ACCELERON PHARMA

WELCOME

11 May 2010

Acceleron Pharma Company Overview

- Founded in 2003 in Cambridge, MA
- Privately held
- Partnership with Celgene for anemia-targeting programs and Alkermes for novel second generation proteins
- Currently ~155 individuals
- Fully integrated biotherapeutic R&D infrastructure
  - Protein engineering
  - In vivo pharmacology
- GMP protein manufacturing facility with seven fusion proteins in development in 2010
- Focus on novel GDF related proteins that modulate the growth of bone, muscle, fat and the vasculature

ACCELERON PHARMA

Company Pilot and GMP Manufacturing Strategy

- Bring Research Reagent, Pilot and GMP production in-house to control quality, capital outlay, and timelines for early phase products
  - Make initial research material to explore biology (rodent, dog, Human, etc.)
  - Use same technology to make non-GMP material for early toxicology studies
  - Using same process, quickly make and release phase 1 and 2 material for clinical trials minimizing capital expenditure

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Design Basis for Disposable Facility

- Focused limited development\production personnel on the process, not support
- Simple facility design focused on controlled areas using one HVAC
- “One product at a time” facility
- **Facility has no water system**. All process solutions delivered in sterile containers
- **Facility has no steam**. All material is delivered clean and sterilely unless cleaned as part of in-process sanitization (column cleaning)
- All process equipment is mobile, to facilitate movement at a future time
- Processes based on a platform, where equipment and number of process steps are substantially the same among different product candidates

ACCELERON PHARMA

Technology Challenges for Single Use Downstream Processing

ISPE May 2010

Parrish M. Galliher

Xcellerex

Presentation Outline

- Current Biopharm Industry trends and drivers
- Limitations of stainless steel mfg. technology
- Review of single use technologies
- Going beyond disposables and integrating - the FlexFactory®
- New single use technologies on the horizon
- Case studies in novel single use manufacturing
  - Microbial mAb production and purification
  - Microbial swine flu production and purification
  - Economics of mAb EB and SMB purification
- Conclusions

Challenges Facing the Biopharm Industry

Industry Challenges

- Global economic downturn
- Industry consolidation
- Fewer blockbusters
- Reimbursement pressure
- Excess capacity from higher titers, smaller pipelines, more potent drugs
- Personalized medicine = smaller markets
- Competition
    - Globalization – Asian offshore capacity coming on-line
    - Emerging follow-on / biosimilars market

Biopharm Landscape – Small vs Large Companies

Small / new company

- Very tight VC funding
- 6-12 months of cash
- Reaching milestones = survival
- Less time to reach milestones
- No reserve cash for delays/errors
- Much more willing to partner vs take more expensive VC money
- Royalty/equity opportunity for CMOs

Larger established company

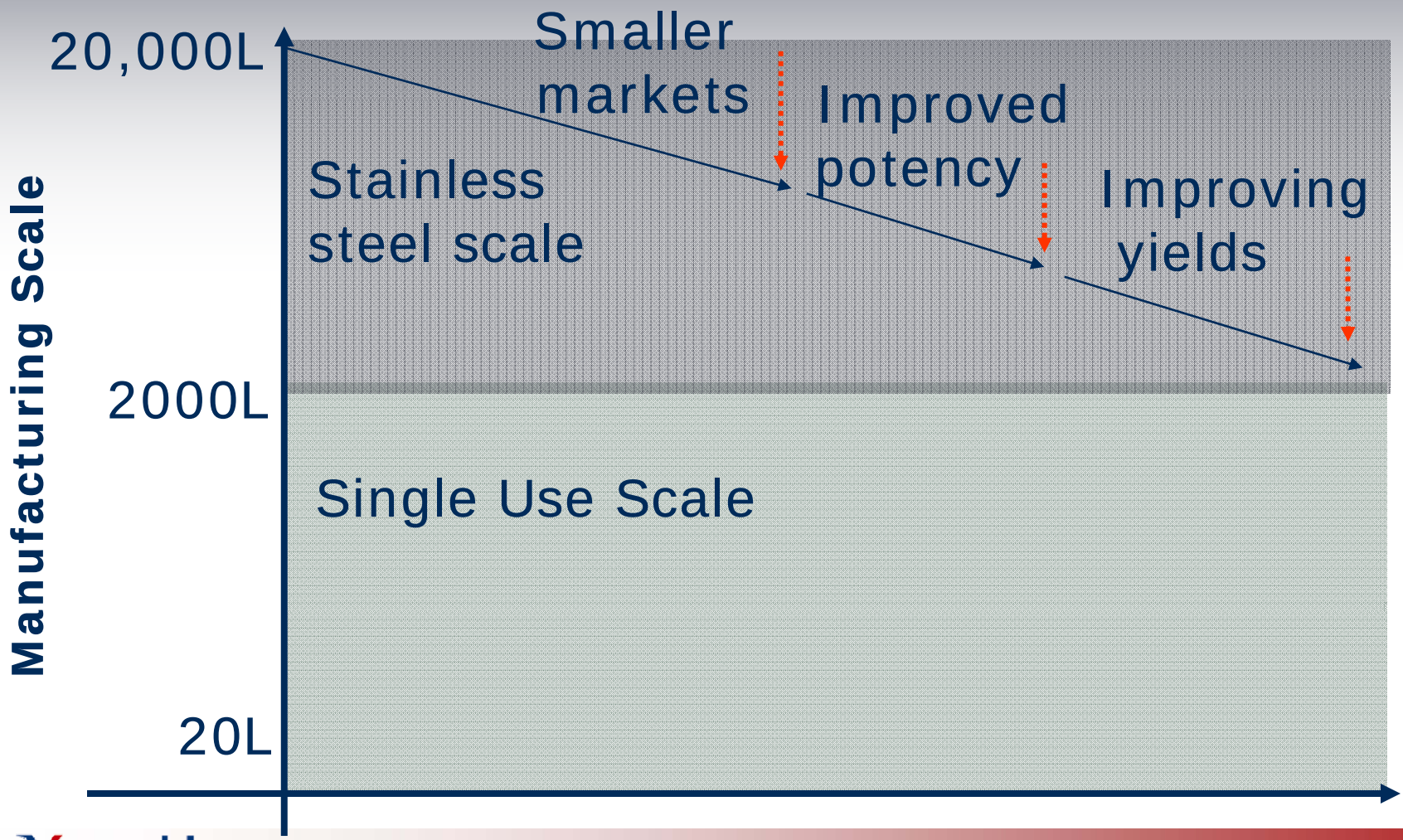
- Many consolidations stalling capacity investments
- Excess mfg. capacity
- More technology conservative-tighter technology budgets
- Concerned about biosimilars and Asian competition
- Forced to evaluate more efficient manufacturing options
- Much more willing to partner-royalty/equity opportunity for CMOs

Traditional Stainless Steel Facilities

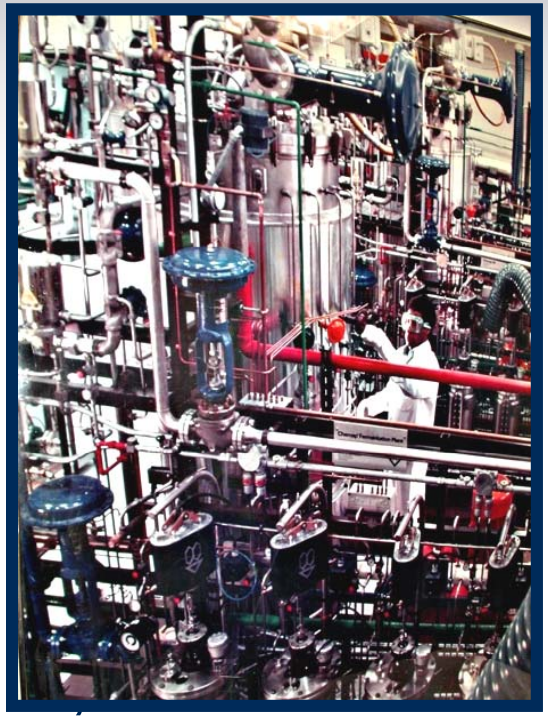
Traditional Stainless Steel Facilities

- Prohibitive cost to build new mfg. capacity… $2,000/sq ft
- $200-$400M total installed capital cost
- 4 year timeline for new capacity
- Risk of committing capital during early high-risk stage
- Expensive to operate
- Expensive to modify
- Limited long-term asset utilization
- Low terminal value (even lower in today's disposable environment)
- Many are obsolete before they are validated

Future Kg demand / Biologic is decreasing: *single use becomes commercial scale*



FlexFactory® Single Use Biomanufacturing:
Escaping the Limits of Stainless Steel



Bioreactor
1982

Bioreactor
1994

Xcellerex 2000L Bioreactor
TODAY

Xcellerex

Single Use Technology Review

Products and vendors listed in the following slides are provided for reference and do not constitute a complete list or an endorsement of any specific vendor or product

Xcellerex family of single use bioreactors

All XDRs have a 5:1 turn down ratio
(Each can operate at 20% working volume)

XDR-50

XDR-200

XDR-500

XDR1000

XDR-2000

XDR-10 and XDR-5000 in development

Xcellerex

www.xcellerex.com

Established Downstream Single Use Technologies

- buffer Storage bags
- buffer Mixers
- Sensors – pressure, pH, conductivity, UV, flow
- Separations – limited to filtration
  - Harvest
  - Virus removal / sterilization
  - Concentration / buffer exchange
- Purification – membranes
- Tubing welders / connectors / sealers
- Integrating stainless and disposables connectors

Advantages of Single Use Systems

Reductions in:

- Cleaning
- Sterilization
- Engineering cost
- Equipment lead time
- Utility requirements
- Validation
- Quality / Regulatory burden
- Space
- Labor
- Waste generation

Lead to

Improvements in:

- 20% reduced capital
- 15% reduced COGs
- 50% reduced facility buildout time
- 20% reduction in plant footprint
- Campaigned product flexibility
- one level increase in manufacturing quality
- 2 hr turnaround cycle time
- > 55% reduced environmental impact

Downstream – Buffer Mixing Systems

Applications:	Media, buffer, product processing, formulation
Capacity:	10 L to 10,000 L
Vendors/Types:	Hyclone MixTainer, LevTech/Sartorius levitated prop tank, Wave FlexMixer, Xcellerex XDM stirred tank
Integration	
Challenges:	powder addition, connectors
Scale Up	
Challenges:	powerful mixing, bags that flex to achieve mixing rely heavily on bag seam strength and durability

Xcellerex XDM, XTM Temp Controlled Quad Single Use Mixers 100L, 200L, 500L, 1,000L

