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The Advantages and Challenges of Operating a GMP Facility Based on Single-Use Equipment

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Outline of Talk

- Introduction to Acceleron
- Acceleron's Basis for Disposable Use
- Facility Concept
- Facility and Equipment design bases
- Facility Operation
- Challenges with use of such a facility

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 ~85 individuals
- Fully integrated biotherapeutic R&D infrastructure
  - Protein engineering
  - In vivo pharmacology
- GMP protein manufacturing facility with seven fusion proteins in development in 2012, and four in the clinic
- Focus on novel GDF related proteins that modulate the growth of bone, muscle, fat and the vasculature

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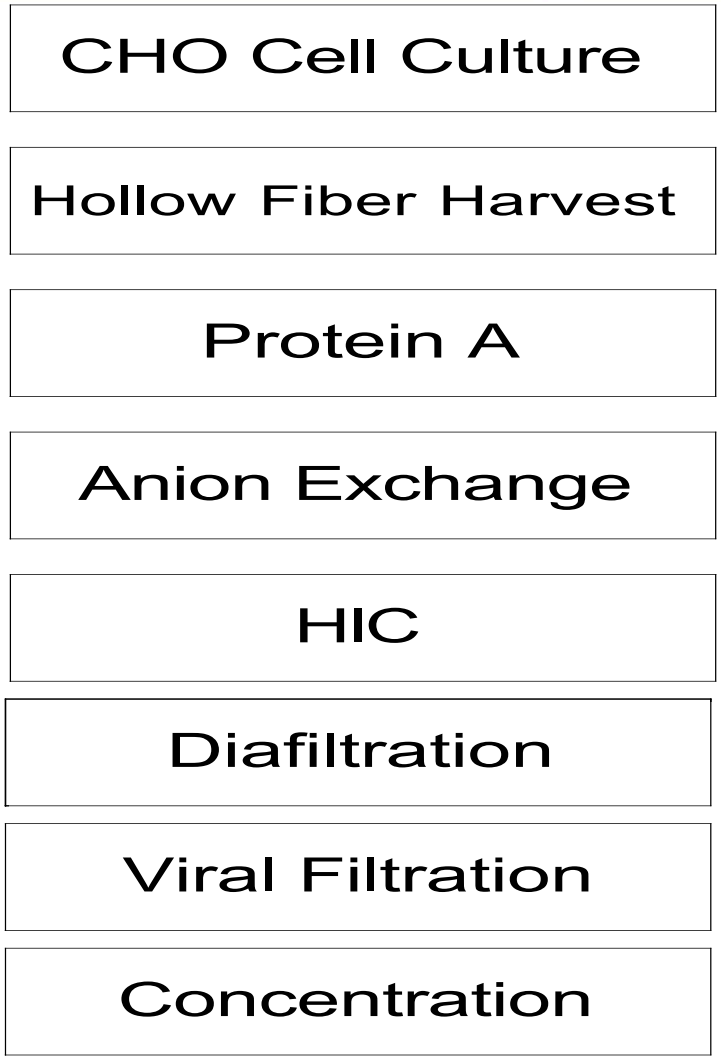
Company Pilot and GMP Manufacturing Strategy

- 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, platform process, quickly make and release phase 1 and 2 material for clinical trials minimizing capital expenditure

Platform Process Schematic



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Design Concepts for Disposable Facility

- **Development\production personnel on the process**, not support
- **Multiple HVACs** to provide flexibility of room uses
- **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

Manufacturing Facility Design Basis

- 2X 1000L Disposable Reactors
- Harvest every week of one bioreactor: up to 40 batches per year @ 1 g/L
- 500g DS batch size – 20kg of protein per year
- Designed to produce a non-sterile, low bioburden, frozen Drug Substance
- Designed for multi-product production
- Provide Quality function space within facility
- Provide Warehouse function in facility

Acceleron 128 Sidney Facility

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Created in 100 yr old building

38,000 ft^2

Manufacturing was originally office area

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GMP Facility Design Details

- Approximately 12,000 ft^2 of GMP Area, with ~4500 ft^2 of production area
- Separate air handling systems for each of the four processing areas. Separate entry area to each process area off common clean corridor
- SOPs in-place to allow different products in the four manufacturing areas
- All media and buffers delivered from adjacent warehouse as portable liquid or pumped from controlled corridor through wall to controlled area.

