Single-use technology in downstream unit operations

ÄKTA™ ready chromatography system and more

Madhu Raghunathan, Bioprocess capability days, Boston

Imagination at work
Presentation outline

Introduction
GE’s single-use portfolio across the bioprocess spectrum
Why consider single-use in your downstream process?

Case study
ÄKTA™ ready: maximizing uptime through single-use technology
ReadyToProcess™ chromatography columns
ReadyToProcess Adsorber membranes

Conclusions
Biomanufacturing is moving towards single-use technologies

Single-use technologies enable flexible and efficient bioprocesses

Compared with traditional stainless steel technology, single-use offers:

• Minimized risk for cross-contamination and reduced time spent on cleaning and sanitization

• Improved turnaround time between batches or products and maximized uptime
GE’s single-use portfolio across the bioprocess spectrum
Medium preparation:
Xcellerex™ XDUO 100 to 2500 L mixers, HyClone™
cell culture media

Buffer preparation:
Xcellerex XDUO 100 to 2500 L mixers, HyClone buffers and process liquids

Cell culture seed train
ReadyToProcess WAVE™ 25 system
Xcellerex XDR 200 L bioreactor
Xcellerex XDR 500 L bioreactor

Cell culture production
Xcellerex XDR 2000 L bioreactor
ReadyToProcess™ filter for CFF

Harvest operations
FlexFactory™ harvest
BioProcess™ NFF Pump System

Virus reduction
Xcellerex XDUO mixers

Purification operations
ÄKTA™ ready system
ReadyToProcess chromatography column
ReadyToProcess Adsorber membranes
ReadyToProcess filter for CFF

Virus filtration
FlexFactory viral clearance
BioProcess NFF Pump System

Bulk formulation and sterile filtration
Bulk fill equipment

Fluid management
ReadyToProcess portfolio
ReadyCircuit™ bag and filter assemblies
ReadyToProcess bins and ReadyCircuit bags
ReadyMate™ aseptic connectors

Fast Trak Services
Process development
Bridge Manufacturing Services
Training and education

CFF = crossflow filtration, NFF = normal flow filtration, UF/DF = ultrafiltration/diafiltration

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Pioneers in downstream single-use technology

ÄKTA™ ready—the first single-use chromatography system

ReadyToProcess™ chromatography columns—the first prepacked columns

Today, number one supplier of single-use chromatography systems and continuously expanding our single-use portfolio

1 According to 7th Annual Single Use Solutions Survey, Aspen Brook, Feb 2015
A continuously expanding single-use offering: the ReadyToProcess™ downstream portfolio

- ÄKTA™ ready chromatography system with a disposable flow-path
- Prepacked ReadyToProcess columns
- ReadyToProcess Adsorber membranes and prefilters
- ReadyCircuit™ sterile assemblies and ReadyMate™ aseptic connectors for simple aseptic connectivity and bioburden control
- Premade buffers
- Bags and bins for sample, buffer, and waste handling
Why consider single-use in your downstream process?
Shorter time to market and CAPEX savings

Less complex installations

Reduced time spent on procurement, sourcing qualification, and validation

Smaller tank farms and reduced utility requirements (WFI and alkali)

CAPEX = capital expenditure, WFI = water for injection
Less clean room space resulting in lower utility requirements and smaller footprint

DSP = downstream processing, Equip. prep. Equipment preparation, Inoc./Prep. = inoculation/preparation
Increased operational efficiency through reduction in labor

- Eliminated cleaning and sanitization in place (CIP, SIP) and related cleaning validation
- Ten-fold reduction in system set-up time with single-use flow paths and prepacked columns

* Some activities may be performed in parallel with the CIP procedure.
Intensifying downstream processes with hybrid solutions

Integrating single-use into existing facilities

Example 1

Single-use chromatography combined with conventional chromatography columns

Example 2

Conventional chromatography system and prepacked chromatography columns
Points to consider before implementing single-use technology

- Quality assurance
- Security of supply
- Qualification strategy
- Validation master plan
- Vendor agreements, support, and documentation:
  - Regulatory compliance
  - Extractables/leachables
  - Traceable material
  - Change control notification
  - Validation and service
Case study
CMC Biologics’ evaluation of ReadyToProcess™ chromatography concept

• CMC Biologics is a contract manufacturing organization (CMO) with multiple manufacturing sites.
• Cleaning and validation impinges on valuable production time.
• CMC Biologics evaluated ReadyToProcess columns as a means of increasing uptime through elimination of some cleaning steps.

