Outline

- Shire Introduction
- Development Process
  - Shire HGT Platform
  - The promise of disposables
- Development Considerations
  - Process and Scale-Up Challenges
  - Process to Product and Other Factors
  - Quality and Supplier Management

Shire

- **Organized in 3 divisions**
  - Specialty Pharmaceuticals (Small Molecules)
  - Human Genetic Therapies (Biologics, single mutation genetic diseases)
  - Regenerative Medicine (Tissue repair & regeneration)
- **Human Genetic Therapies (HGT)**
  - leading-edge expertise in enzyme replacement therapy (ERT)
  - Unique human cell line technology platform
  - A number of effective treatments for conditions caused by enzyme or protein deficiencies
  - Three ERT's on the market currently. Elaprase, Replagal and VPRIV.
- **Active ERT Projects in Development**
  - HGT 4510: Duchenne Muscular Dystrophy (DMD)
  - HGT 2310: Hunter syndrome CNS
  - HGT 1110: Metachromatic Leukodystrophy (MLD)
  - HGT 4101: Sanfilippo A syndrome
  - HGT 3010: Sanfilippo B syndrome

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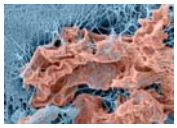
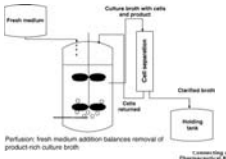
Shire HGT Platform

- **Large molecule drugs**
  - Proteins
- **HT1080 cells**
  - Human fibrosarcoma cell line



- **Perfusion process**
  - Cell aggregate suspension culture
  - 20-45 day culture duration
  - Perfusate is maintained in a cold room environment

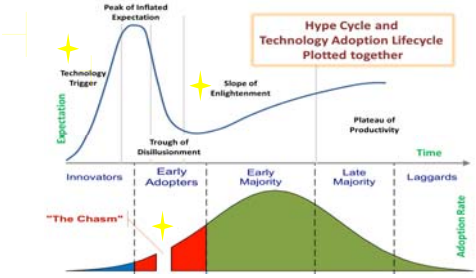


The Promise: Single Use Paradise

The Reality:

Years of Wandering through the Development Desert

The Hype Cycle & Technology Adoption Lifecycle



The Chasm: the point at which the adopter is forced to fit existing processes to new technology or adapt the technology to the process.

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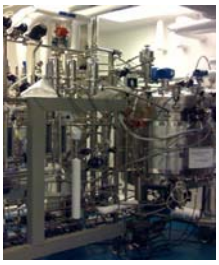
The Process Challenge

- **2006-7:** Hybrid System for perfusion developed by coupling existing technologies



- **Challenge**: How to facilitate cell retention function with disposable systems?
- **Solution**: ?

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New Technology Evaluation

Application

- Who else is using them?
  - For how long?
  - For what purpose?

Characterization

- Do we have good characterization information?
  - How do we get it?
  - Does the supplier have it?

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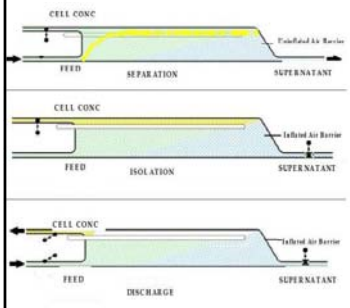
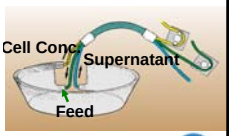
The Single Use Centrifuge

- How does it work?



- Key parameters:
  - Separation speed/ time
  - Percent solids
  - Discharge rate/time
  - Residence time



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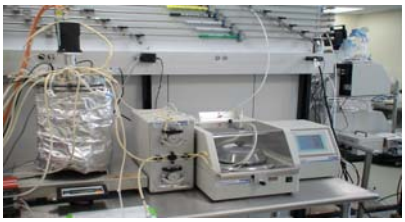
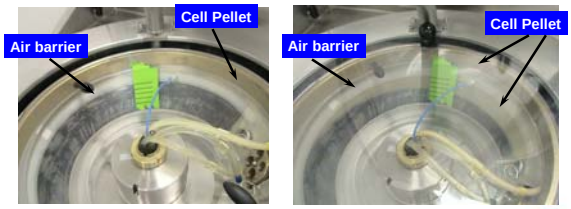
Proof of Concept for Process Integration

