ENGINEERING PHARMACEUTICAL INNOVATION

What a Process Technology Transfer Needs to Accomplish Hurdles and Techniques

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Biotech Process Scale-up & Tech Transfer
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In This Presentation

- Technology Transfer Defined
- Scope of Presentation
- Guiding Principles
- Readiness for Process Tech Transfer
- Tech Transfer Governance Structure
- Example Tech Transfer Project Structure
- Originating & Receiving Organization
  - Key Requirements and Common Pitfalls
- General Client / CMO considerations
- Project Management - Key Success Factors

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Process Technology Transfer Defined

The faithful and compliant transfer of all technology, information, documentation, and skills required for a manufacturing process from the process owner (originating organization) to a GMP manufacturing site (receiving organization) where the process has not run previously.

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Scope of Presentation

In-house process transfers

1. Pre-Clinical or Clinical Drug Substance (DS) process transfers:
   - Process Development to Commercial MFG
   - Make DS for clinical programs
2. Licensed, commercial DS process transfers
   - To a new commercial facility within the company

External process transfers

1. Commercial MFG to a Contract MFG Organization (CMO)
2. Clinical DS to a CMO

Out of scope for this presentation

1. Drug Product transfers to CMO fill sites – A different type of transfer
2. Assay and analytical method transfers
   - In parallel with process transfers
   - Can be managed together or separately

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Guiding Principles

- Minimize equipment and process variability
  - Change as little as possible between donor & receiver
- Partner with Quality Units, early and often to assure and maintain compliance
- Establish a pre-defined, mutually agreed upon governance structure……and follow it!
- Extensive planning and schedule development
- The Power of Team-Owned Decisions
  - When the TEAM knows that it OWNS all decisions, blaming behavior is minimized and team accountability is real

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Guiding Principles - continued

- Break project into 5-8 discrete stages of work
- Perform a rigorous facility fit assessment to identify equipment compatibility and gaps
  - before you sign a contract or commence with internal transfers

- **Technology Transfer is Hard Work ….To Do It Well You Need:**
- A well-structured tech transfer business process
- Middle and senior management support

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Receiving Organization
Assess Readiness for Process Tech Transfer

Transfer readiness improves with experience at increasing scales

- If already a commercial product, the question is moot

Conduct technical feasibility assessment of process readiness

- A key activity before starting tech transfer
- Standards of productivity & product quality for early-stage clinical products may be lower than for a licensed process

Does it deliver appropriate product quality and quantity as you scale up?

- At lab scale
  - With only small-scale data, Receiving Organization must conduct rigorous assessment of manufacturability
- At Pilot or near-commercial scale
  - Manufacturability assessment still critical
  - Operational experience increases confidence and improves likelihood of successful tech transfer
  - Process characterization and robustness studies a plus
  - Lower risk of scale-up related problems

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Tech Transfer Governance Structure

Question: Why Governance?

Answer:

- Decision making and project management is efficient
- Teams can be officially sanctioned and held accountable
- Resource allocation can be efficiently managed

Elements

- Pre-define with internal management and with CMO
- Create a management structure - Org Chart
  - Defined Roles and Responsibilities for all levels
  - Establish a formal escalation process
  - Define communication and reporting channels
- Establish performance measurements (e.g., schedule adherence)
- Develop a responsibility assignment matrix (RACI)

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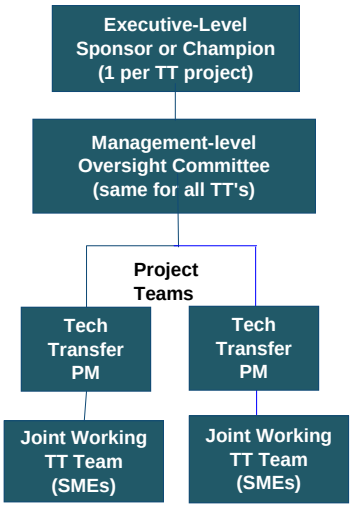
Tech Transfer Governance Structure
Typical Org Chart
with Roles and Responsibilities for all levels