• Study considered man-hours needed to clean equipment in a production campaign, comparing conventional chromatography with ReadyToProcess chromatography.
• Based on modeling and data from normal routines within the CMC facility.
• Columns and systems were of comparable dimensions.
CMC increased capacity by 30% by introducing ReadyToProcess™ platform

ÄKTA™ ready: maximizing uptime through single-use technology
ÄKTA™ ready in downstream bioprocessing

- Disposable flow paths
- Based on the ÄKTA system platform and designed for use with ReadyToProcess™ columns
- Controlled by UNICORN™ software or DeltaV™ control system
- Small footprint
- Two system versions available
- Flow kits kept in stock
The flexibility resides in the single-use flow path

ÄKTA™ ready supports two different flow kits

- Low flow: 3 to 175 L/h
- High flow: 7.5 to 510 L/h
- Available in both isocratic and gradient versions

Sensors in flow path:

- Triple pressure
- Conductivity
- Temperature
- UV
- Flow
- pH (optional)
Easy flow path installation ensures fast turnaround

Intuitive wizard for flow kit installation requiring less than 15 min hands-on time

Installation test confirms set-up

No calibration required

Delivered in a “double bag” to facilitate use in clean room
Part of the ÄKTA™ system family facilitating scalability from research to manufacturing

Comparable chromatograms for a gradient run performed on ÄKTAprocess™ (A) and ÄKTA ready (B) systems
Critical for success: a robust supply chain and good track record on extractables and leachables

**Lead times and quality**
- Items kept in stock
- Integrity tested
- Sensor cells tested

**Documentation support**
- Development tests
- Bioburden levels
- Thorough studies performed on extractables
- Performance testing of flow kit
- Sensor calibration methodology
- Change control notifications (CCN) service

**Contamination control**
- Clean room assembly
- Delivered in double bag
- Gamma radiated/autoclaved
- All wetted components disposed after use
Continuously evolving downstream single-use technology
Extended ÄKTA™ ready: technical specification

- Automatic air trap fill
- Six inlets on gradient
- Up and down flow on column
- Precolumn conductivity sensor
- Integrated computer
- Possible integration to external PLC/DCS (e.g., DeltaV™ or Rockwell™ software)

DCS = distributed control system, PLC = programmable logic controller

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Bringing confidence to filtration single-use tangential flow filtration system

- Designed with user and application in focus
- One integrated, automated platform for filtration
- Wide application range
- Large number of verified and pre-programmed methods to fit various application needs
- Intuitive installation of Flow Kit allows completion within 15 min
- Working volumes kept at a minimum to support high concentration factors
ReadyToProcess™ chromatography columns
Evolution of ReadyToProcess™ columns

2008-2009
• Launch of ReadyToProcess columns
• 20 cm bed height
• 8, 12.6, 25, 36 cm inner diameter
• MabSelect™, Capto™, Sepharose™ 6 Fast Flow resins
• Validated pack methods

2011-2012
• Custom products with ReadyMate™ connectors
• On-request columns
• Collaboration with CMC Biologics; enabling 30% higher project throughput when using prepacked columns

2014
• Prototype columns with 8-30 cm bed heights

2015
• Polishing resins
• Capto S ImpAct
• Capto ImpRes
• Sepharose High Performance
• Wide range of stock items
• Customer safety stock offerings