- Not quite “plug-n-play”
- Trial and error characterization for model development
- No heuristics for scalability



Process Characterization

Separation Time (s)	% chamber Filled	Throughput (L/day)	Cell Loss (%)	Pellet Clearing
5	33	1229	1.2	Clear
7	44	1408	1.5	Clear
8	49	1474	1.7	Clear
9	55	1531	NA	Build up



Limiting Factor: Pellet Buildup

Points to Consider for Process Scale-Up

- Throughput
- Cell shear
- Residence time
- Connectivity
- Additions
  - Top
  - Sub-surface

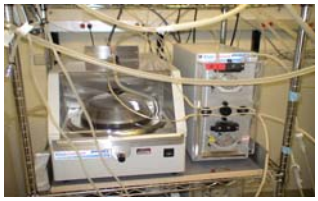
Bioreactor

- Line dimensions
- Mixing
- Heat transfer
- Mass transfer
- **MOC!!!!**

10 L to 200L was fairly simple to implement, but was it correct?

Product Development

- 3 Rs for Connections:
  - Reduce
  - Re-size
  - Re-form



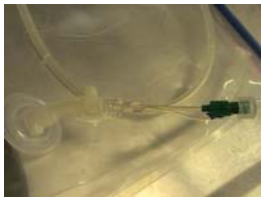
- Reducers and hose barbs should be removed wherever possible!
- Molded assemblies provide the least amount of concern.

Process Engineering to Product Engineering

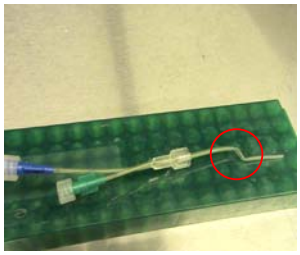
- Is the technology there to fit your needs?

- Can it be made consistently and more importantly correctly?

Process Engineering to Product Engineering



- The addition assembly looks fine on the outside. BUT:



- Can it be made consistently and more importantly, correctly?
- Product characterization
  - define failure modes and mitigate risk

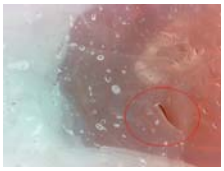
PD ≠ Process Development

PD = Process / Product Development

The Human Factor

- Understand product and equipment capabilities
  - You have to teach steel dogs plastic tricks
- Reproducible actions
  - placement of tubing

- Understand the constraints of operational environment
  - Welding in Cold rooms
- Sharps
  - Un-Packaging
  - Sampling and equipment placement



- No re-steam or pressure test on these systems
  - One shot deal, integrity is of paramount importance

Skilled Artisans not just Technicians

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Disposal of Disposables

- Is your facility ready for the magnitude of waste?
  - Movement
  - Storage
  - Disposal

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Your Quality Family

- Heavy reliance on suppliers and their sub-suppliers
  - It's not a date, it is MARRIAGE!
  - Pick your partner carefully, you are marrying their family as well…
  - And consider a prenup… (i.e. technical quality agreements, supply agreements)

- Your new best friends
  - Vendor quality assurance
  - Supply chain

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Supplier Qualification

- Do they understand their product?
  - Extractables?
  - Mean time before failure?
  - Shelf life?
- Where does the product come from?
  - US, Europe, China?
- What inventory do they stock?
- Can they ship in time?
- Do they have control of their supply chain?
- Do they have packaging expertise?

Ask your supplier to help you understand their processes and constraints

Conclusions

- The adoption of single-use systems significantly alter the development paradigm
  - Get ready to perform as much "product" as "process" development and characterization
- Single-use systems are not as "plug-n-play" as perceived
  - Get ready to face scalability/process integration challenges and perform extensive in-house product characterization/ process modeling studies
- Successful commercialization of single-use technology platforms require careful consideration of the human factor
  - Make provisions for transfer of the skilled art along with the exact science
- To avoid the "unintended long term side effects" of single-use systems, bring supply chain and quality into the game early on and truly partner with your suppliers
  - Quality planning and supplier qualification MUST be part of your development process
  - Quality by Design (QbD) truly applies to the equipment aspect of single-use systems

Acknowledgements

- Shire Cell Culture Process Development (CCPD)
- Shire Large Scale Development Laboratory (LSDL)

Questions?