Xcellerex

Cell Harvest – centrifugation, filtration

Application:	Separation of cells from growth medium during perfusion or for terminal cell harvest.
Capacity:	Up to 100-200 L/hr
Vendors/Types:	Pneumatic scale (unifuge), Spectrum and GE , WaterSep (recirc. hollow fiber), Millipore POD system, Cuno, Pall depth filtration. All product contact surfaces disposable
Integration Challenges	connectors
Scale Up Challenges	recirculating systems: disposable tubing not amenable to high flow rates and pressures

Dead End / Depth Filtration

Application:	Clarification / sterilization of media, buffers and process intermediates, cell harvest, and removal of particulates.
Capacity:	Syringe filters, 30” capsules, flat membrane generally available, (larger by custom order)
Vendors / Types:	Millipore POD, Pall, Sartorius, Meissner, Cuno – larger capsules coming available, many available pre-sterilized and integrity tested.
Integration Challenges:	connector compatibility
Scale Up Challenges:	>2000L capacity is lacking

Tangential Flow Filtration

Application:	Perfusion, cell harvest, purification, concentration, and formulation / buffer exchange
Capacity:	Up to 13 m^2
Vendors / Types:	Spectrum HF, GE, WaterSep hollow fiber
Integration Challenges:	disposable pump integration that is durable yet disposable
Scale Up Challenges:	recirculating systems: disposable tubing not amenable to high flows/pressures

Purification – Pre-packed Chromatography

Application:	binding or Flow-through removal of contaminants and/or product bind-and-elute purification of small or dilute process streams.
Capacity:	variable
Vendors/Types:	GE Healthcare, Repligen, Applied Biosystems
Integration /scale up Challenges:	GE supplies GE resins only with fixed bed height, largest scale Repligen packs any resin to any height, limited to 10L columns

Purification – Membranes

Application:	Flow-through removal of contaminants, bind-and-elute purification of small or dilute process streams.
Capacity:	20 L/min., 5g DNA binding capacity
Vendors/Types:	Pall, Millipore and Sartorius functionalized filter membranes.
Integration Challenges:	connectors, area
Scale Up Challenges:	less binding capacity compared to chromatography resins in general

Virus Reduction

Application:	Mechanical reduction of viral load by nanofiltration.
Capacity:	15 - 200 L/hr. (depending on pore size, filter medium & process stream)
Vendors/Types:	Millipore dead end, Pall dead end, Asahi-Kasei
Integration Challenges:	connectors
Scale Up Challenges:	larger scale requires more area

Vial Filling

Applications:	Aseptic filling into vials
Capacity:	Clinical to commercial {?}
Vendors/Types:	Millipore Acerta bag based filling system, MedInstill injection filling/laser sealing, Bosch
Integration Challenges:	connectors
Scale Up Challenges:	not clear yet

Sensors

Applications:	Process wide
Capacity:	N/A
Vendors / Types:	Wave Biotech, (pH, DO2), Flourometrix, Finesse and PreSens optical sensors, microprobes
Integration Challenges:	Cytoxicity, irradiatability, fit up into bags, tubing, dead zone elimination, signal response time
Scale Up Challenges:	stability, non-fouling, validatable

Economics of Disposables vs Stainless courtesy Foulon et al, Roche June 2008

Figure 3: Start-up phase, highest savings (summary cost breakdown)

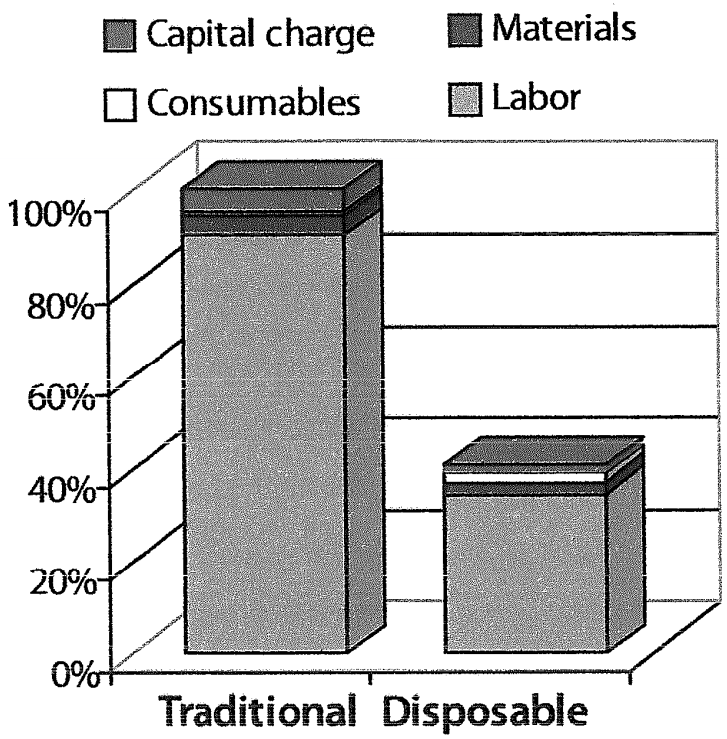
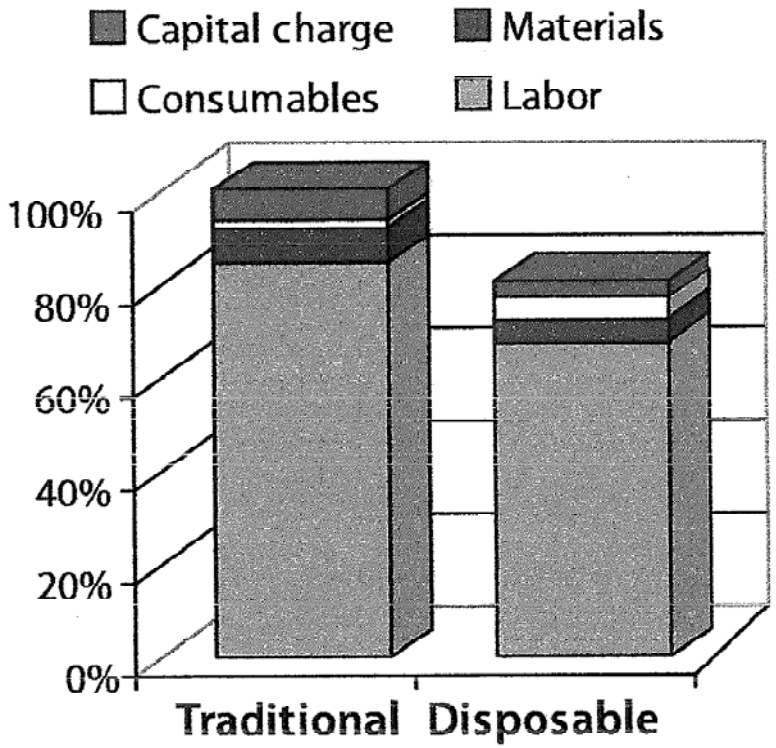


Figure 4: Regular production, highest savings (summary cost breakdown)



Environmental Advantages of Disposables:
Water Consumption & Waste Generation

Water Usage - Traditional (L per batch)

WFI	PW	Process	Cleaning	TOTAL
36,201	41,358	11,174	66,384	77,559

Waste - Traditional

Aqueous	Plastic
79,155	67

Water Usage - Xcellerex (L per batch)

WFI	PW	Process	Cleaning	TOTAL
9,957	-	9,957	-	9,957

Waste - Xcellerex

Aqueous	Plastic
11,554	189

- ~85% reduction in water usage & waste
- 3x increase in lbs of plastic usage & waste

Environmental Advantages of Disposables: Carbon Footprint

POUNDS CARBON / BATCH	Single Use	%	Stainless	%	Diff.
SIP	0.0	0.0%	388.5	1.0%	388.5
CIP	30.5	0.2%	1,988.0	4.9%	1,957.5
Transporting Plastic	148.5	0.8%	0.0	0.0%	-148.5
Pumping Water & Wastewater	3.7	0.0%	28.7	0.1%	25.0
Steel Fab. Amortized per Batch	2,970.7	16.6%	7,723.8	19.2%	4,753.1
Polymerizing Plastic per Batch	799.3	4.5%	0.0	0.0%	-799.3
Extruding Plastic	499.6	2.8%	0.0	0.0%	-499.6
WFI Still	7,308.7	40.8%	29,828.8	74.3%	22,520.1
Cleanroom Energy	132.1	0.7%	204.1	0.5%	72.0
Incinerating Plastic	6,029.3	33.6%	0.0	0.0%	-6,029.3
TOTAL	17,922.4		40,161.9		22,239.5

Courtesy Leveen & Monge, ISPE Tampa Conference, 02 March, 2009

55% reduction in carbon footprint

Going beyond just disposables Introducing the FlexFactory®

- **FlexFactory ™**
  - Portable mini-clean rooms
  - Disposable mfg. equipment
  - Automation - eFactory™
    - Process control
    - e-process control/doc. software
    - On-Line quality assurance
    - On-line environmental monitoring

The Fully Integrated Disposable FlexFactory®

Hundreds of disposable processing components

Fully integrated GMP FlexFactory

Xcellerex

Going beyond just Single Use: Advantages of the FlexFactory®

Reductions in:

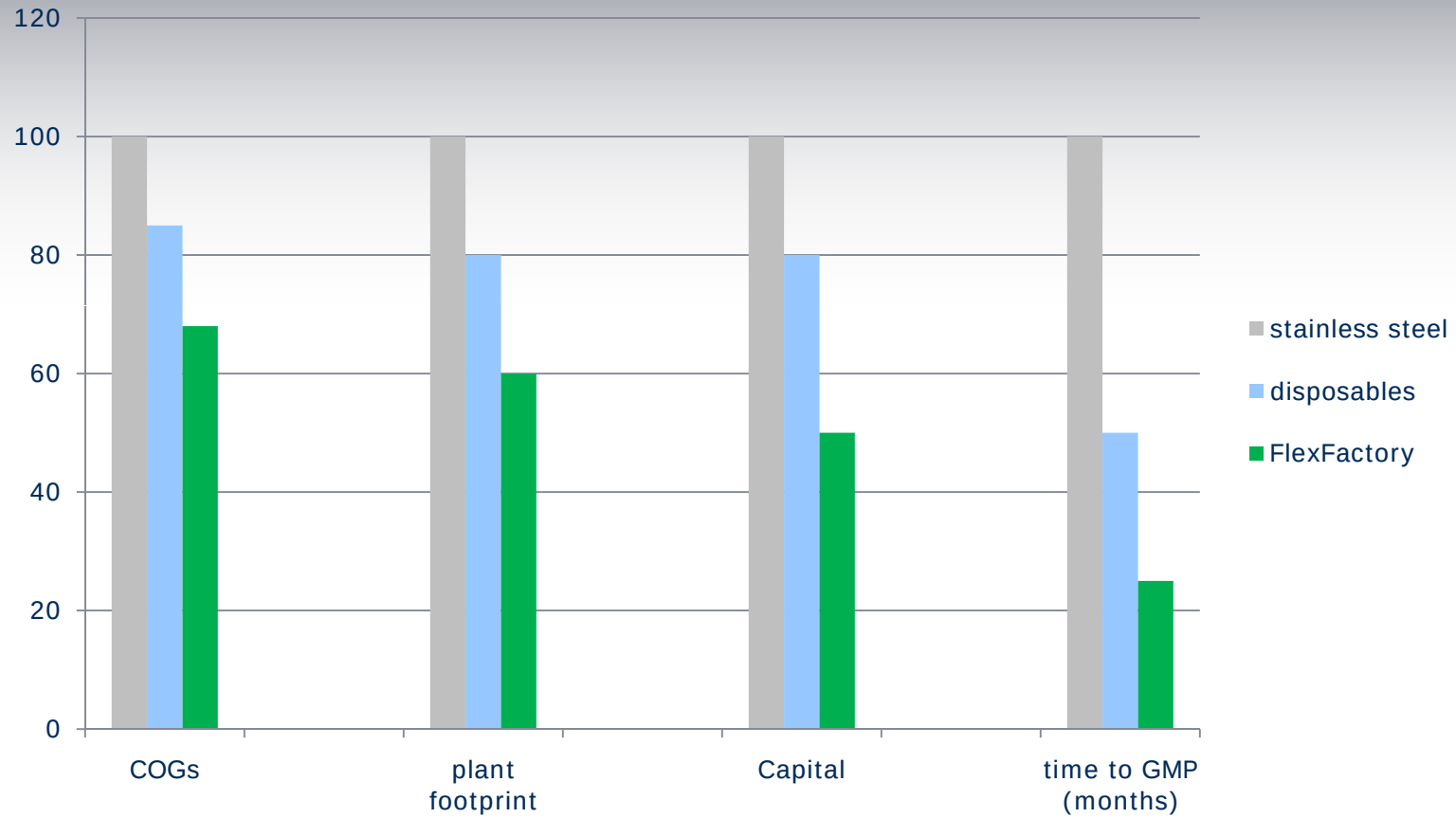
- Cleaning
- Sterilization
- Engineering cost
- Equipment lead time
- Utility requirements
- Validation
- Quality / Regulatory burden
- Space
- Labor
- Waste generation

Lead to

Improvements in:

- ~~20~~% 50% reduced capital
- ~~15~~% 30% reduced COGs
- ~~50~~% 70% reduced facility buildout time
- ~~20~~% 40% reduction in plant footprint
- ~~Campaigned~~ simultaneous product flexibility
- ~~one~~ three level increase in manufacturing quality
- 2 hr turnaround cycle time
- > 55% reduced environmental impact

Economic comparisons – biopharm facilities stainless steel vs just disposables vs FlexFactory



New technologies in Downstream Single Use Manufacturing

Single use tubular bowl centrifuge – Pneumatic scale

Single pass ultrafiltration - Pall

Pre-packed chromatography: GE, Repligen, Natrix

Simulated moving bed chromatography – Tarpon, Novasep

Expanded bed chromatography – Upfront

Genderless, re-useable sterile connectors

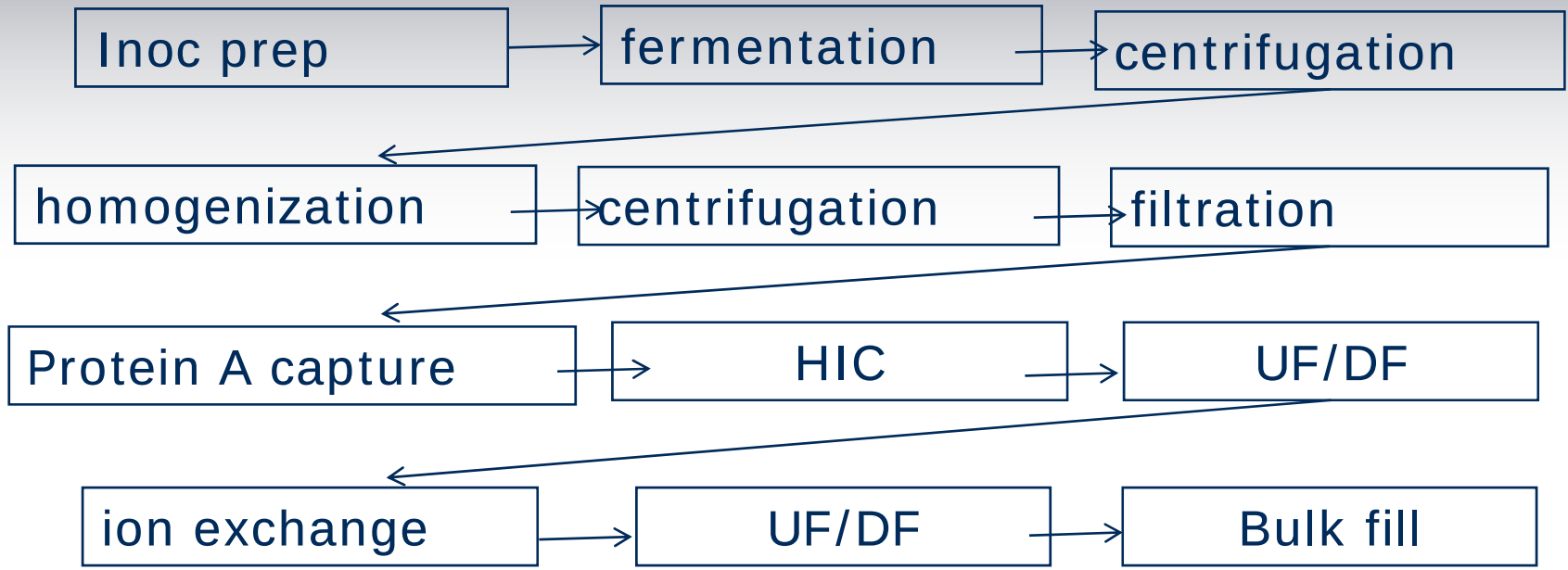
Case studies:
Microbial single use manufacturing:

1) Purification of mAb using:
   - single use expanded bed
   - single use prepacked simulated moving bed

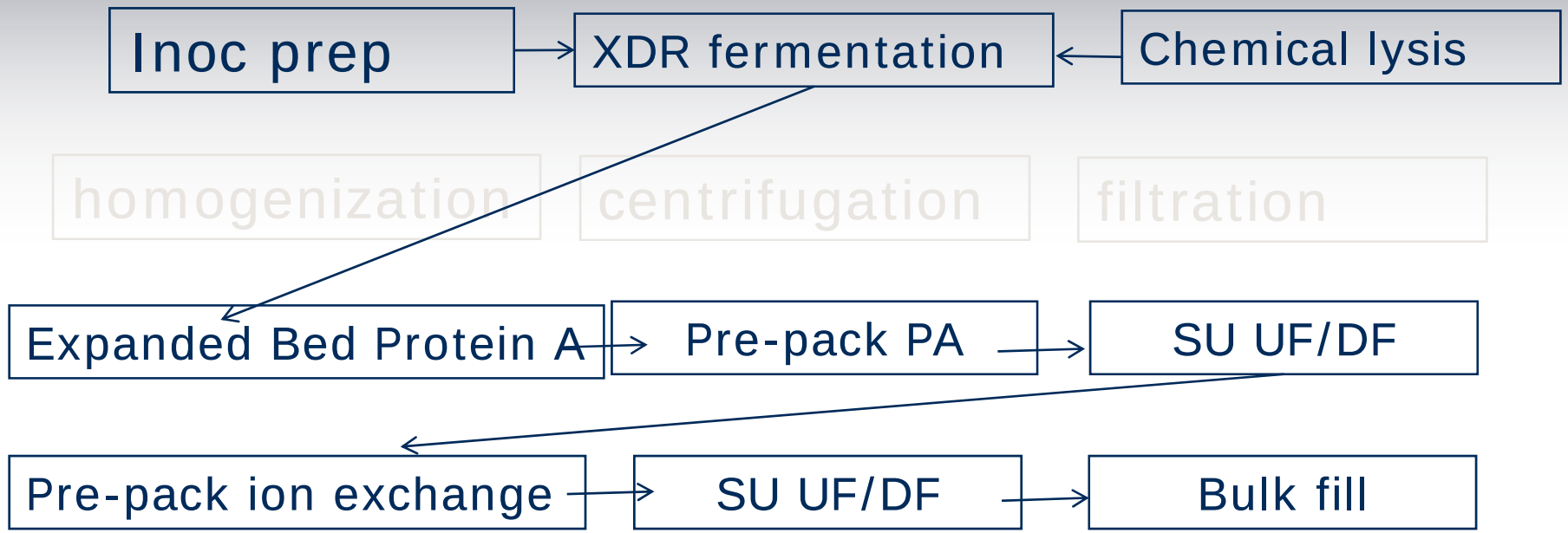
2) Purification of Swine flu HA:
   - single use prepacked chromatography