Tech Transfer Governance Structure



	Role	Responsible	Members
Executive-Level Sponsor or Champion (1 per TT project)	- Set direction - Final arbiter - Roadblock remover	Organization	VP or AVP level
Management-level Oversight Committee (same for all TT's)	- Manage TT Project Portfolio	Oversight & Approvals	Director or Sr. Manager level TT Project Managers
Tech Transfer PM / Tech Transfer PM	- Project Governance - Main facilitator	Project Owner	One PM / Project
Joint Working TT Team (SMEs) / Joint Working TT Team (SMEs)	SME Pool	ManageTask Execution	As Selected (Functional Areas)

Tech Transfer Project Structure
- A gated, stage-based approach

Use specific stages or phases to define each major group of activities

- **Create a high-level Process Map to define major 'buckets' of work**
- **View each stage as being bound by a gate**
  - **Not intended as a hard stop but as discipline to complete work within each phase**
- **Each stage contains discreet deliverables**
  - **Translate into a punch list or checklist of activities**
  - **Use checklist as a framework for schedule creation**

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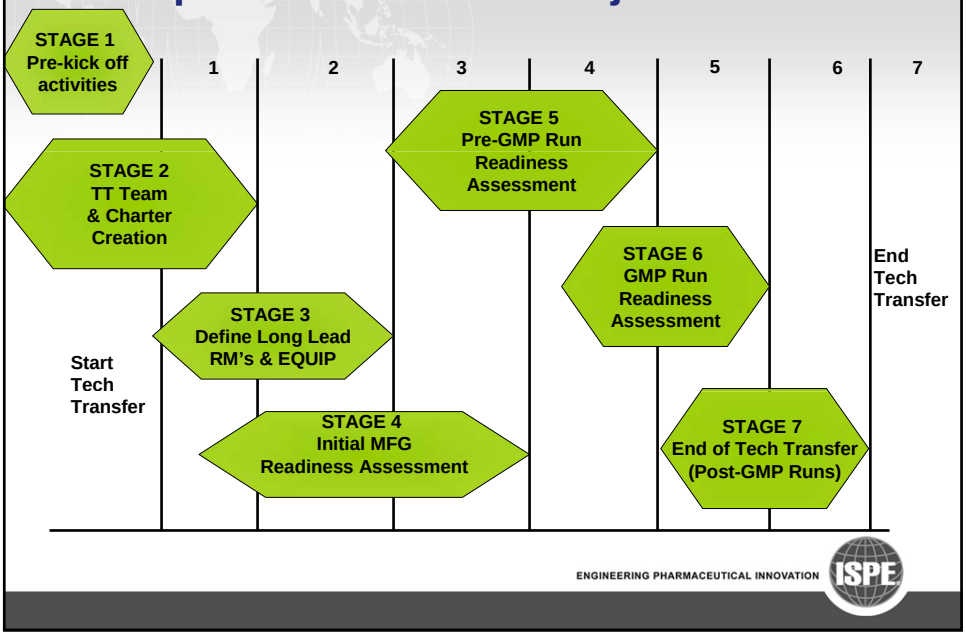
Example Tech Transfer Project Structure