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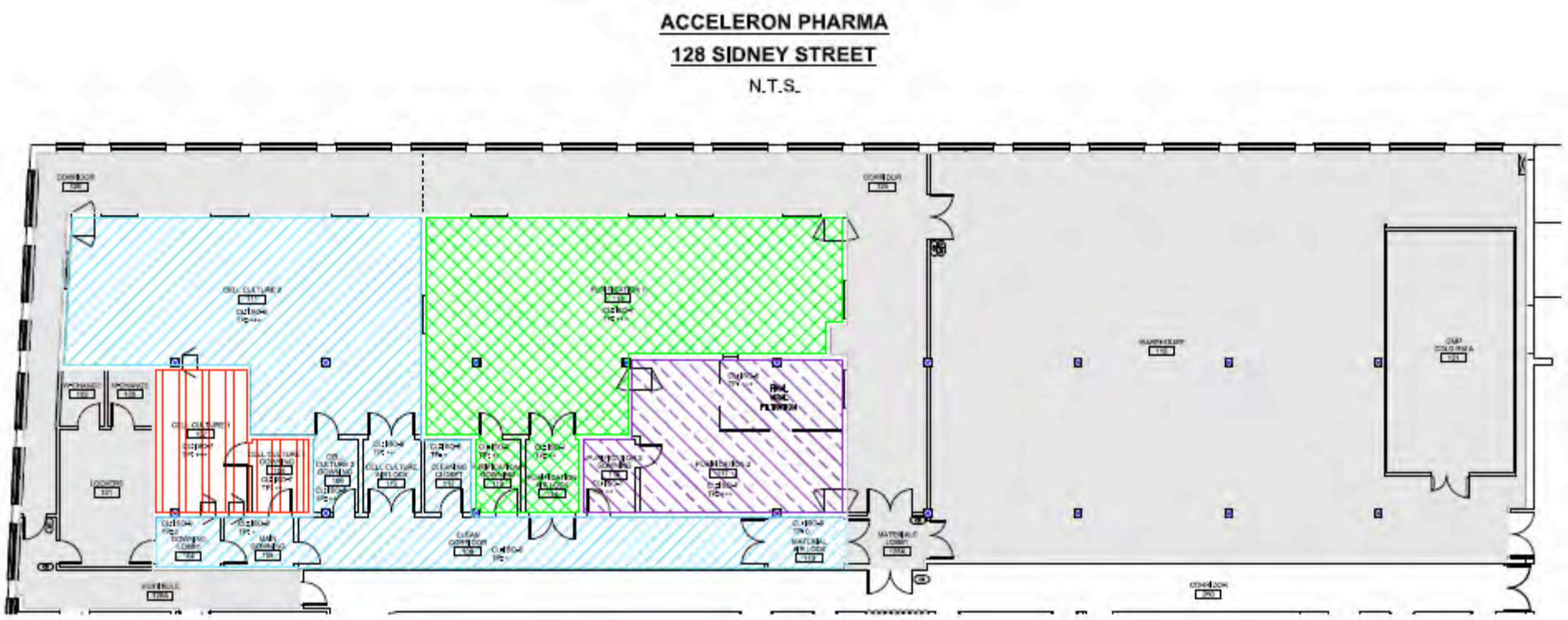
Acceleron 128 Sidney CMF Production Area



Sidney Street Facility

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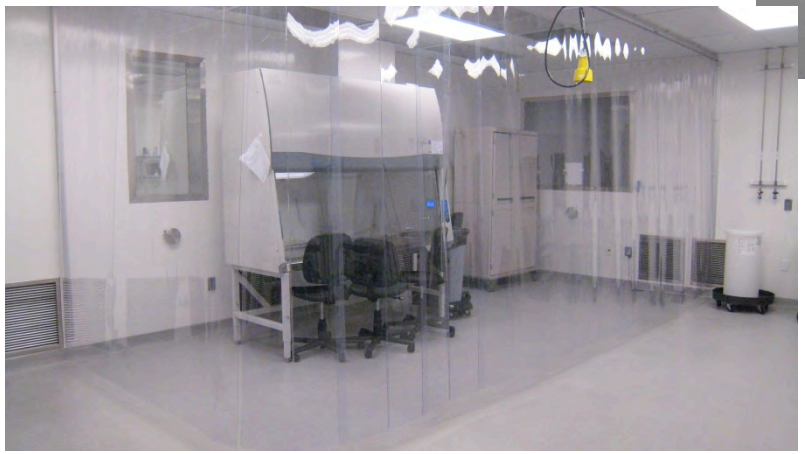
GMP Areas

Small Cell Culture Area (Inoculum)

Large Cell Culture Area

Grey Corridor

Large Purification Area



Small Purification Area (post viral filter)

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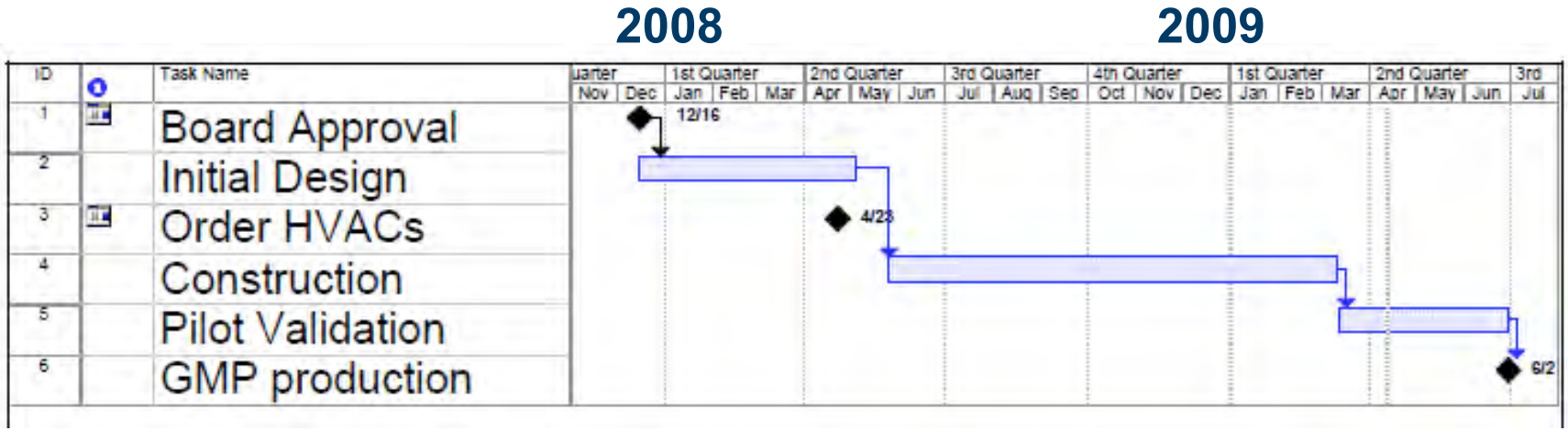
Process Equipment Design Criteria

- Single Use Process Equipment for all Operations – except columns and DO probes (resins dedicated to product) – **No Sterilization or cleaning validation**
- All process equipment without CIP (except columns)
- All buffers, product intermediates, and waste contained in bags within Totes
- Buffers and media delivered sterilely in limited to 20L to 500L aliquots – **No WFI, DI Water Systems**
- All liquids transferred using disposable tubing
- All disposables delivered sterilely
- Sterile connections made using tube welding and CleanPak connections