3) EB and SMB economics

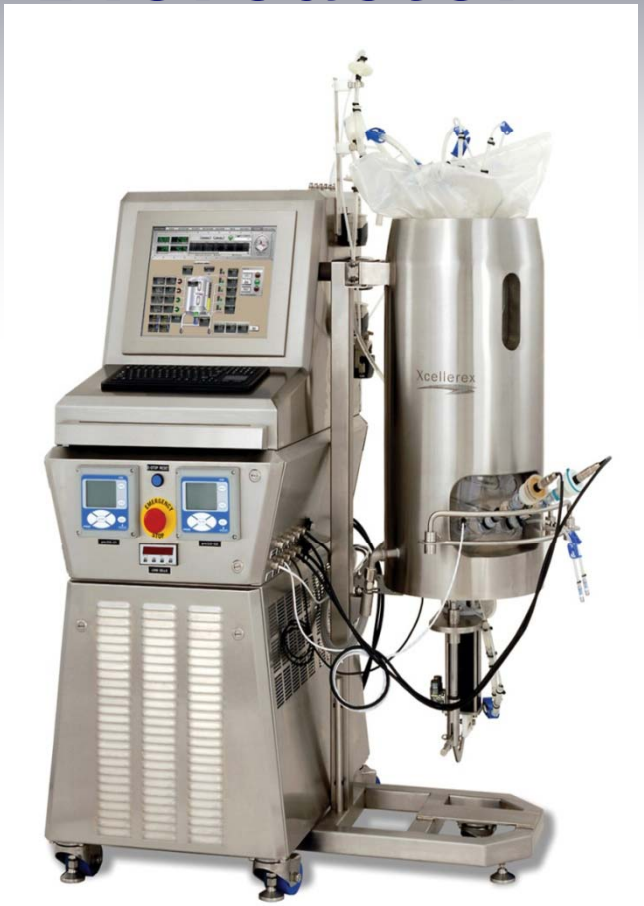
Traditional microbial mAb production



Single use microbial mAb production



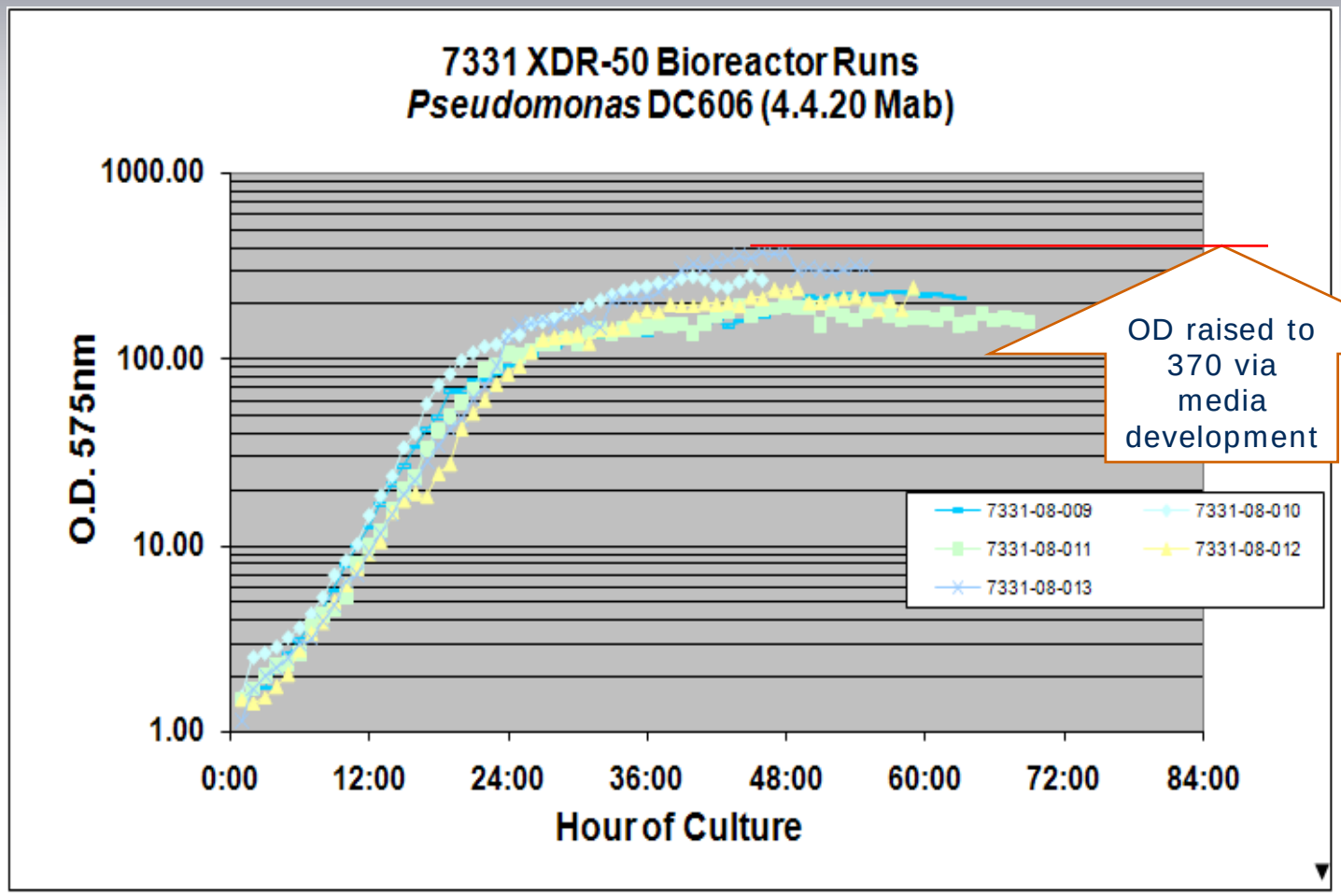
Microbial XDR-50L Single-Use Bioreactor



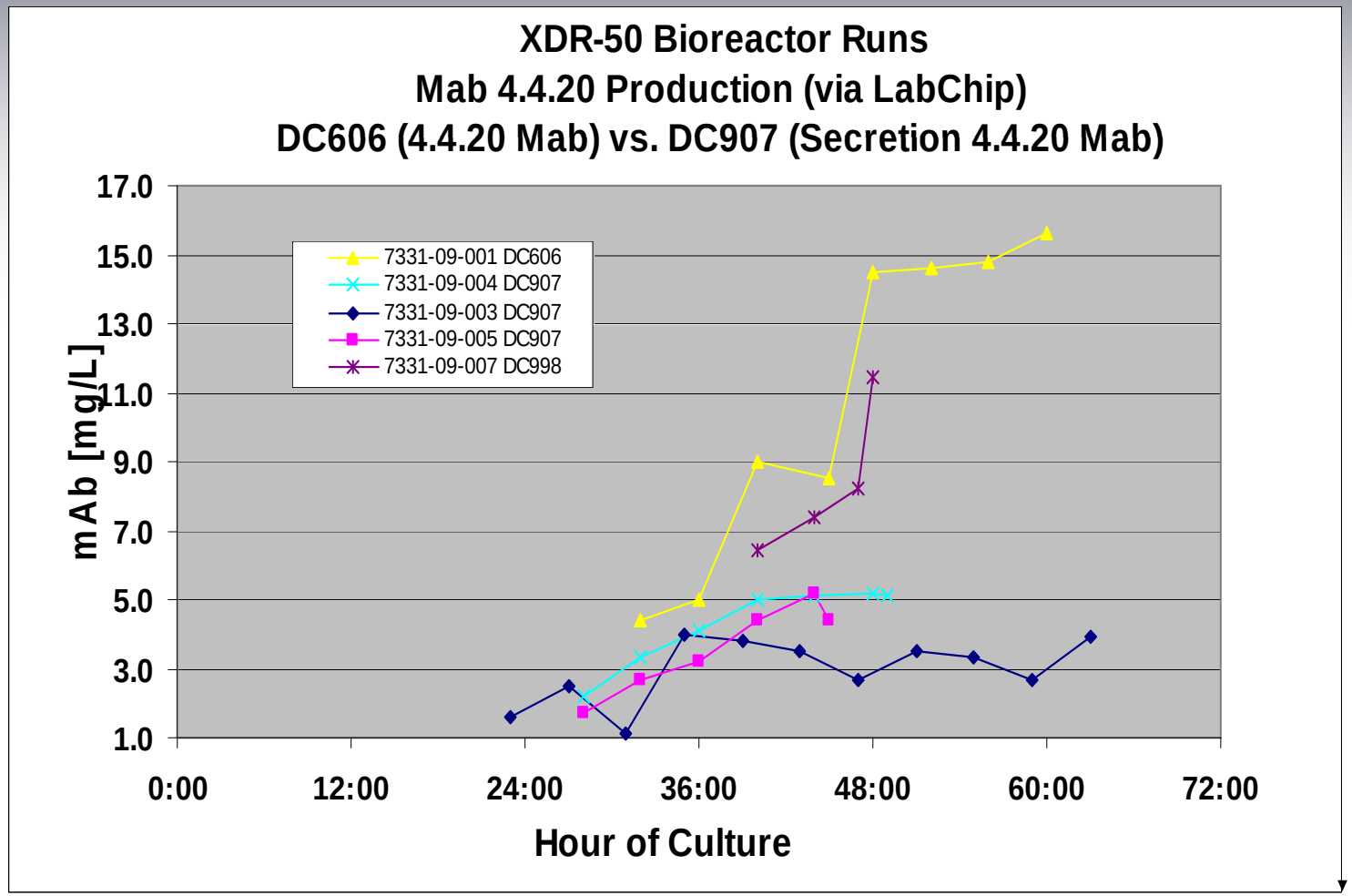
Microbial turbo XDR-50

- 6 blade rushton turbine
- 6 blade upper pitched blade
- baffled
- 400 rpm
- 1000 hr-1 kLa
- Glycol jacket cooled
- Electronic exit gas condenser
- 370 OD
- 125 g/L DCW

Pseudomonas bacterial fermentations XDR-50 – HA subunit vaccine and anti-fluorescein mAb



XDR-50 Pseudomonas (Pfenex, Inc.) bacterial fermentations – mAb titer (fully folded)



Expanded Bed Protein A capture System now available in single use

Upfront Rhobust System/10 cm column
3 L Protein A Resin in Expanded Bed Mode

Xcellerex

www.xcellerex.com

Expanded Bed System
cell lysate load onto Protein A

Upfront Rhobust System/10 cm column
2 L Protein A Resin in Expanded Bed Mode
Wash Cycle

Figure F-3. The 10cm Rhobust system during wash step following load of unclarified harvest lysate on Protein A resin.

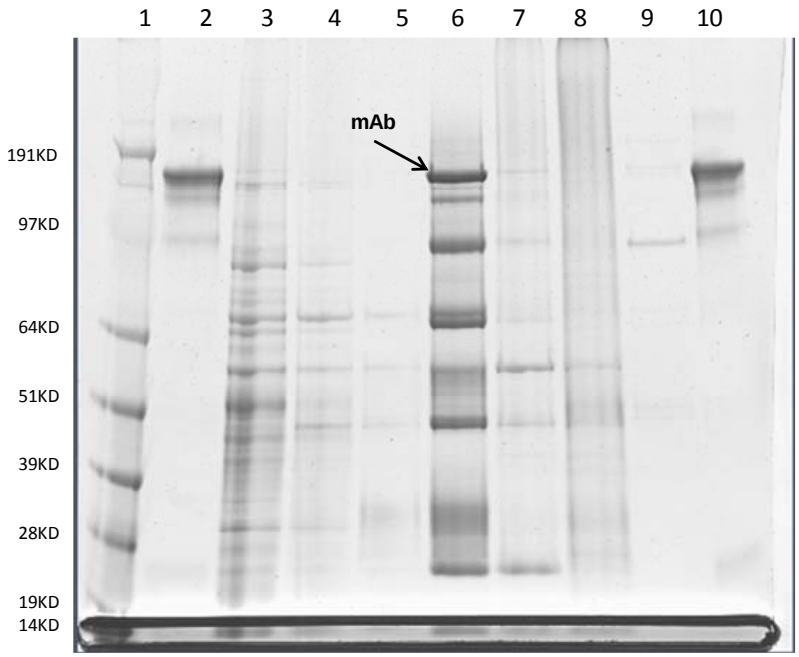
Expanded Bed System – PA mAb elution

Upfront Rhobust System/10 cm column
2 L Protein A Resin in Expanded Bed Mode
Elution Cycle

Figure F-4. The 10cm Rhobust system during the elution step of product from unclarified harvest lysate.