Schedule

The schedule is the key management tool for accurate project tracking

2 Week Lookahead - All Functions

Activity ID	Activity Name	Original Duration	Start	Finish	Total Float
	Tech Transfer Project - Level III	133	09-Jul-09 A	18-Jan-10	104
	Process Development	0	25-Nov-09	25-Nov-09	21
20470	Approve Rev 0 Process Description - Thaw --> BRX	0		25-Nov-09*	21
20810	Approve Rev 0 Process Description - Clarification & Capture	0		25-Nov-09*	21
	Engineering	93	09-Jul-09 A	10-Dec-09	129
	URSs	88	09-Jul-09 A	04-Dec-09	134
-5380	Approve URS - Harvest Clarification & UF/DF Capture (Shire)	5	17-Jul-09 A	01-Dec-09	137
-5390	Issue URS - Harvest Clarification & UF/DF Capture	0	01-Dec-09		137
-5330	Approve URS - Cell Expansion for Bioreactor Production (Shire)	10	09-Jul-09 A	03-Dec-09	134
-5340	Issue URS - Cell Expansion for Bioreactor Production	0	04-Dec-09		134
	FS Scope Documents	54	24-Sep-09 A	10-Dec-09	15
3650	Draft FS Scope Document - BRX-1300/1800 Integration	5	24-Sep-09 A	25-Nov-09	15
3660	Review FS Scope Document - BRX-1300/1800 Integration	5	25-Nov-09	03-Dec-09	15
3670	Approve FS Scope Document - BRX-1300/1800 Integration	5	04-Dec-09	10-Dec-09	15
	Procurement	113	21-Aug-09 A	18-Jan-10	104
	BRX-1300 Integration (Centrifuge, Bleed Bag, Harvest Break Bag)	113	21-Aug-09 A	11-Jan-10	0
4640	Request/Review/Approve Quote - BRX-1300 50L Harvest Brea...	10	21-Aug-09 A	03-Dec-09	14
3820	Procure Electrical/Controls Contract - BRX-1300 Integration	10	25-Nov-09	10-Dec-09	20
4580	Procure BRX-1300 200L Bleed Bag Tote/Scale	60	05-Oct-09 A	14-Dec-09	17
4600	Procure BRX-1300 50L Harvest Break Bag Tote	10	04-Dec-09	17-Dec-09	14
4590	Procure BRX-1300 Harvest Break Bag Scale	25	16-Sep-09 A	04-Jan-10	4
4570	Procure BRX-1300 Bleed Bag Pumps	30	16-Sep-09 A	11-Jan-10	-1
	BRX-1800 Integration (Centrifuge, Bleed Bag, Harvest Break Bag)	113	21-Aug-09 A	11-Jan-10	0
-14670	Request/Review/Approve Quote - BRX-1800 50L Harvest Brea...	10	21-Aug-09 A	03-Dec-09	15
-23830	Procure Electrical/Controls Contract - BRX-1800 Integration	10	25-Nov-09	10-Dec-09	18
-14720	Procure BRX-1800 200L Bleed Bag Tote/Scale	60	05-Oct-09 A	14-Dec-09	19
-14690	Procure BRX-1800 50L Harvest Break Bag Tote	10	04-Dec-09	17-Dec-09	15
-14700	Procure BRX-1800 Harvest Break Bag Scale	25	16-Sep-09 A	04-Jan-10	5

ORIGINATING and RECEIVING ORGANIZATION

Points to Consider

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ORIGINATING ORGANIZATION
Key Requirements & Points to Consider

- **Allocate sufficient time for development of process**
- **Create an accurate and locked-down process description (both upstream and downstream) as early as possible**
  - **…or at least a PFD with operating and performance parameters / ranges**
  - Identify critical quality attributes, if possible
  - If process description is not fully developed, have a solid PFD and input / output process parameter tables ready
  - Do as much process characterization as possible up front, you'll be doing the receiving organization a big favor!

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ORIGINATING ORGANIZATION
Common pitfalls

Different for internal tech transfers vs transfers to CMO

INTERNAL Tech Transfers

- Pre-Commercial / Clinical
  - Downstream process tends to receive less time for development versus upstream process
  - In aggressive TT projects, process characterization and optimization is ongoing after transfer activities start
    - Creates risk for engineers specifying equipment

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ORIGINATING ORGANIZATION
Common pitfalls

EXTERNAL Tech Transfers to CMO

- Can be difficult to assess CMO capabilities
- Not all issues with CMO can be anticipated and addressed before entering into a contract
  - Pre-define change order costs with CMO
- Failure to perform thorough due diligence and standardized risk assessment of CMO capabilities can result in unpleasant surprises…..and a lot of extra work
  - Look at documentation practices
  - Look at Quality Systems
  - Look at EVERYTHING

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RECEIVING ORGANIZATION
Key requirements & Points to Consider

- ✓ Process Capability Assessment
  - Confirm that process delivers appropriate productivity and product quality for its life cycle stage (clinical)
    - At least at lab scale
    - Preferably at pilot scale
- ✓ Facility Fit
  - Assess equipment and utility requirements first
  - Develop a comprehensive capital equipment inventory
- ✓ Risk Assessments
  - Conducted at outset of transfer & updated while moving through stages
- ✓ BOMs
  - Develop and lock-down as early as possible

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RECEIVING ORGANIZATION
Common pitfalls