Timeline for Construction

Concept to GMP Production 19 months



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Operations

and

Challenges over the Last Three Years

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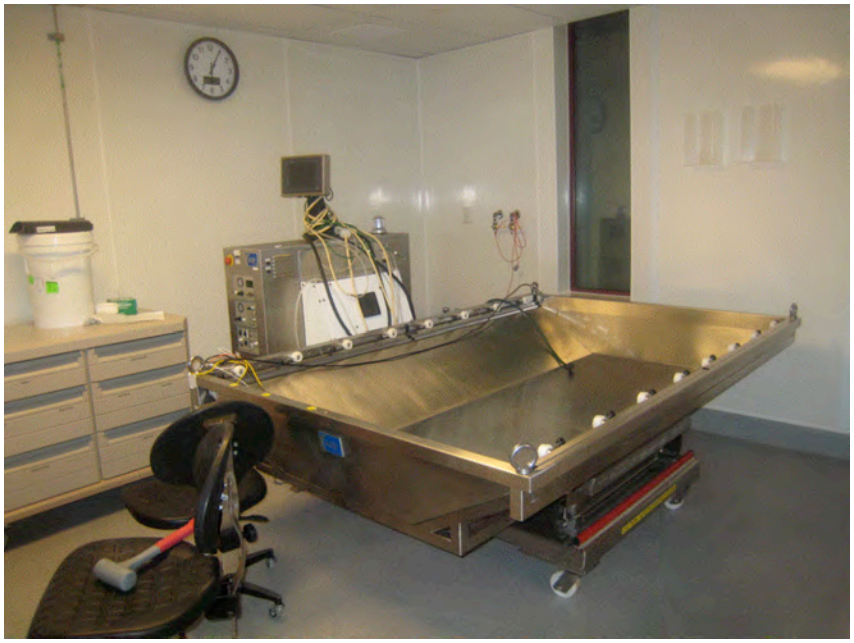
Challenges: Disposable Bioreactor Turnaround without Media Pre-Treatment

Schedule for Bioreactor

• Harvest	3 hr
• Clean\Replace Bag	2 hr
• Fill Bioreactor	6 hr
• Warming Media to Temperature	12 hr
• Inoculate Bioreactor	2 hr

SUB Challenges



- Simple versus complex set up
- Control of process variables
- Variability of cell growth based on configuration

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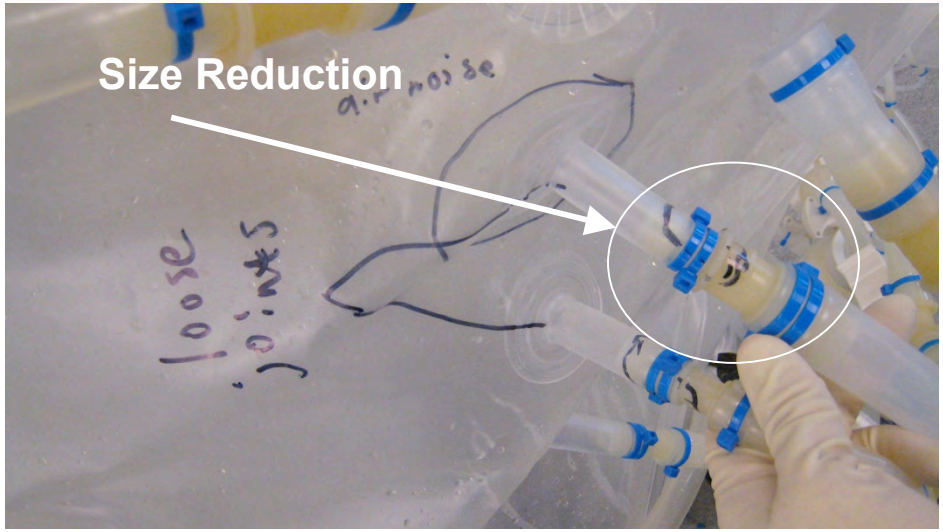
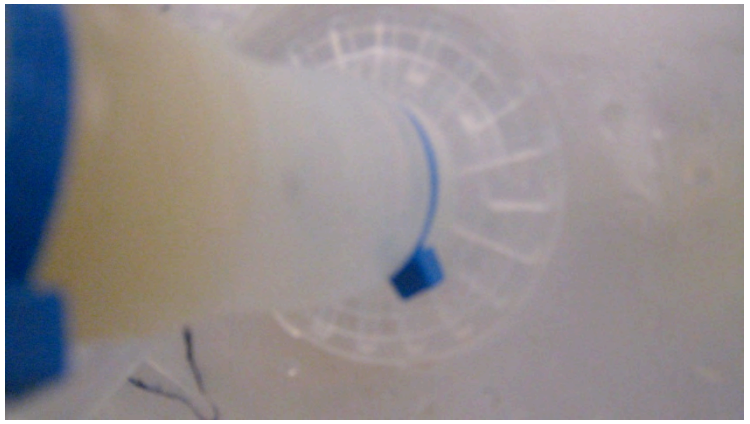
Challenges: Port Cable Ties and Ports