Expanded Bed PA mAb Capture

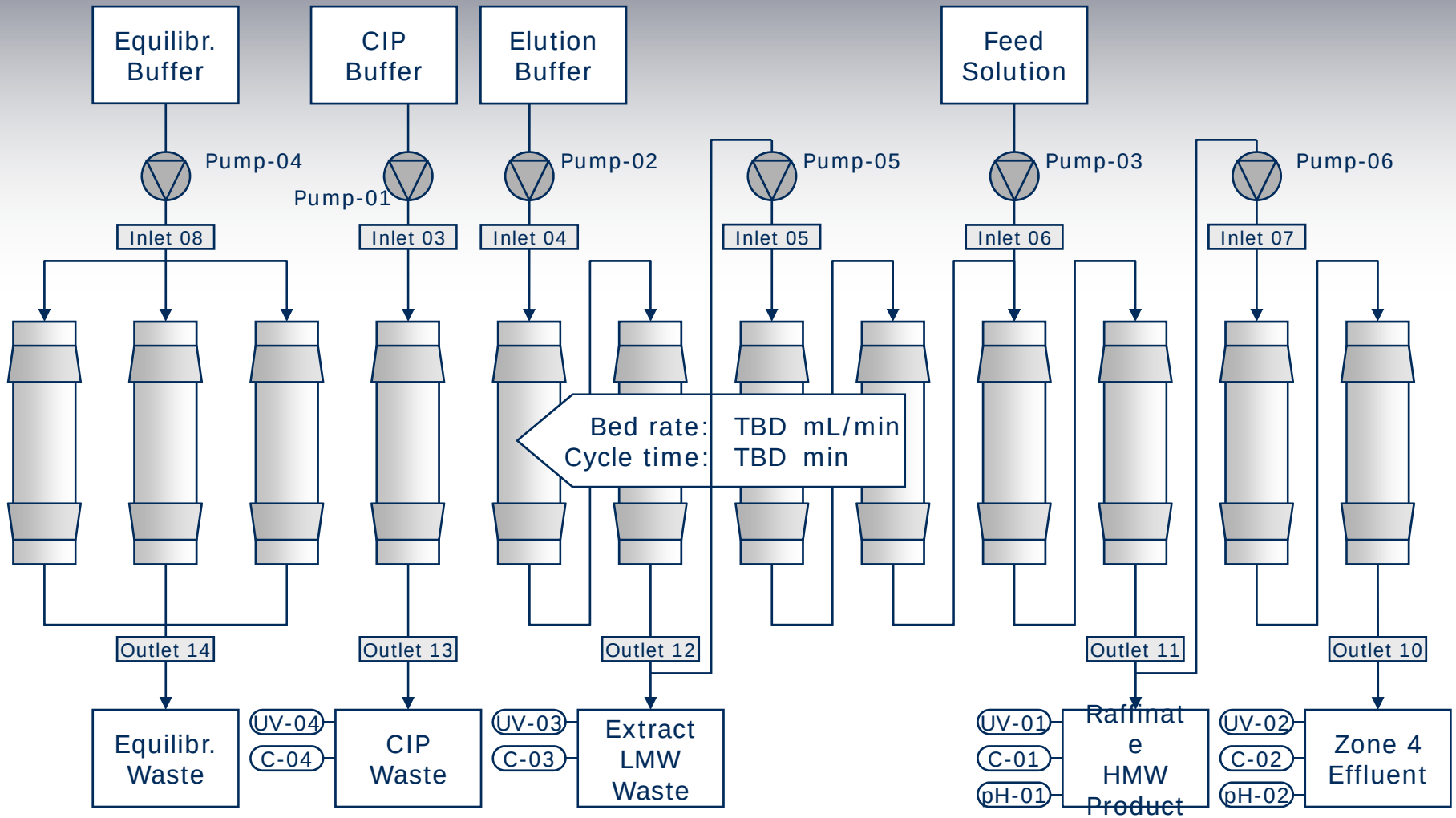
Purification of XDR50 DC606 08-009, 4-4-20 mAb using Upfront Protein A EBA in Batch Mode
Bind and Packed Bed Wash and Elution
4-12% NuPage BIS Tris MOPS Non-reduced Gel (50min, 200V, 120mA, 25W)
Release Method – Thawed harvest, 5X Lysis Buffer
Clarification Method – None



1. SeeBlue MW Std
2. IgG Standard
3. Load (diluted 1:10)
4. Flowthrough
5. pH 5.0 Wash
6. pH 3.5 Elution (pH adjusted to 8.3)
7. 0.1M HCl Strip (pH adjusted to 7.8)
8. 0.1M NaOH Strip (pH adj. to 8.2)
9. Peroxide/DTT treated Anti-Shiga sample
10. IgG Standard

20uL loaded for each

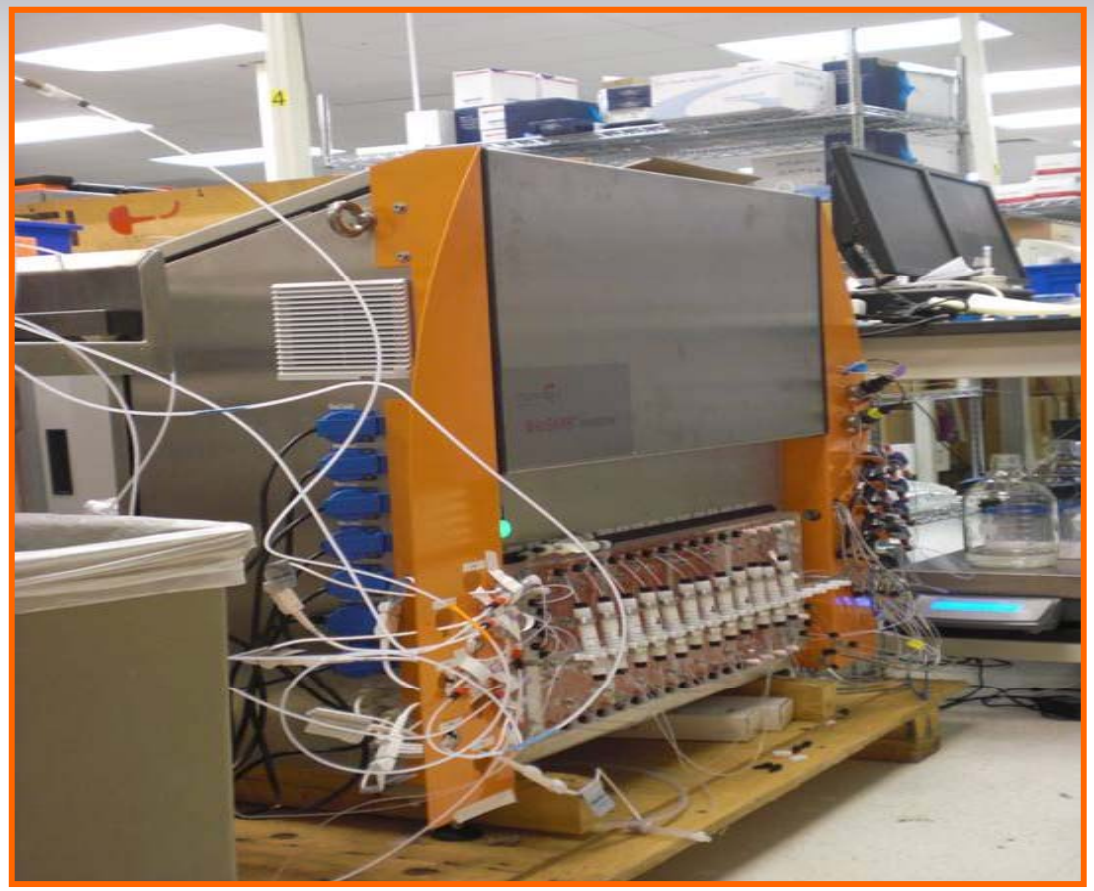
Single Use Simulated Moving Bed Process Flow Diagram - courtesy Tarpon Biosystems



Xcellerex

www.xcellerex.com

Single use simulated moving bed chromatography – beta system courtesy Tarpon Biosystems



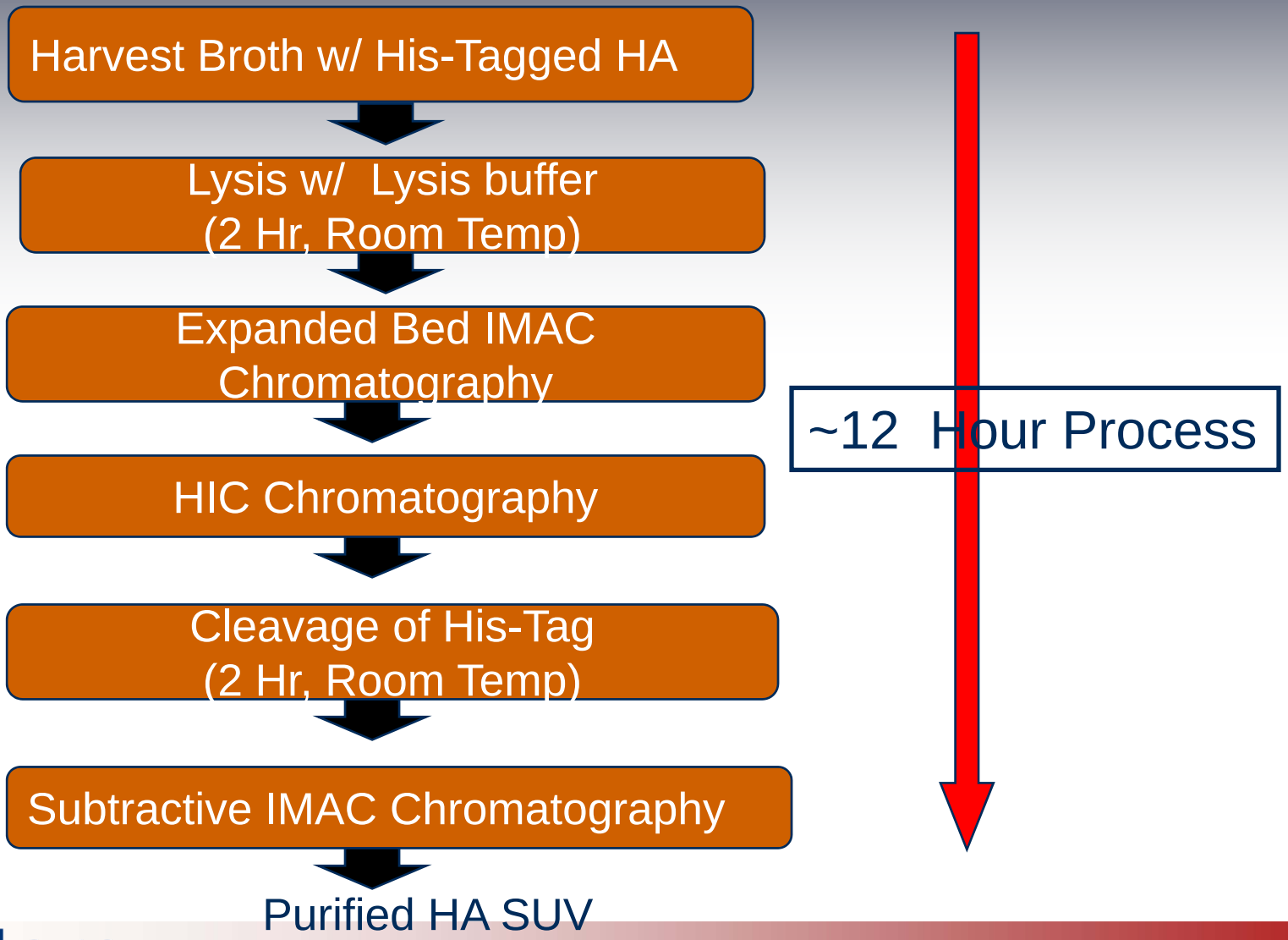
SMB Impact vs Batch Protein A Chromatography scale up example:

- 3.5 g/L mAb titer
- 2000L batch

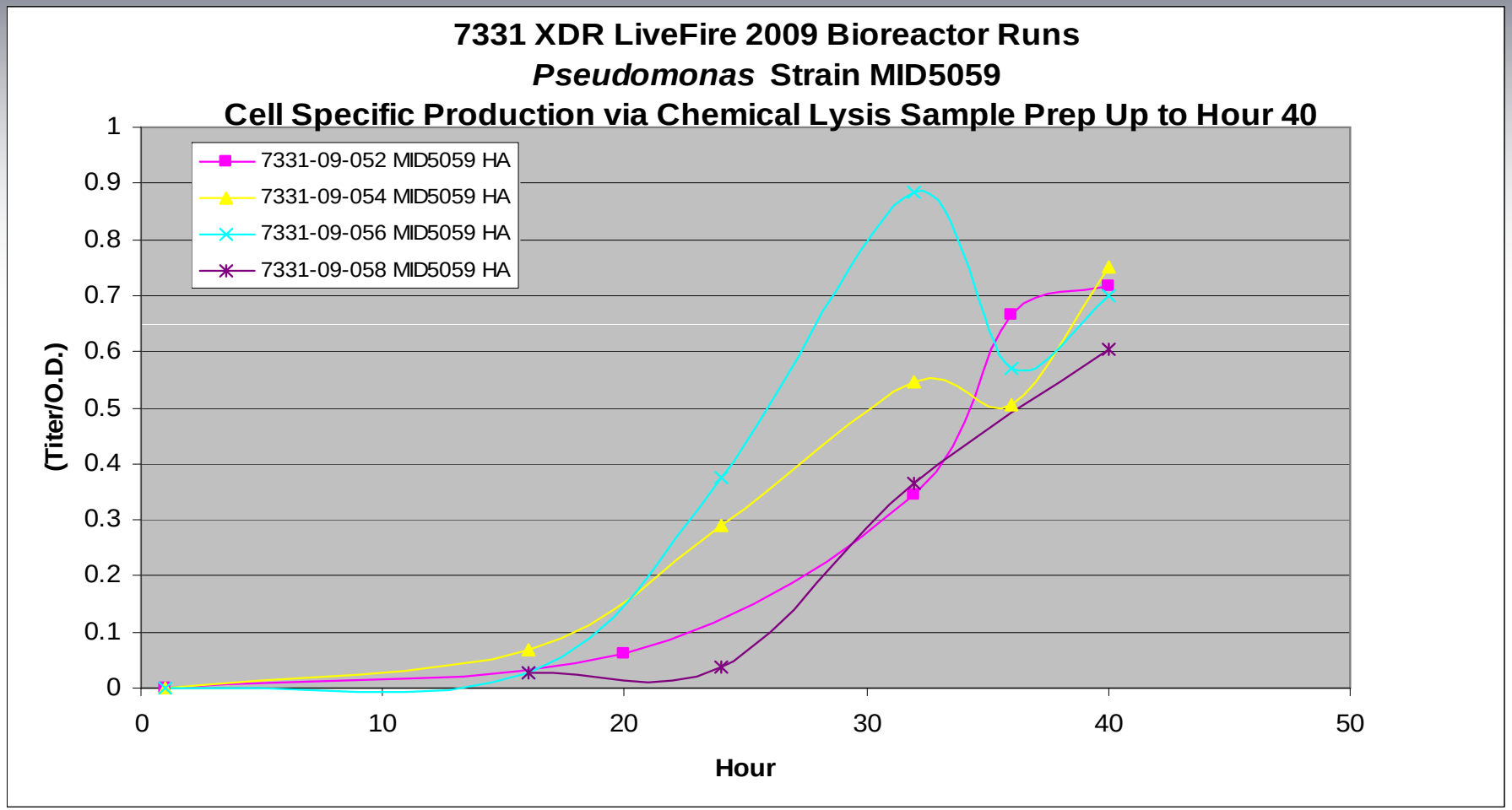
	Batch	SMB
# columns:	1	8
productivity g/L-day:	360	2630
processing time:	5 hrs	8 hrs
liters PA resin:	88L	8L
cycles/batch	2	19
$ protein A resin:	$880,000	$80,000

courtesy Tarpon Biosystems

Swine Flu HA Downstream His-tag-SUMO Purification Platform



XDR-50 Pseudomonas (Pfenex, Inc) bacterial fermentations - swine flu HA



Pre-Packed Chromatography
HA subunit vaccine purification

BioFlash

GE Healthcare

AKTA Ready with 8 cm BioFlash IMAC column

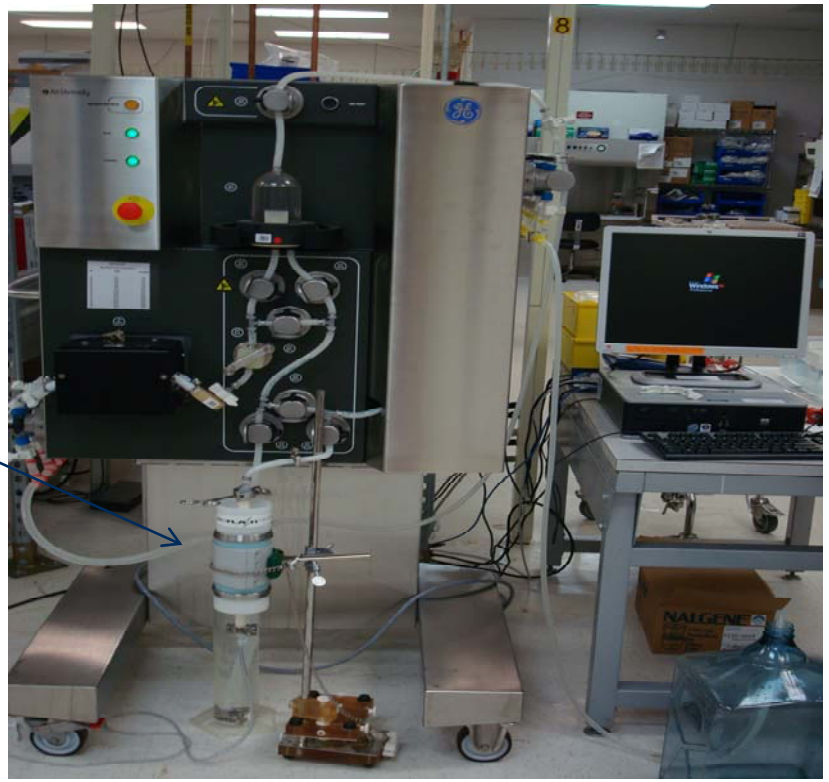
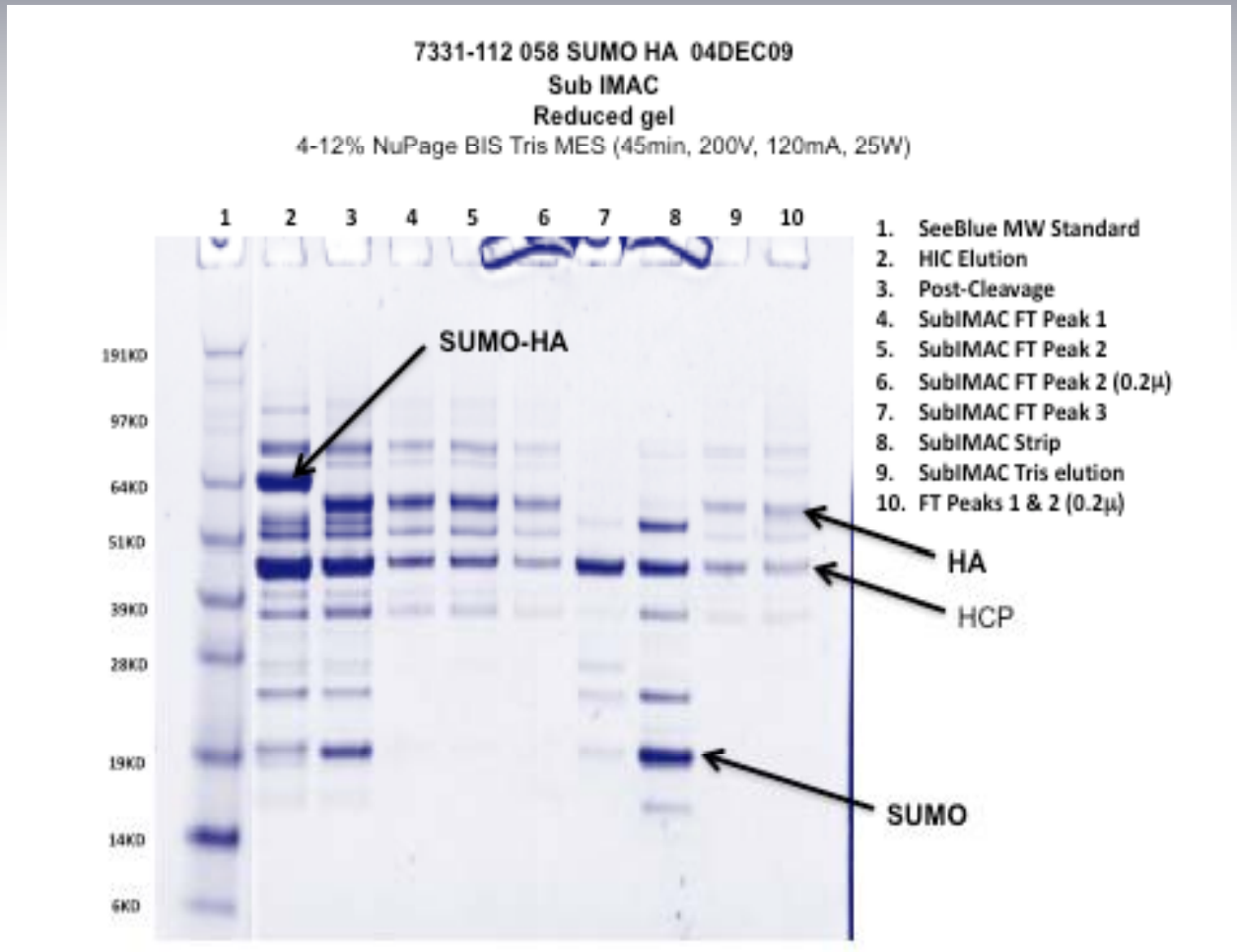


Figure F-104. The AKTA Ready chromatography system with a BioFlash 8cm IMAC disposable column in line.