- Automation
  - Expect process interruptions and bugs during pre-GMP runs
  - Have automation engineers and operations staff work closely together
- CIP cycle development and validation often takes longer than expected
- Documentation processing and readiness for GMP runs
  - Allow sufficient time to revise documents before GMP runs
- Insufficient time allocated for training
  - Take advantage of training on draft documents
  - Try to maximize MFG operator experience with engineers and development staff

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General Considerations For the CLIENT

Pre-commercial

- Make sure the process can deliver appropriate product quality and quantity for your clinical program

Commercial

- Create a comprehensive process description
- Share ONLY what the CMO needs to make your product but is sufficient to avoid numerous change orders
- Perform a thorough facility fit assessment
- Ensure that material vendors extend same pricing to CMO
- Make sure CMO has adequate proprietary information segregation and protection practices
- Pre-define plant access rules carefully

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General Considerations For the CMO

Pre-commercial

- Make sure the process can deliver appropriate product quality and quantity for your clinical program
  - Review the data that proves this

Commercial

- Review the process description carefully
- Insist that all meeting minutes are taken by the CMO
- Define terminology and payment schedules for:
  - Starts
  - Batch completions
  - Raw materials
  - Breach of contract

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General Considerations For the CMO - continued

Commercial

- Establish clear, responsible business communication practices: Verbal, Written, Email
- Define what types of electronic devices the client may use while in the plant
- Establish communication forums for data exchange early
- Agree to a validation philosophy to ensure it aligns with client expectations
  - Bracketing or Family Approach
  - Mock versus real process soils
  - ICV (yes or no)
  - Protocol approval (joint or CMO only)
  - Define PQ expectations and requirements

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Project Management Summary of Key Success Factors

- ✓ Create a management-approved project scope, stick to the plan, and minimize scope creep
- ✓ Effective meeting management
- ✓ Anticipate trouble spots and keep governance apprised
- ✓ Build a detailed, baseline (Level III) schedule as early as possible
- ✓ Establish team ground rules and hold people accountable
- ✓ Develop standard reporting tools and templates
- ✓ Define a Communication Strategy and use it
- ✓ Use Collaboration Tools that the whole team can access
  - Example: Portals such as eRoom and SharePoint sites

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QUESTIONS ?

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Technology Transfer

What You Need Before You Start…and Probably Don't Have

Sheila G. Magil

BioProcess Technology Consultants

January 26, 2010

Outline

- Definition
- Kinds of transfers
  - What is to be transferred, method or process
- Protocols
- Materials
- Knowledge

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Technology transfer is:

- the process of sharing of skills, knowledge, technologies, methods of manufacturing, samples of manufacturing and facilities among …to ensure that scientific and technological developments are accessible
- the process of transferring scientific findings from research laboratories to the commercial sector.
- the transfer of technology or know-how between organizations through licensing or marketing agreements, co-development arrangements, training or the exchange of personnel
- the transfer of knowledge generated and developed in one place to another, where is it is used to achieve ...
- The process whereby one organization or group within an organization transfers a process to another organization or group within the same organization so as to enable the receiver to perform the process with the same outcome as obtained by the originator

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Types of Tech Transfers

- Process
- Analytical Methods
- The same or different ?

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Kinds of Technology Transfer

- Within an organization
  - Between departments such as development and manufacturing or QC
- Between organizations
  - From an academic laboratory to a biotech
  - From an in-house group to a CMO
  - Between two CMOs

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What is needed?

- Something to transfer
- A clear goal for the transfer
- A formal written protocol describing the transfer
- A suitable receiving organization
- Commitment by both organizations

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Something to Transfer

- Clear description of the process or method
- Knowledge about the process, preferably documented
- Materials to enable the transfer
- Definition of a successful transfer

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A Goal for Tech Transfer

- Enable the receiver to replicate the results obtained by the originator
- Phase and understanding appropriate
  - Co-development or validation
  - Scale up from development

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Transfer Protocol

- Clear identification of responsibilities, materials, activities, equipment, personnel
- May be preceded by feasibility work
- Identify any limitations due to differences in quality organization

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A Suitable Receiver

- What does that mean?
- Suitable equipment
- Trained personnel

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A Knowledgeable Originator

- During early development this may be the area with the biggest deficit
- Know what you know but also know what you don't know
- Knowledge must be organized