Sturdy Large Port

Less Sturdy Small Port

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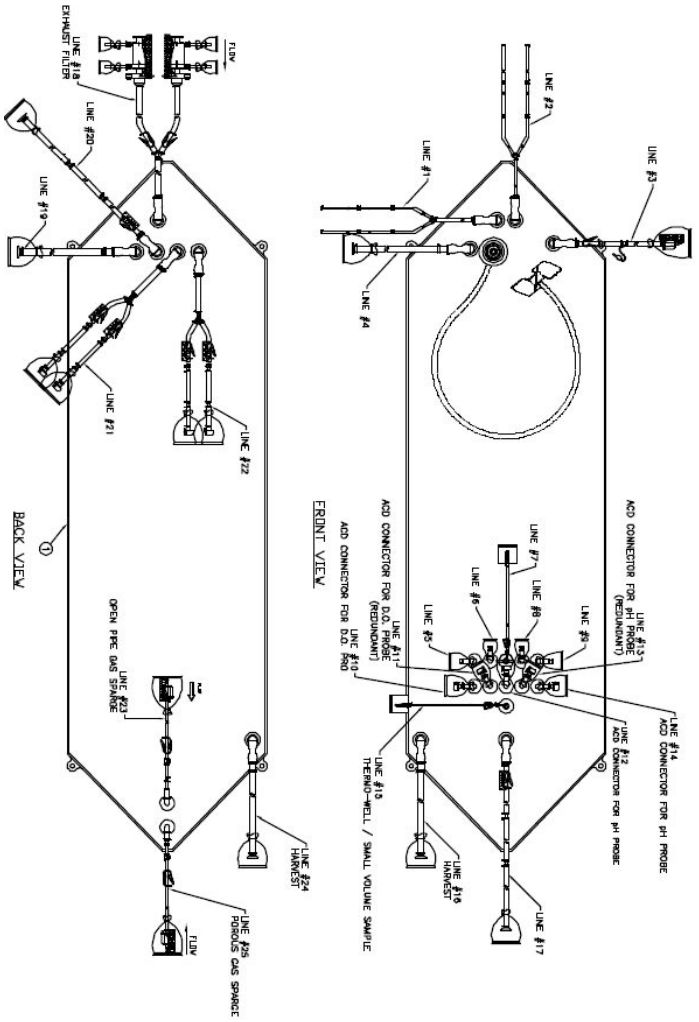
Implementation Challenges: Complex Assemblies

- **1000L SUB Bag**
  - 100s of cable ties (manually assembled & checked)
  - Connectors
  - Tubing/filter assemblies
  - Ports for probes (DO, pH)
  - Impeller (top down)
  - Rev F
  - Partner with vendor to optimize design
  - Custom
    - 24 customers/24 bag designs



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Customer Use From 1Q 2008

ThermoFisher SCIENTIFIC
The world leader in serving science

	No. of SKU's	No. of Customers	Total Purchased
1000 L SUB	24	24	922
500 L SUB	19	9	434
250 L SUB	65	67	1,523
100 L SUB	15	17	370
50 L SUB	54	92	1,232
TOTAL	177	209	4,481

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Harvest Challenges

Simple, Not Sterile,
bit messier

More complex, sterile, and,
sometimes,
more protein loss

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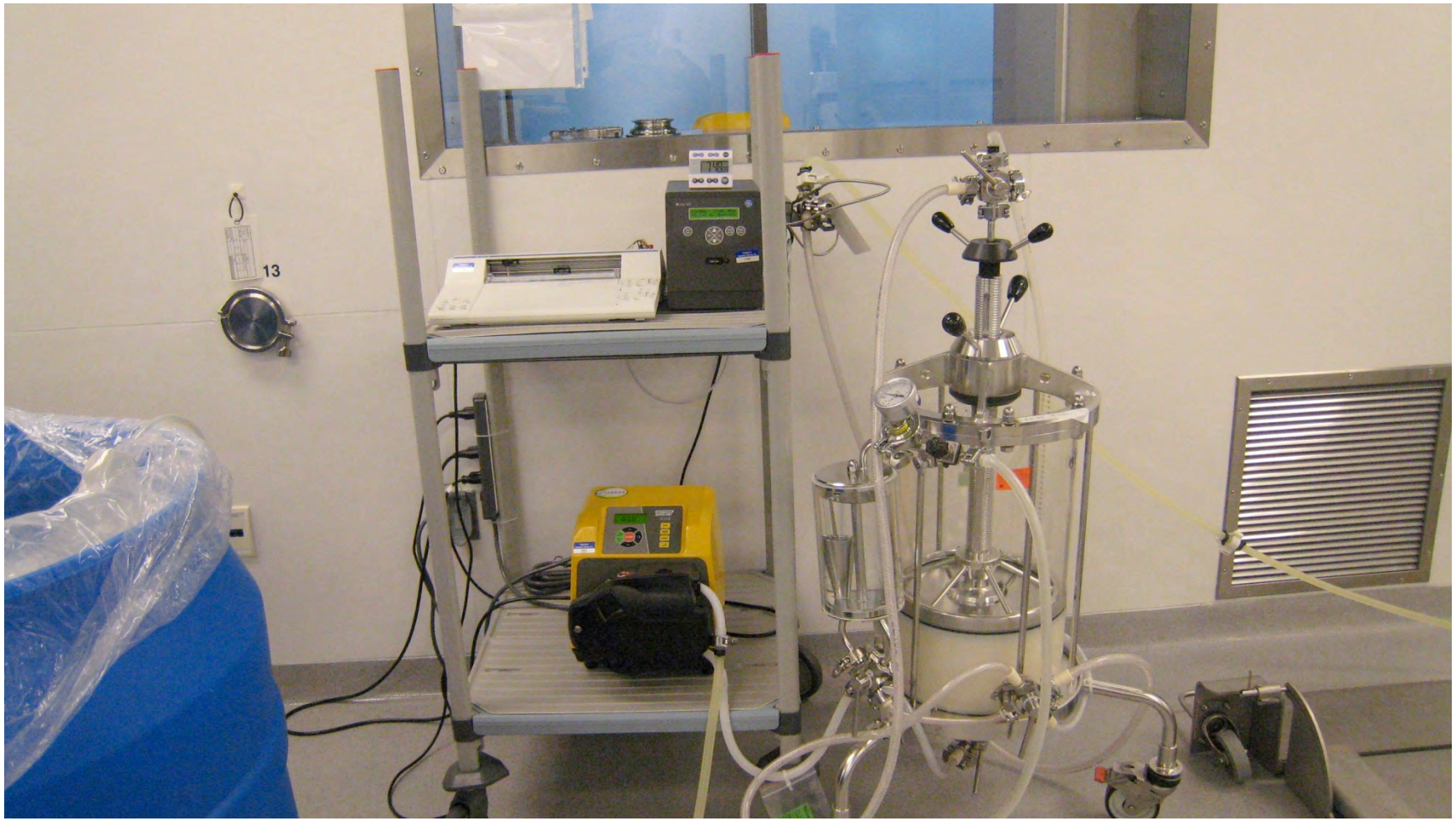
Simple, “Mostly” Disposable Chromatography Modules