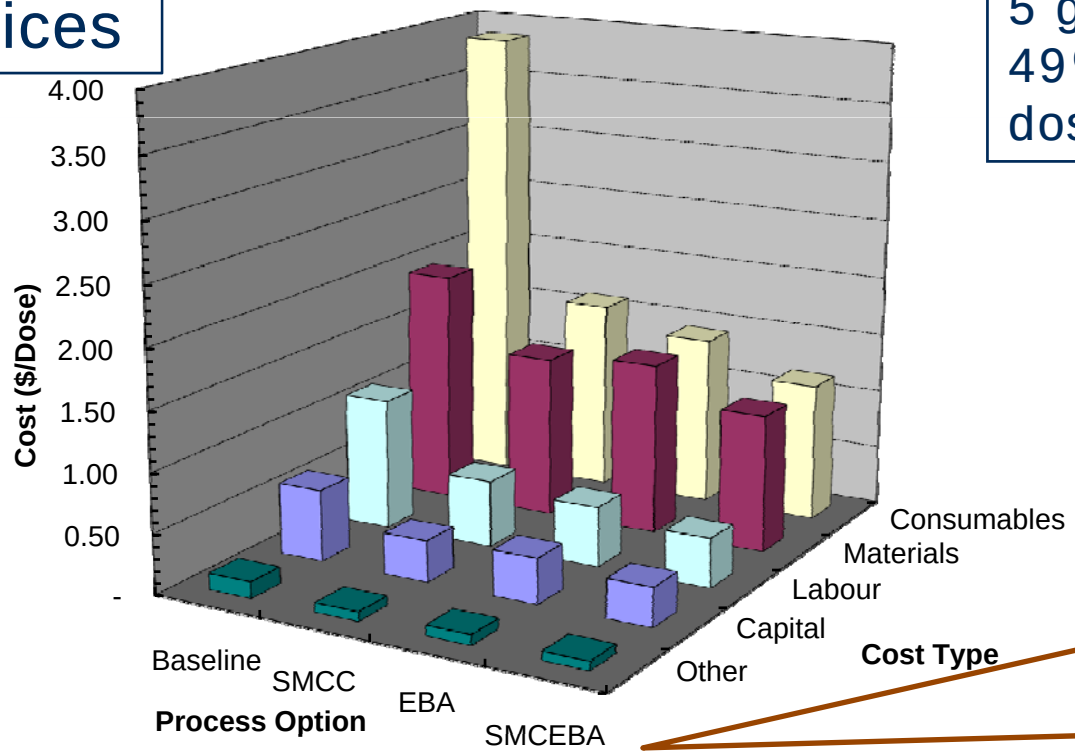
Pre-Packed Chromatography
HA subunit vaccine purification



Economics: baseline vs SMB/EB

Option	Baseline	SMCC	EBA	SMCEBA
Capital	0.60	0.35	0.38	**0.32**
Materials	1.96	1.36	1.44	**1.16**
Consumables	3.87	1.61	1.43	**1.16**
Labour	1.10	0.56	0.50	**0.41**
Other	0.14	0.08	0.09	**0.07**
TOTAL	7.66	3.95	3.83	**3.13**
Relative Cost	-	-49%	-50%	**-59%**

Courtesy Biopharm Services



2000L perfusion
5 g/L titer
49% yield
dose = 400mg

COGS Savings:

SMB	-49%
EB	-50%
SMB/EB	-59%

Xcellerex

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Conclusions

- Single use technologies for downstream are improving:
  - Expanded bed simplifies primary capture
  - Prepacked chromatography facilitates plug and play
  - SMB - major breakthroughs in COGS, high titer capable
- FlexFactory: integrating downstream disposables with USP
  - Open platform, simultaneous multi-product manufacturing
  - 70% reduction on time to build/validate to GMP ready (9 mo.)
  - Reductions: capital: 60%, footprint: 40%, COGS: 30%: time 70%
  - Eco impact: -85% water use, -55% carbon footprint, 3 x increase in waste plastic

THANK YOU!

170 Locke Drive, Marlborough, Massachusetts 01752

www.xcellerex.com

1.866.Xcellerex

Successful Implementation of Single Use Systems for Commercial Scale Biomanufacturing: The Industry/Supplier Partnership

Paul Slaman
Shire HGT

James Dean Vogel, P.E.
Process Facility Services

Shire

Our purpose
We enable people with life-altering conditions to lead better lives

bpf bio process facilities

Summary

- **ISPE Single Use Technology: Approaches in Unique Facility Design, Successful Implementation & Exploring Future Growth Opportunities**
  Date: 11 May 2010

  This presentation will be held at the Acceleron Pharma facility in Cambridge, which has embarked on a manufacturing strategy using single use technology. We will explore facility design considerations through a tour of the Acceleron Pharma facility, learn of the successful implementation strategy for commercial scale biomanufacturing at Shire HGT, and learn from Xcellerex's founder about novel applications in downstream processing.
- **PLEASE NOTE:** The Acceleron Pharma Facility Tour SOLD OUT. The networking reception and following presentations are still available and are OPEN to Members and non-members.
- **Location:**
  Acceleron Pharma, Inc.
  128 Sidney Street, Cambridge, MA 02139
- **Speakers:**
  Bob Steininger, Senior Vice President, Manufacturing, Acceleron Pharma
  Paul Slaman, Manufacturing Technical Services, Shire HGT
  James D. Vogel, Consultant, Process Facilities Services, Inc.
  Parrish M. Galliher, Founder and Chief Technology Officer, Xcellerex. Inc.

Shire

Summary-

- **Successful Implementation of Single Use Systems for Commercial Scale Biomanufacturing: The Industry/Supplier Partnership**
- *Paul Slaman, Manufacturing Technical Services, Shire HGT*
- *James D. Vogel, Consultant, Process Facilities Services, Inc.*
- The basis of design for the Shire HGT ATLAS plant incorporates single use/disposable components at all unit operations with key bioprocess unit operations performed in these systems. The use of these components will permit the organization to achieve speed to market and benefit from the overall simplification of tasks associated with plant design, construction, ICV, and routine operations. The use of these systems does present some unique challenges for a validated, commercial facility that will need to be addressed to be successful.
- Of critical importance is interpretation and adherence with CFR 211.65 and other applicable regulatory requirements. Understanding and characterizing the risks associated with single use components requires an assessment of the impact and a decision on choosing the right component for the application. This decision making process does not occur unilaterally; strong supplier partnerships are required for success.

Shire

Shire Human Genetic Therapies (HGT)

- **Shire HGT** is a global business unit dedicated to discovering, making and supplying treatments for rare genetic diseases to patients around the world.
- We have a robust pipeline of products in development, and target genetic diseases caused by single-gene mutations such as Hunter Syndrome, Fabry and Gaucher diseases. Our commercial products include:
- VPRIV®
- Elaprase®
- Replagal ®
- Because of the small patient and healthcare provider population associated with these diseases, we are committed to building outstanding relationships with these groups and providing the best therapies possible.

Shire To be as brave as the people we help

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Shire HGT LTP-400 “ATLAS”

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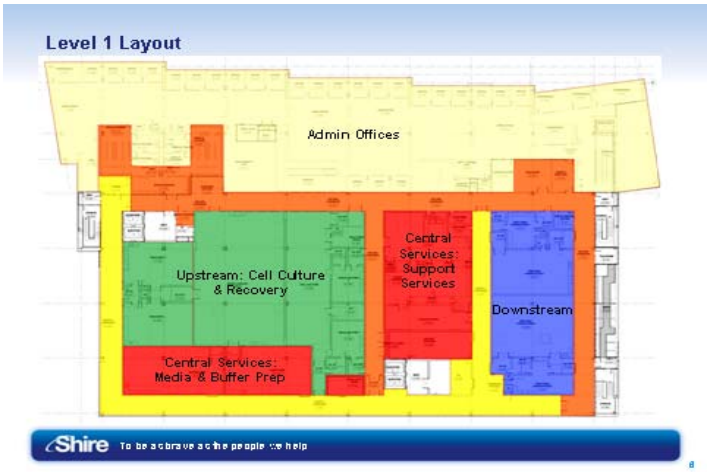
Shire HGT Lexington Commercial Manufacturing Facility



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Why ATLAS?

- Shire HGT's growing demand for licensed commercial products
- Robust Pipeline/Clinical products
- Next Generation products
- Our basis of design (BOD)

Why Single Use?

- Multi-Product Facility Challenges
- Maintaining Flexibility
- Operational Considerations
- Speed

Unique Challenges associated with Single Use Systems

- Technical Challenges
- Business Challenges
- Regulatory Challenges

Shire HGT Single-Use Risk Assessment Program

- The Goal is to apply the industry's best practices to improve Shire's level of control of their Components, Assemblies and Materials
- Key is that we ensure that the Shire Staff are proficient and understand the process!
- Help Vendors understand the process!