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Commitment by Both Organizations

- Tech transfer is a consumer of time and resources
- You can't skimp on the resources
- Without goodwill on both sides there is a guarantee that it won't work
- Both groups must be involved in defining the process

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What You Need But Don't Have

- Enough Information
- Enough Resources
- Enough Time

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Specifically What is Missing

- Information
  - Effect of equipment changes
  - Critical parameters, process or method
- Resources
  - People dedicated full time to transfer
  - All the equipment needed at transfer
- Time
  - Need it yesterday

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Overcoming What Is Missing

- Lack of Information
  - Regular joint meeting between initiating group and receiving group
- Lack of Resources
  - Commitment of senior management
  - Clear and realistic timetable
  - Clear and realistic plan, including required resources

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Overcoming What is Missing

- Good will on both sides
- Clear objectives
- Clear metrics

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Summary

- What is needed
  - Information
  - A real plan
  - Good will

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Thank you and
Any Questions?

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Tech Transfer from Development to cGMP Manufacture

Challenges and Solutions in Scaling up a New Microbial Process from 5L to 1000L+

Susan Dana Jones

BioProcess Technology Consultants

January 26, 2010

BioProcess Technology Consultants

Microbial Process Development

- Microbial manufacturing processes are developed individually
  - Process is dependent on the unique structure of the product
  - Platform processes are usually not applicable and therefore the development timeline can be longer
- Technology transfer to cGMP manufacturing must include detailed assessment of each unit operation, performance requirements, and any variance noted during development
  - Critical process parameters may be identified during development and can provide essential information to guide successful tech transfer
  - Each product has unique unit operations

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Microbial Process Scale Up Strategies

- Technology transfer and scale up from development laboratories to cGMP manufacturing environment can be challenging
  - Requires significant process evaluation and rigorous analysis of multiple parameters
  - To mitigate scale up risk, initial scale up is normally from 5-10 L lab scale to 100-200 L process demonstration scale
  - Secondary scale up to cGMP scales of 1,000+ L is driven by data from initial scale up and by facility limitations
- With rigorous development and testing at small scale, tech transfer and scale-up directly from lab scale to production scale is feasible
- This approach will save time and money for companies that are developing products expressed in microbial systems

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Case Study: Scale up from 5 L to 1,000 L

- E. Coli-based process was developed at the 5 L scale and parameters were fixed based on multiple process demonstration runs at that scale
  - Product is ~25kD recombinant protein expressed intra-cellularly
  - Product is soluble intracellular
  - Inducible expression using T7 promoter with IPTG induction of T7 polymerase expression
- Scale up to the 1,000 L scale was seamless in most parameters due to the wealth of information obtained at the small scale and included in tech transfer package
- Unit operations that did not transfer easily will be described

SynCo Bio Partners

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Process Development Considers Tech Transfer

- Use established *E.coli* fermentation medium, conditions, etc that are compatible with large scale facility
  - No animal derived media components
  - No complex feeds or supplements other than pH and dO2 control
- Knowledge of facility operations at large scale influenced process development choices at 5 L scale
  - Simple batch operation (quick, robust)
  - Minimize downstream steps while achieving product quality and purity
  - Use half of fermentation culture for downstream processing at scale

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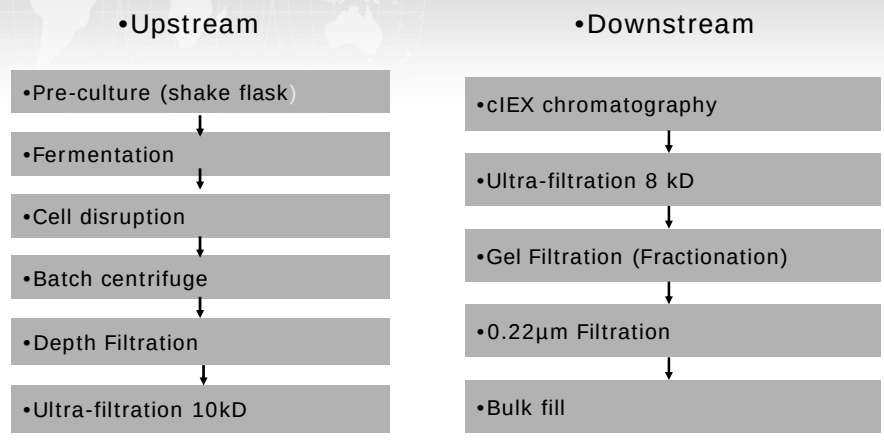
5 L Process Description