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Instrumentation Challenge: Sterility of Probes

Disposable Sensors Implementation Issues

- **Pre-Calibrated, Disposable, Single-Use Pressure Sensor**
- **MFG needs to verify Column Pressures**
- **Issue**
  - **Vendor claims 'can be' but 'does not' gamma radiate**
  - **Mfg/Quality approach towards Sterility "unclear"**
- **Solution**
  - **Partnership with Vendor on Testing**
- **Lessons learned**
  - **Gather & *evaluate* all vendor's documentation**
  - **Upfront Quality Req. & Testing Responsibility**

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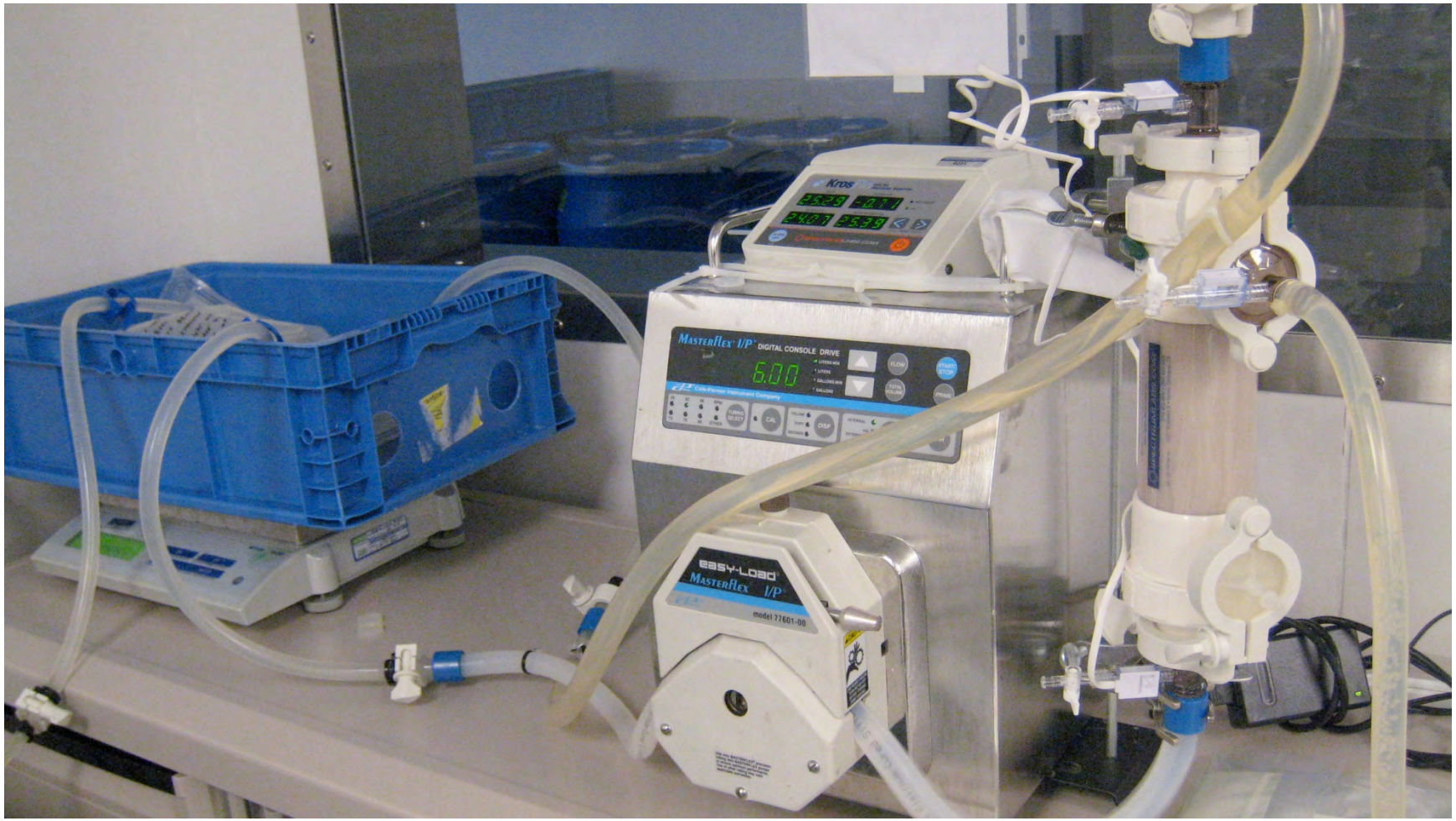
Single Use, Disposable Diafiltration\Concentration



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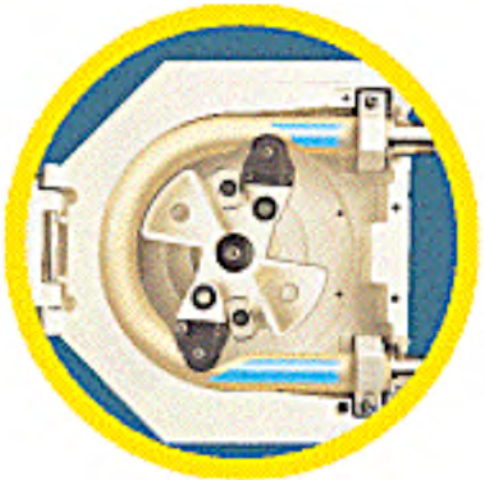
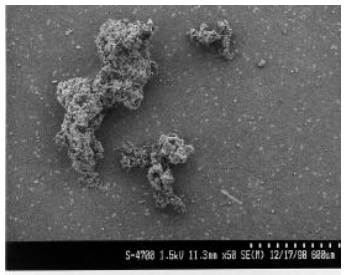
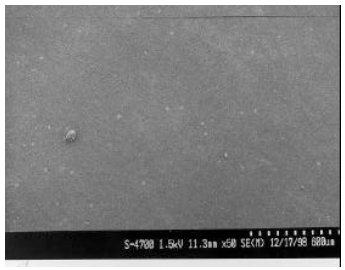
Peristaltic Pump: Tubing Spallaging







Spallation: Particle abrasion from the inside of the tubing

Temperature	Spallation (mg)	
	6 hours	24 hours
37 °C	1.1	1.0

- Resistance to spallation
- Reduced spallation

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Biggest Challenge: Quality and Logistics

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Challenges: Back-up Suppliers of Disposables – Are they interchangeable? Reliable?