Shire HGT Single-Use Risk Assessment Program

- Considerations:
  - Regulatory
  - Industry Understandings
  - Process Requirements
  - Material and Equipment Science
- Today-State of the Industry
- Future-Ensure the program evolves with:
  - Changes in the Regulations and Industry
  - Successful vendor partnerships

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State of the Industry

- Single Use components are used in the Biopharmaceutical Industry
  - Long standing items used for years.
    - Transfer operations (filters and tubing)
    - Short exposure times
  - Recent Trends
    - Gama Irradiation
    - Large Scale
    - Less Stainless Steel

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State of the Industry

- Recent Trends at Shire HGT
  - Bag assemblies
    - Product
    - Solutions
    - Sampling
    - Large Scale up to 2000 liters.
    - Mixing
    - Sensors
    - Filtration
  - Integrated Manifolds
    - Sampling
    - Product and solution transfer
    - Filtration

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Regulatory Requirements

- FDA
  - cGMP-211.65
  - GMPs of the 21st century
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
  - Q8-Pharmaceutical Development
  - Q9-Risk Management
  - Q10-Quality Systems

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CFR 211.65
Equipment Construction

- (a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- (b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

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Industry Activities

- The industry is evolving.
  - Bio-Process Systems Alliance (BPSA)-Industry consortium which has published many guidance articles.
  - PDA-Technical Reports
  - ASME BioProcessing Equipment (BPE) Standard-Published first requirements in 2009.
  - ISPE
    - Product Quality Lifecycle Implementation (PQLI)
    - Baseline Guides
    - Disposables Community of Practice

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ASME BPE 2009 Edition-Published!

PM-7 Single-Use Components and Assemblies

An Internationally recognized Conscientious Standard coordinated with the BPSA and ISPE.

- Identification
- Labeling
- Certificate of Compliance
- Inspection and Packaging
- Joining Methods
- Biocompatibility
- Sterilization

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Evolution vs. Revolution

- Single Use Risk Assessment is an Evolution
  - Within Shire!
  - Within the Industry!
  - Especially with the Vendors!
- The Goal is to apply the industry's best practices to improve Shire's level of control of their Components, Assemblies and Materials
- This is a gradual process…An Evolution
- Key is that we ensure that the Shire Staff are proficient and understand the process!
- Help Vendors understand the process!

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Vendors are key to Shire HGT's Success!

- Strong Vendor partnerships are required:
  - To meet today's needs and
  - To ensure success in the future
    - Technical
    - Business
    - Regulatory

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SHIRE HGT SINGLE-USE BUSINESS PROCESS

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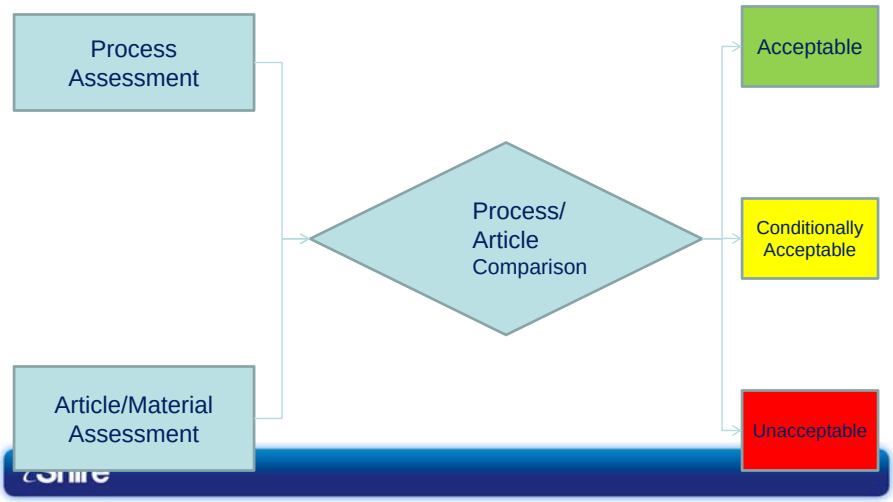
Overview

- This procedure is used to **define and evaluate the risk** associated with the application of components, assemblies (including single-use) and their materials in Shire HGT manufacturing processes. …
- Will **result in an assessment of the potential impact** that a component, assembly and its materials may have on a manufacturing process….
- Result in the **best possible decision** in choosing components/assemblies and their materials **for use in the manufacturing process.**

Shire Article and Material Risk Assessment Procedure



MATERIALS REVIEW

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Article/Material Capability

The capability of the Article/Material to meet the process demands. This will be demonstrated by:

- Vendor and or Shire testing and documentation to support the Article/material's application to the process.

The goal is to substantiate the Article/material's:

- Robust Manufacturing Practices
- Robust Supply Chain Practices
- General BioProcess Performance.

Process Comparison-

- Was the Article/Material used before?
- Previous Process Comparison?

First Time Evaluation?

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Single Use Component Information Received

Article/Component Information
- Drawings
- Certificates of Compliance
- Animal Free Statements
- Extractable Studies
- Leachable Studies
- Validation Studies
- Product Communication

Vendor information
- Client Forms and Responses
- Audits
- Vendor Communication

Lot Information
- Sterilization
- Certificates of Analysis

Commercial Information

Supply Chain Information

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Article/Material Assessment

- Certificate of Analysis
- Test Results
  - USP Class VI
  - Leaks.
  - Material properties testing.
  - Pretreatment
  - Assembly assurance.
  - Extractables.

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Materials Review Continued

- The following categories are assigned:
  - Acceptable of Green
  - Conditionally Acceptable or Yellow
  - Unacceptable or Red

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Materials Review

- Balance - Need to assess all probable risks. Theoretical risks should be considered, but only formally addressed through risk assessment if they carry extraordinary patient safety or regulatory compliance significance.

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Extractables vs. Leachables (BPE)

- Extractables: Chemicals that can be removed from articles using appropriate solvents (e.g. polar and non-polar) for the purpose of identification and quantification of potential leachables.
- Leachables: Chemicals that migrate from the article into the process fluid of interest (e.g. water, buffered solutions, drug product, etc.) under normal and/or accelerated conditions (typically exposure time and/or temperature). Leachables are typically a subset of extractables, but can also be created as a result of chemical reactions with other leachables and/or components.

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Types of Extractables/ Leachables Studies

- Exhaustive Solvent Extractables
  - Organic solvent
  - Water (Purified and WFI)
- Extractables per known protocol
- Extractables/Leachables (Lextractables)
  - Water conditions
  - Common solutions
    - PBS
    - NaOH
    - Phosphoric Acid
- Leachables
  - Product
  - Drug Substance
  - Intermediate Solutions
    - Buffers
    - Media

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Material Review-Vendor role

- Yesterday-Shire HGT received what was available.
- Today-Shire HGT is stating what is minimum.
- Future-Shire HGT requests the proper information is available to ensure Risks are addressed!
  - Vendor Technical Information
  - Vendor Quality Systems
  - Vendor Supply Chain Management
  - Shire HGT/Vendor Partnership
  - Component Change Management!

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PROCESS REVIEW

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Process Design Space

- The Design Space for each aspect considered are evaluated.
- The potential of the process to interact with the article/material is essential for this evaluation.

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Process Assessment

- Product/Process Contact
- Process Step
- Process Conditions
- Volume/Surface Area
- Time of Exposure
- Pretreatment

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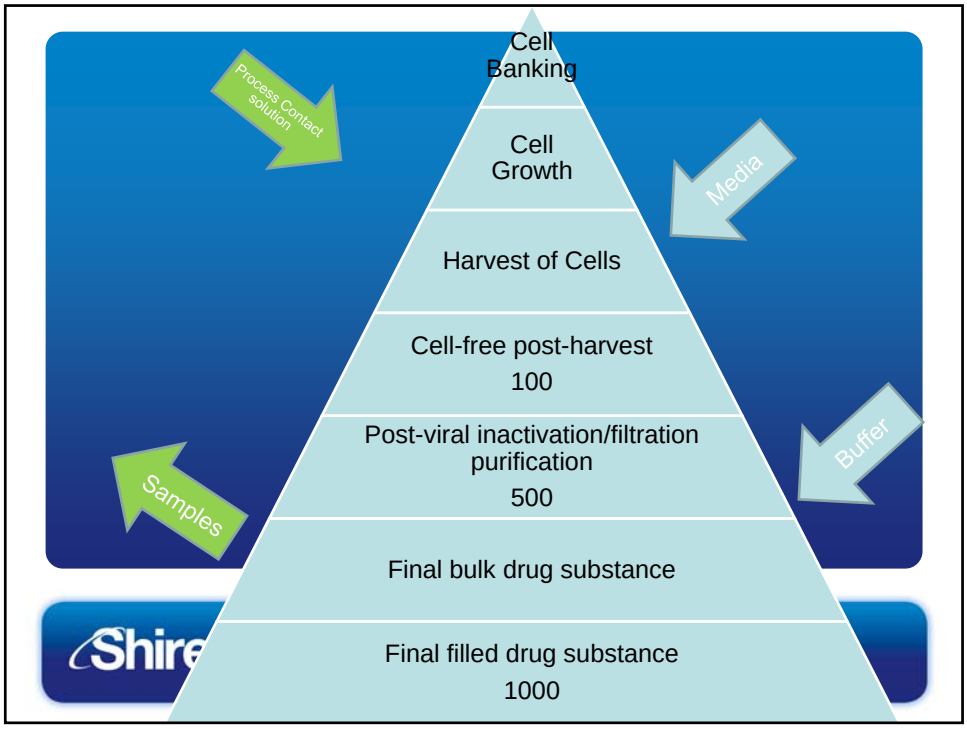

ASSESSMENT PROCESS DESIGN SPACE RISK VS. ARTICLE/MATERIAL CAPABILITIES

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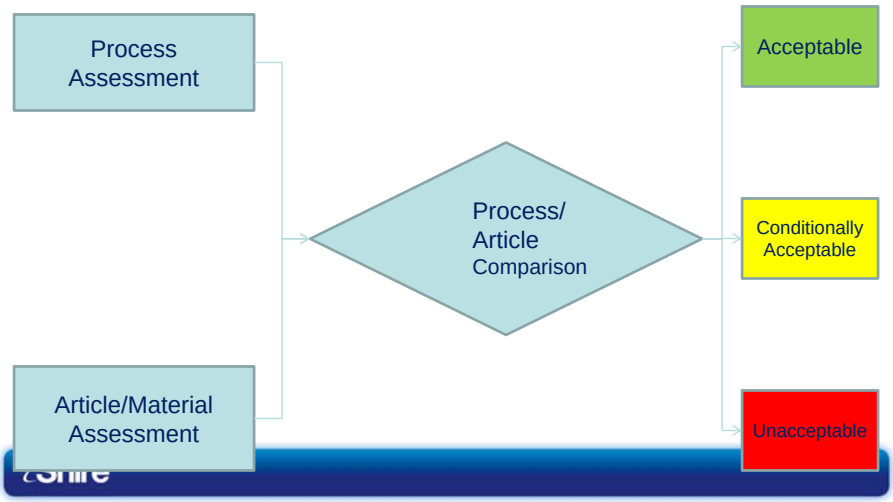
Assessment

- The Process Design Space **Risk** will be evaluated against the **ability** of the Article/Material Capability **to meet the Risk**.
- The assessments will be classified as:
  - Acceptable
  - Conditionally Acceptable
  - Unacceptable

Shire Article and Material Risk Assessment Procedure



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