fiber



Reduced overall process time with 40% using ReadyToProcess™



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Process Intensification in DSP

Example 100L Mab process:

Process step	ReadyToProcess™	Traditional
Capture*	8 h	17 h
Buffer exchange	3.5 h	6 h
Polishing**	5 h	14 h
Formulation	4.5 h	6.5 h
Total time	21 h	43.5 h

* Two cycles including preparations

** One cycle including preparations

50% reduction in process time

ASME conference 2008, Poster, GE Healthcare, CMC biologics
ReadyToProcess increases facility capacity and shortens change-over time

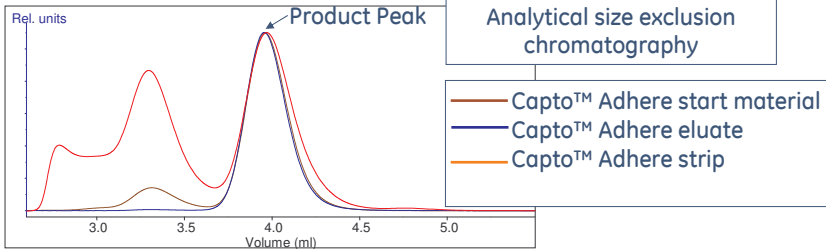


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Summary – Mab process



Yield:

Traditional run: 81%

ReadyToProcess™ run: 81%

Analysis	ReadyToProcess™	Traditional
Start aggregates	10%	12%
Final aggregates	0.4%	0.6%
Final HCP	1.0 ppm	1.3 ppm
Final ligand leakage	0.13 ppm	0.04 ppm



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News, Outlook & Challenges



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Environmental assessment

GE Healthcare

Environmental life cycle assessment of disposable bioreactors

Requirements:
 Biopharmaceutical manufacturing industry seeks speed, simplicity, safety, and environmental performance.
Speed: Ready for immediate use, enabling efficient change over
Simplicity: Reduced plug and tear operations, no cleaning
Safety: Sterile aseptic design, Single Use prevents cross-contamination.

Environmental: Reduce energy and water consumption, Net environmental life cycle benefit.

Measurement:
 Environmental Life Cycle Assessment (LCA)
 Assess overall environmental impact throughout product life cycle:
 • Energy consumption
 • Water consumption
 • CO₂ emissions
 • Ozone depletion
 • Surface toxicity
 • Surrogate energy equivalent
 • Eutrophication
 • Acid equivalent

Analyze and interpret:
 Conventional bioreactor system
 WAVE disposable bioreactor system

Control:
 Environmental LCA tools provide detailed insight about the net environmental performance of complex product systems. This helps our customers better understand the environmental performance and trade-offs of manufacturing equipment options, thereby helping them to better meet their environmental performance goals. This guide our product designers and engineers as they continuously improve the operational and environmental performance of our product offerings. Additional LCA studies are underway at GE Global Research to assess a broader range of GE Healthcare's Respi/TissueX products.

Acknowledgment:
 Heggi Hölster
 Graduate Student, TUM University

10 X Cost Savings

GE Global Research
 Ecosystems Center of Excellence

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Mixing and homogenization in a Bag

Figure 5: Effect of recirculation flow rate on mixing in a 20 liter bag with a stratified high viscosity solution with inlet & outlet on bottom of bag

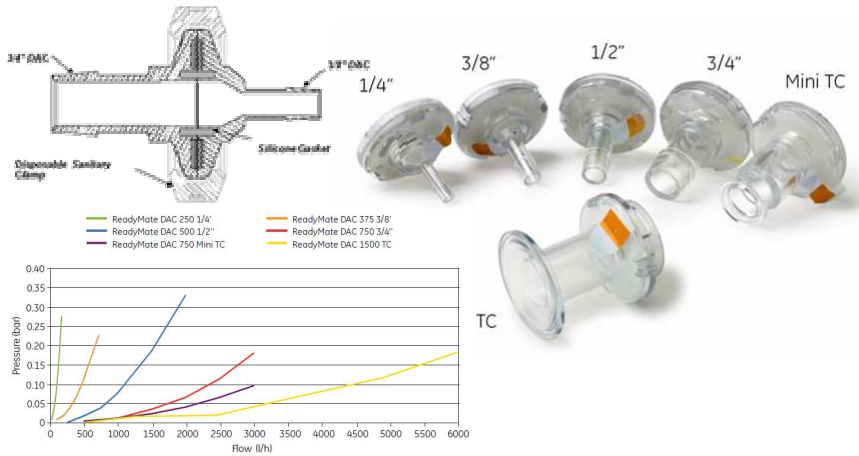
flow rate [L min ⁻¹]	time to homogenize [min]	mixing time [min]
1.0	~3.0	~3.0
1.5	~3.0	~2.5
2.0	~3.0	~2.0
2.5	~3.0	~1.8
3.0	~3.0	~1.5
3.5	~4.5	~1.2
4.0	~8.0	~1.0
4.5	~9.0	~1.0
5.0	~9.5	~1.0