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Scale up Strategy and Considerations

- Verify all operating parameters at 5 L scale with 3 verification batches prior to engineering batch at scale
  - Use raw material lots intended at scale
- Linear scale up for chromatography and filtration steps
  - Collect fractions in chromatography steps to allow for flexible pooling strategy at scale (good IPC required)
- Break through studies at small scale can support choice of filter area at scale
  - Commercial availability and sizes of some units determines choice at scale
  - Blocked filters can be easily replaced (design in) at scale but may impact overall process yield
- Process hygiene generally improves at scale
  - IE, endotoxin levels always decrease

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Scale up Considerations

- Process time increases with scale- product stability can be an issue
  - 5 L process indicated homogenate was stable for 12 hrs at 4^{o}C
- Process volumes need to be manageable – volumes <250 L are mobile and generally easy to cool/store
- Increasing column size gives increased pressure at scale and possible lower linear flow rates

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Column Scale-up and Sizing

- Balance Cost of Production (COP), Production Rate (g/hr) and Productivity (g/hr/L support)
  - Trade-off between capacity, throughput, and cost
  - Multiple cycles vs. a larger column?
  - Wider or taller?
  - How frequently should media be replaced?
  - Support equipment sizing and cost

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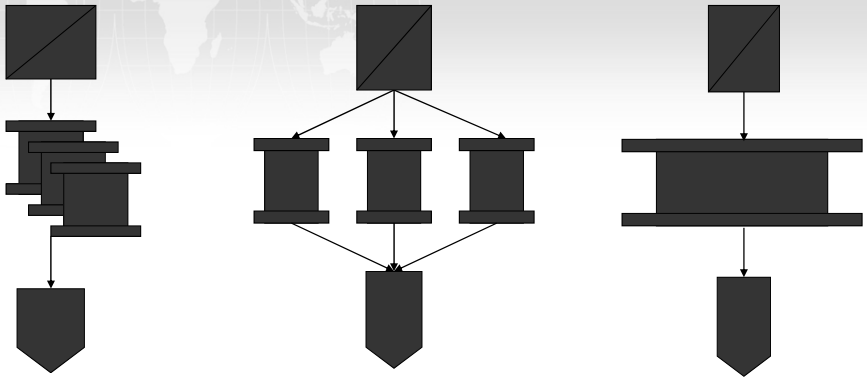
Column Operating Options



•Cycling Small Column in Series

•Multiple Small Columns in parallel

•Single Large Column

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Scale up -Volume and Time

Step	5L scale		1000L scale	
	Volume	Process time	Volume	Process time
Pre-culture I/II	1 x 150ml	10-14 hrs	1 x 150ml, 4 x 2.3L	10-14 hrs stage 1 10-14 hrs stage 2
Fermentation	4.5L	9-11 hrs 12-15 hrs 4ºC	1000L	9-11 hrs 12-15 hrs 4ºC
Cell disruption	4.5L	0.5 hrs	500L	1.5 hrs
Centrifugation	4.5L	1 hr @5000x *g* *(batch)*	500L	2-5 hrs @ 4500x *g* *(continuous)*
Depth Filtration	4.5L	2 hrs	500L	6 hrs
Ultrafiltration	0.75L	5 hrs	120L	3-5 hrs
Cation Exchange	750ml (load), 180ml (eluate)	2 hrs 0.3 hrs	120L (load), 10L (eluate)	2 hrs 0.3 hrs
Ultrafiltration	30ml	2 hrs	1L	2 hrs
Gel Filtration	3ml fractions	3 hrs	250ml fractions	3hrs