COMPONENT	VENDORS
Flasks	1
Bags	2
SUBS	1
Tubing	2
Solutions	2
Membranes	2
Filters	2

Vendor Audit/Qualification Program Essential

Vendor Controls what contacts your product!

- **Vendor Qualification Classification**
  - Accepted/Approved/Certified Vendor
  - Utility Validation Program
- **Vendor Ranking Criteria**
  - Critical Part; Sole supplier; Lead Time;
  - Cost, Quality; Vendor-History
- **Quality Agreement**
  - Change Control/Deviation Notification
  - Confidentiality Disclosure
- **Audit Program**
  - GMP Mfg, Cleanrooms, Quality Systems, **Utilities**
  - Med. Device QSR vs. GMP, New Vendor!

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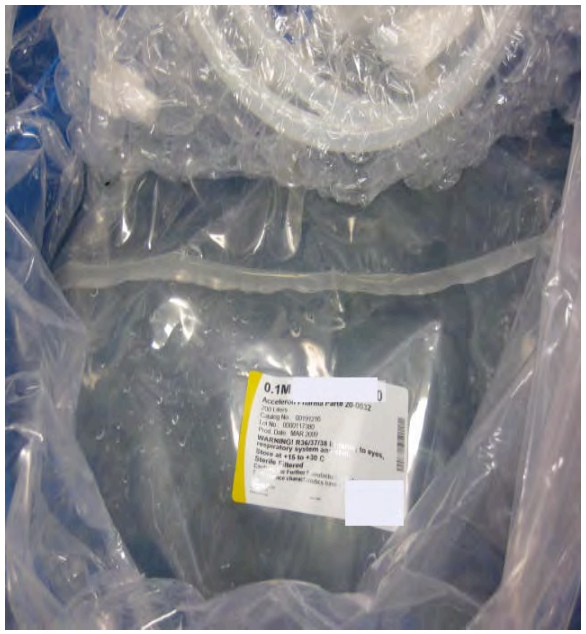
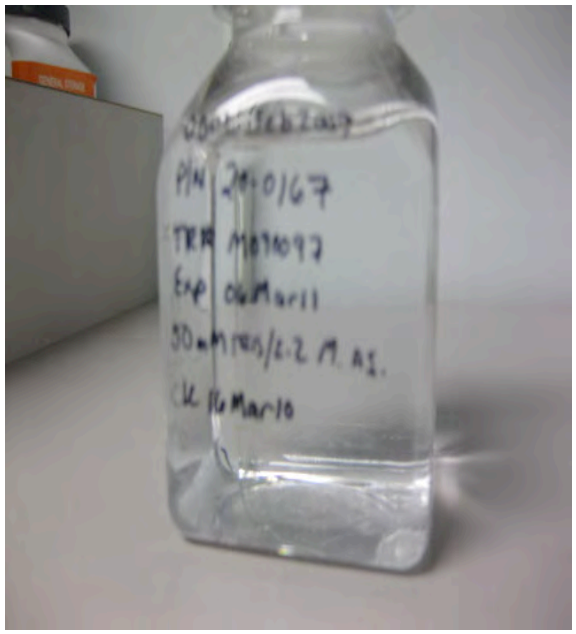
Required Ongoing Compatibility Assessment!

AT DELIVERY



AFTER 15 MONTHS

IS THE BUFFER OKAY???



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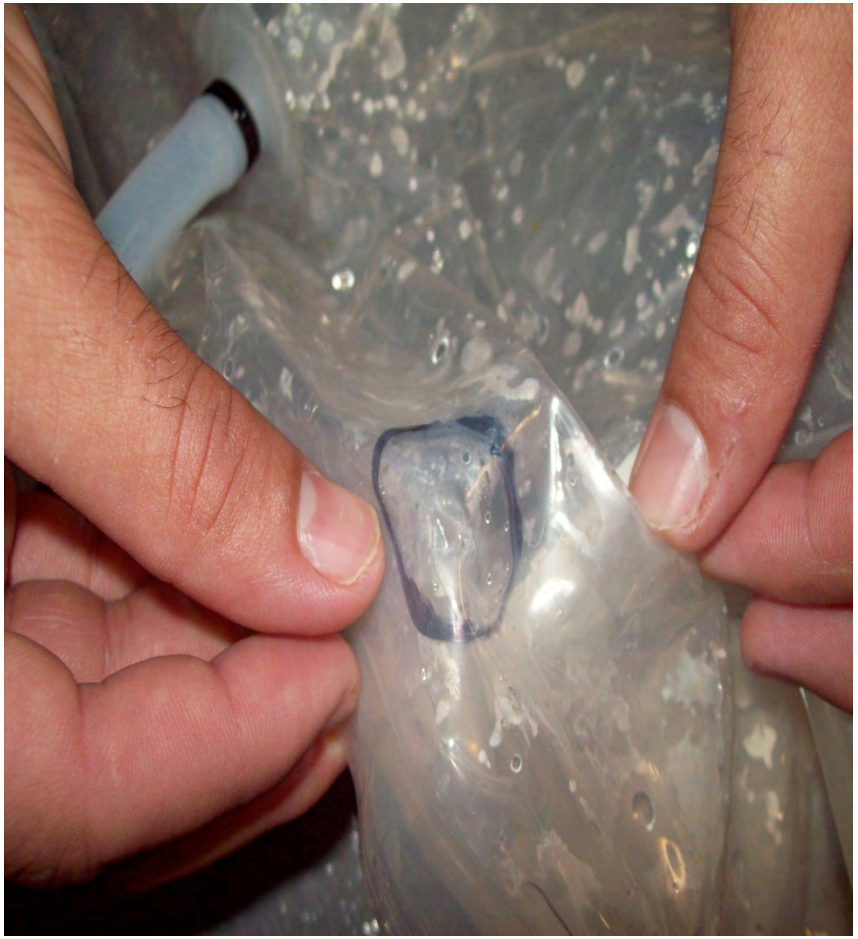
Implementation Challenges: Shipping/Containment