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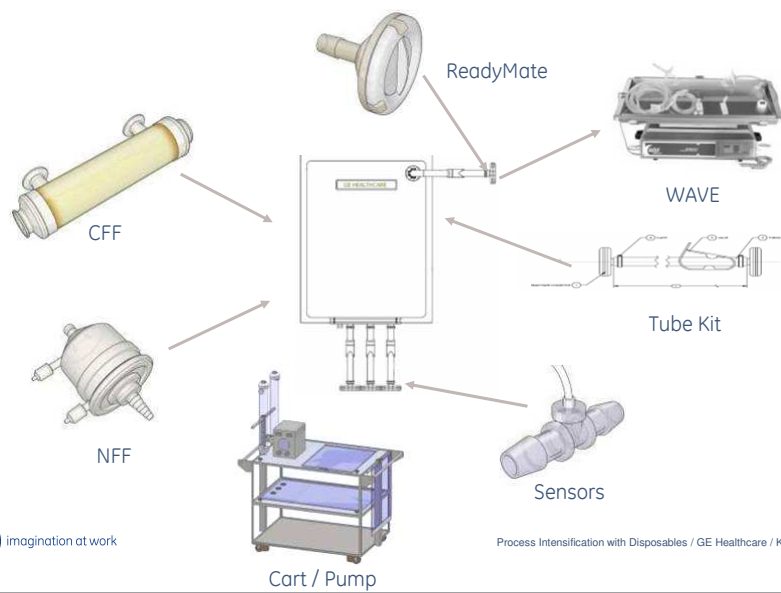
Connectivity

ReadyMate™ Disposable Aseptic Connectors



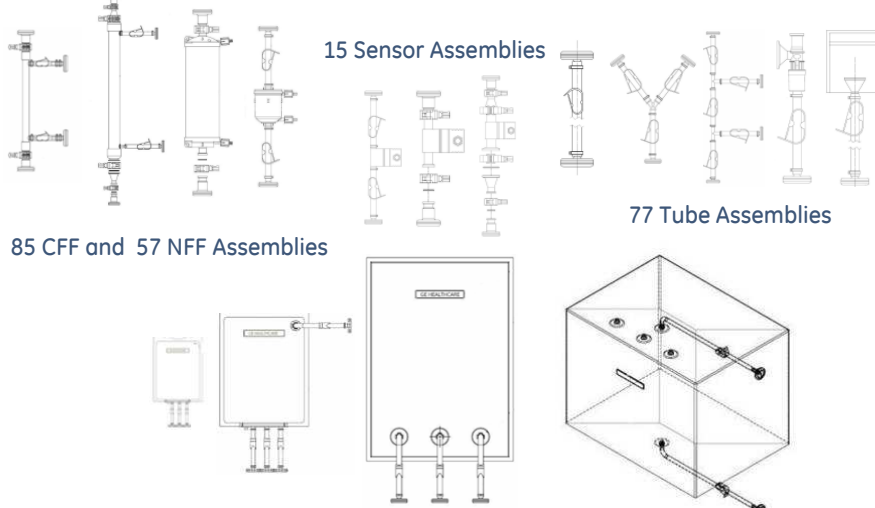
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ReadyCircuits



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250 Standard ReadyCircuit Sub Assemblies – Design Your Own



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16 Bag Assemblies from 250 ml to 200L

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GE's Configuration Tool On-Line. User designs a Circuit and gets a

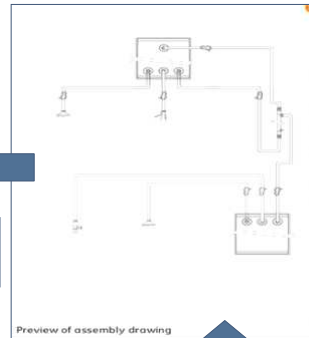
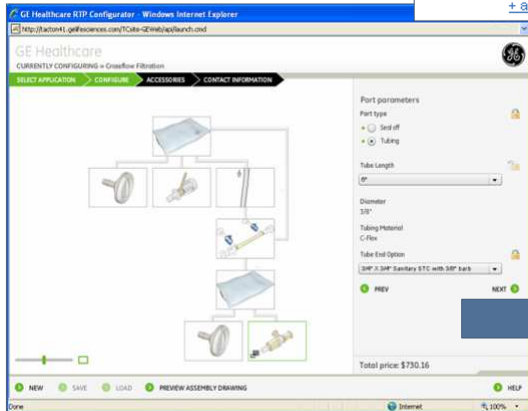
- drawing,
- BOM &
- price

Available Q2 2010

\$1,375.00



+ add to hot list



Preview of assembly drawing

GE Healthcare

Bill of material

Ready To Process

Qty	Part Number	Description
1	20 Liter Filter Bag upto 3 ports	20 Liter Filter Bag upto 3 ports
1	unknown	Resizable DAC with 3/8" barb
1	unknown	3/8" ID x 3/8" OD C-Flu 3/4 tubing
1	unknown	Male (Coupling) Inlet MPC Connector with 1/4" barb
1	unknown	1/4" ID x 3/8" OD C-Flu 3/4 tubing
1	unknown	1/4" ID x 3/8" OD C-Flu 3/4 tubing
1	98-4110-33	RTPLP#98-4110-33
1	10 Liter Filter Bag upto 3 ports	10 Liter Filter Bag upto 3 ports off 200%
1	unknown	Male Luer with 1/4" barb
1	unknown	1/4" ID x 3/8" OD C-Flu 3/4 tubing

Total Price: \$1730.16

Prices shown in this document are estimates only. Volume discounts are available.

“Disposable” Hardware ReadyKart



ReadyKart with
CFF ReadyCircuit



ReadyKart with WAVE

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“Disposable” Hardware ReadyKart



ReadyKart Mab Process



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“Disposable” Hardware ReadyKart

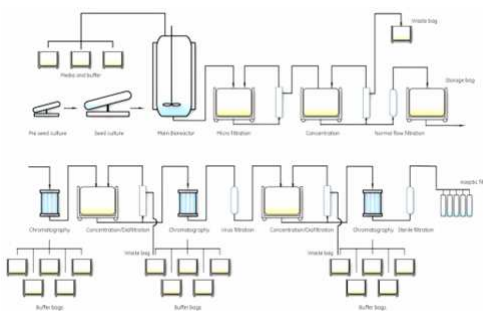


ReadyKart



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Vision: Driving Towards a ReadyToProcess™ Factory



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Questions?



www.filterbrain.com



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