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Scale up - numbers

Unit operation	5L scale	1000L scale
Centrifugation	Batch centrifuge	Continuous centrifuge
Depth Filtration	Cuno 60 0.0021m^2/L harvest Cuno 90 0.0015m^2/L harvest Lifeassure 0.014m^2/L harvest	Cuno 60 0.0072m^2/Lharvest Cuno 90 0.0036m^2/L harvest Lifeassure 0.014m^2/L harvest
Ultrafiltration	0.1m^2 (0.01m^2/L harvest)	5.0m^2 (0.01m^2/L harvest)
Cation Exchange	2.6cm diameter 5.3 cm^2 surface area 15 cm bed height	30 cm diameter 706.9 cm^2 surface area 15 cm bed height
Ultrafiltration	0.05m^2 (0.27m^2/L harvest)	0.2m^2 (0.2m^2/L harvest)
Gel Filtration	1.6cm diameter 2.0 cm^2 surface area 67 cm bed height	14 cm diameter 153.9 cm^2 surface area 67 cm bed height
Final Filtration	0.0008m^2	0.01m^2

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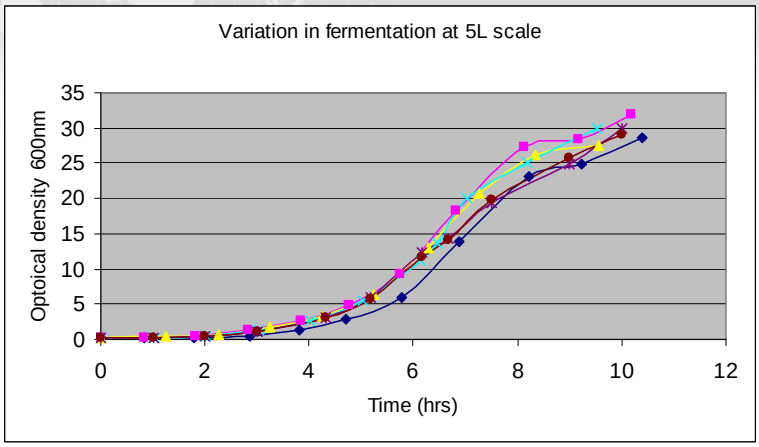
Process Reproducibility at 5L Scale



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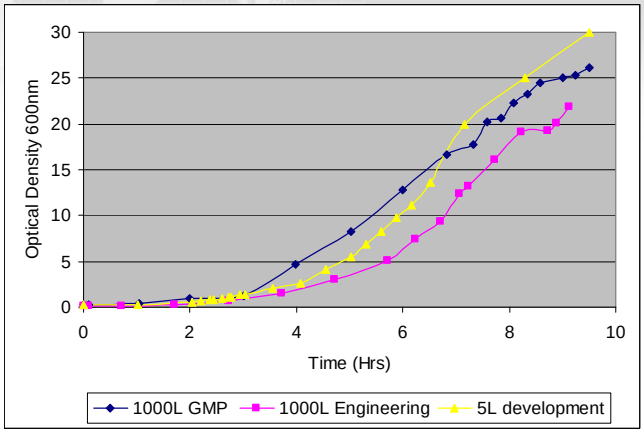
Fermentation- 5 L vs. 1000 L



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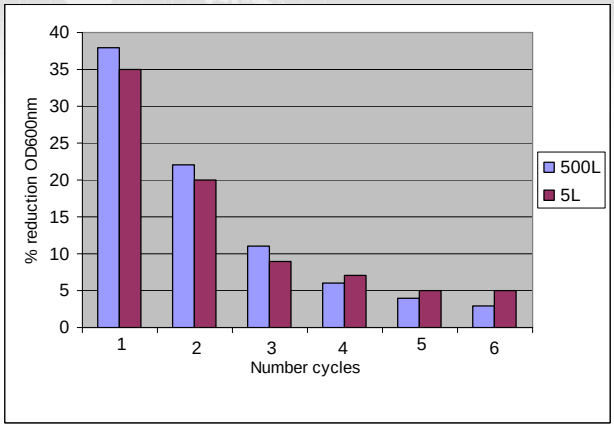
Cell Disruption- 5 L vs. 500 L



- In Process Controls:
- Optical density reduction >95% initial value
- Temperature

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- Data courtesy of SynCo BioPartners

Centrifugation

- Difficult to scale batch ➔ continuous centrifuge
  - Sedimentation models provide indicators for initial parameters
  - Fixed speed and adjust flow to increase/decrease retention time
- Particle distribution pattern changes
- Often see product loss

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Depth Filtration at Full Scale

- Life Assure filters blocked during first batch at full scale (Engineering Batch).
- Flow rate decreased in GMP batch to prevent similar blockage
- Centrifugation and filtration are challenging to scale up and are not a direct process transfer from development to production.