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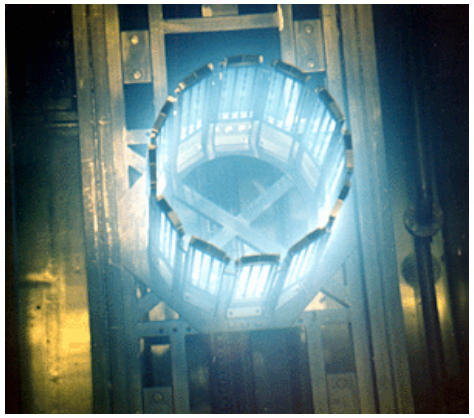
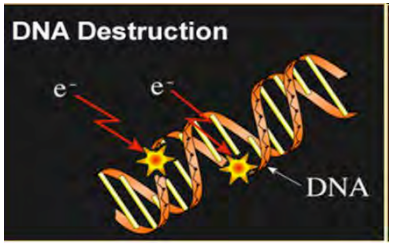
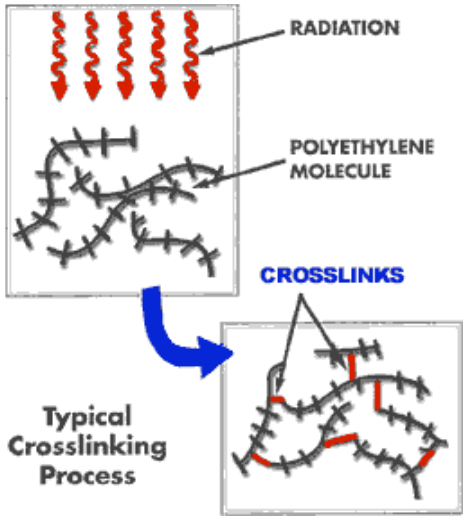
Rely on Sterility from Vendor

- **What is Effect of Gamma Irradiation?**
  - **Microorganisms\Viruses inactivated by damage to DNA but –**
  - **Effect on Plastics**
  - **Effects on Extractables**
  - **Effect on Life of Components**







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Storage of Drug Substance

- Solutions stored in PETG Container in Freezer at -80°C
- Risks Involved in Assessment
- Brittleness Temperature = -40°C
- Careful container/material selection can avoid product loss!
- PP bags are worse!

Material	Brittleness Temperature °C
Polypropylene	0
PETG	-40
Polycarbonate	-135
Teflon (PFA)	-270
Celsius Pak (EVA)	-80
Stainless Steel	N\A
COP Resin	-196

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Additional Challenges: Raw Materials

- Vendor Quality Programs – Mistakes are more difficult to catch externally
- Cost of small orders
- Availability of Raw Materials - Delivery
- Shipping of Material: $0.1-0.8 /1000 Liters/mile
- EU Testing and Release of Sterile Solutions in Bags
- Stability of Solutions\Assay Test Variability
- Disposal of Waste: 50 x 200L drums\2 weeks

Future Considerations: Facility Design and Operation

- Durability over Multiple Campaigns
- Durability of Facility as far as Environmental Monitoring
- Limitations of Purification Scale
- Ability to Run and Sustain 40 batches per year
- Further optimization of capital and FTE time
- User Group for such Facilities –

Acknowledgements and Questions

- Acceleron Manufacturing, Facility and Quality Staff
- Industrial Facility Design, Inc.
- J. Calnan and Associates
- ISPE Engineers in Boston Area
- Disposable Community (with special note to P. Galliher, A. Sinclair, and M. Monge)

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Any Interest in Viral Removal Data Exchange and ASTM Biotechnology Standards?