2016+
• Addition of 18 cm inner diameter columns
• Larger stock
• Program to even further improve scalability and flexibility

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## ReadyToProcess™ columns

<table>
<thead>
<tr>
<th>Offering</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Volumes 1, 2.5, 5, 10, and 20 L</td>
<td>• Standard format allows validated packing methods and design</td>
</tr>
<tr>
<td>• Total 33 chromatography resins including mAb toolbox resins</td>
<td>• Consistent performance for modern resins from GE</td>
</tr>
<tr>
<td>• Three years shelf life</td>
<td>• Packing methods well-suited for modern resins from GE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supply chain benefits</th>
<th>Process economy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Same supplier for resins and columns</td>
<td>• Significant time-savings for downstream processing</td>
</tr>
<tr>
<td>• Standard formats allow safety stock</td>
<td>• Prequalified and presanitized</td>
</tr>
<tr>
<td>• Wide range of stock items available</td>
<td>• Reduced cleaning and validation</td>
</tr>
</tbody>
</table>

Validated design

Validated performance

Validated stability

Extractables and leachables assessment

Validated sanitization

Validated packing methods

Certification

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Supply chain control

- Same supplier for resin and format
- Technical support of both resin and column
- Stock item availability for short lead times
- 4 to 6 weeks delivery lead time for non-stock items
ReadyToProcess™ Adsorber membranes
When to consider membrane chromatography?

- The concentration of target to be bound is low
- The process time needs to be short
- The molecular weight of the binding species is high
- Examples
  - mAb second or third step polishing
  - Bind-elute (B/E) purification of viruses
  - Processing of labile proteins
ReadyToProcess™ Adsorber membrane Q, S, and Phenyl—extended product range

- Convenient single-use membrane for polishing
- Enabling short switching times and fast processing
- Well-proven Sartobind™ membrane technology for efficient purification at high sample loads and flow rates
- Seamless integration with ÄKTA™ systems and easy connectivity with ReadyCircuit™ assemblies
- Available from PreDictor™ 96-well plates to 5 L membrane cartridges for large-scale manufacturing
# ReadyToProcess™ Adsorber—product line scalability

<table>
<thead>
<tr>
<th>Bed Height</th>
<th>PreDictor™ 96-well Plate</th>
<th>Pico 0.08 mL</th>
<th>Nano 1 mL</th>
<th>75 mL</th>
<th>200 mL</th>
<th>400 mL</th>
<th>600 mL</th>
<th>2.5 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mm</td>
<td>96-well plate</td>
<td>Pico 0.08 mL</td>
<td>Nano 1 mL</td>
<td>75 mL</td>
<td>200 mL</td>
<td>400 mL</td>
<td>600 mL</td>
<td>2.5 L</td>
</tr>
<tr>
<td>8 mm</td>
<td>PreDictor 96-well plate</td>
<td>(Pico 0.08 mL)</td>
<td>Nano 3 mL</td>
<td>150 mL</td>
<td>400 mL</td>
<td>800 mL</td>
<td>1.2 L</td>
<td>Jumbo 5 L</td>
</tr>
</tbody>
</table>

*ReadyToProcess Adsorber Phen Pico with 0.08 mL volume has a 4 mm bed height. However, this size is typically used as 8 mm bed height by connecting two membrane capsules in series.*
Optimizing productivity in the polishing step: chromatography membrane vs resin

- Membrane chromatography is more cost-efficient for small to medium productions at relatively low frequency.
- Packed bed chromatography is more cost-effective at larger scales and highly repetitive manufacturing.

Data from A-Mab: a case study in bioprocess development version 2.1, CMC Biotech Working Group (2009). Reprinted with permission from CASSS.
Summary
Fast turnaround time drives implementation of single-use products in downstream processing

GE supports the single-use evolution

Strong knowledge in chromatography and single-use technology

Expansion of ReadyToProcess™ downstream platform

Enabling transformation of existing facilities through hybrid solutions
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