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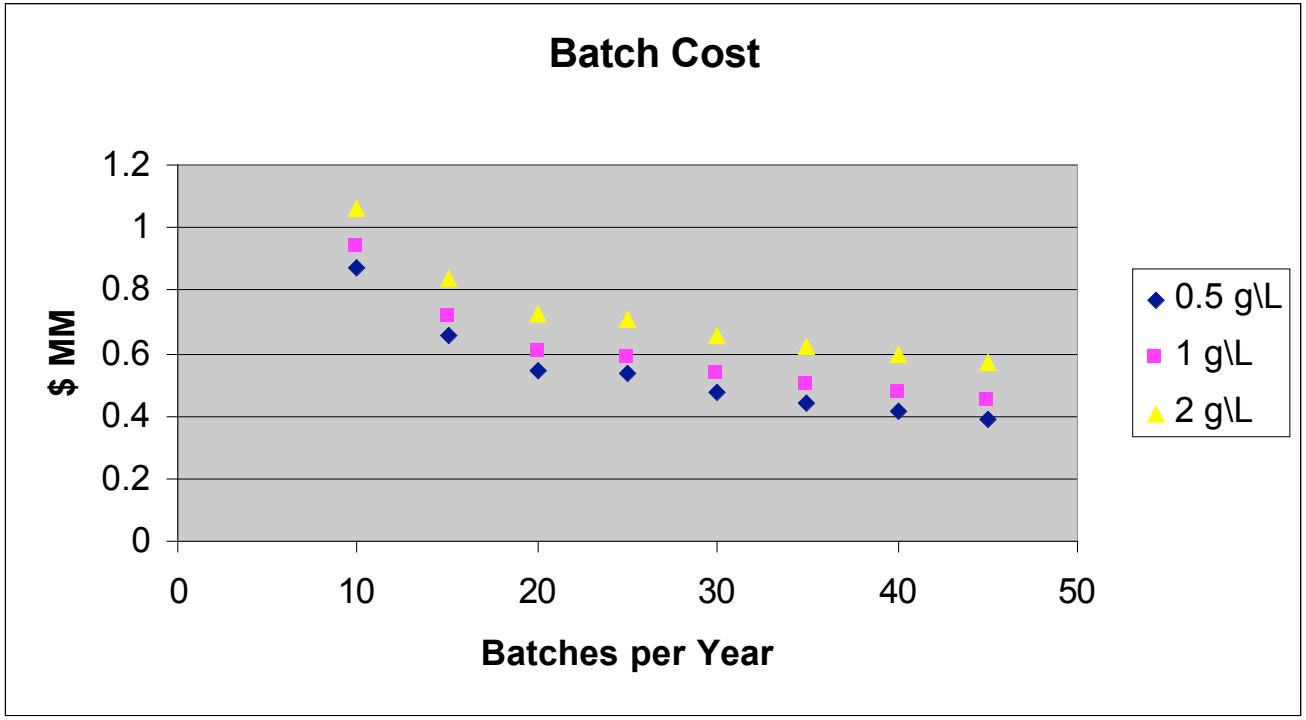
Operations: Batch Cost in Plant



- 1000L bioreactor

~ $400,000-$1,000,000 batch cost in Disposable Plant Model

~ $600,000-900,000\batch at CMO with present process

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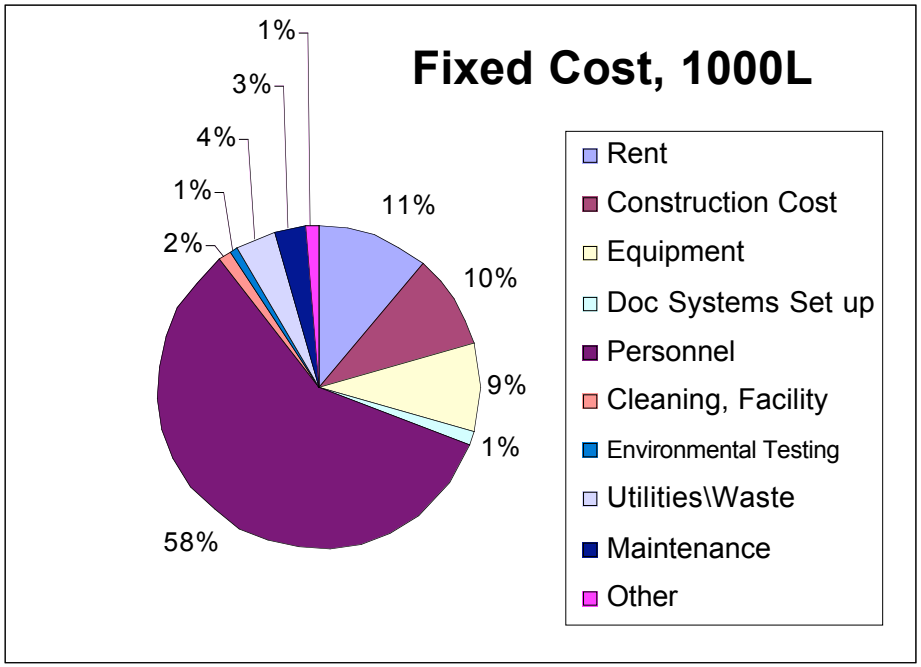
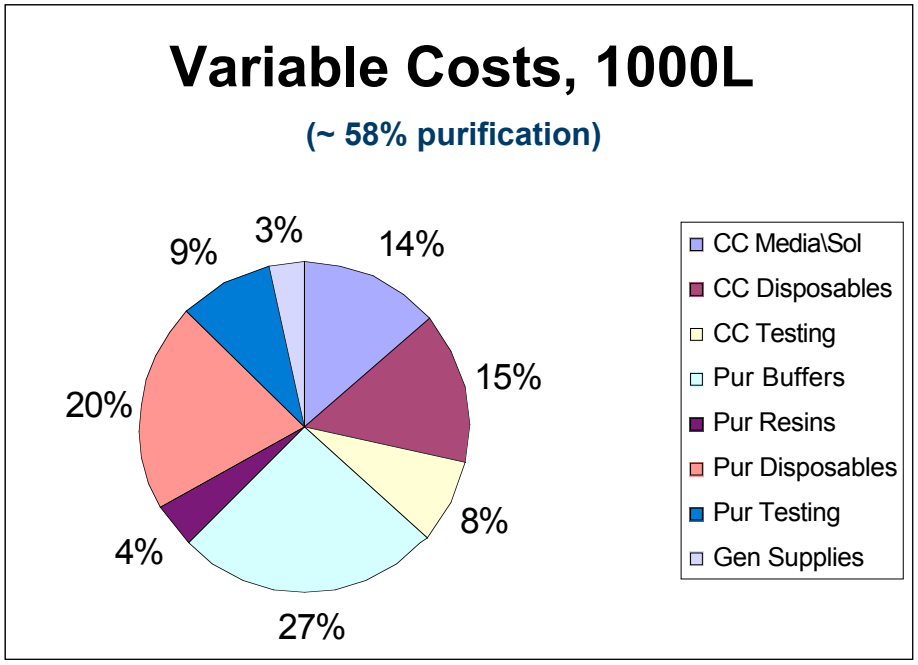
Operations: Material Costs Breakdown





Fixed Cost is 50% of batch cost

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