Parameter	Engineering	GMP
Flow rate (L/hr)	230	125
CUNO 60 (m^2)	3.6	3.6
CUNO 90 (m^2)	1.8	1.8
Life Assure (m^2)	13.7	13.7

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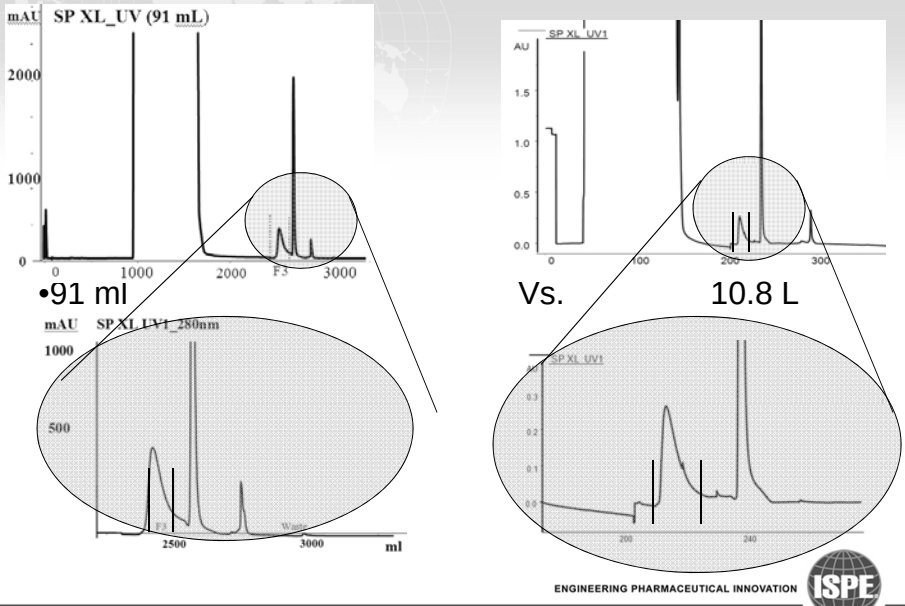
cIEX Chromatography



•91 ml Vs. 10.8 L

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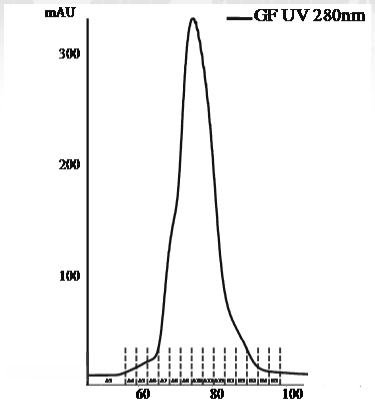
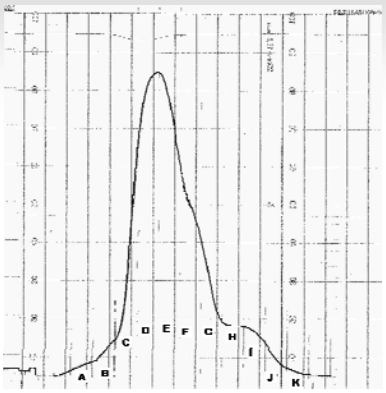
•Data courtesy of SynCo BioPartners

Gel Filtration





•Small scale (135ml) vs. •Large scale 10 L

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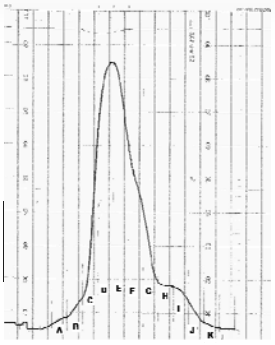
•Data courtesy of SynCo BioPartners

Gel Filtration

•Pooling of Fractions based on Purity and concentration

	purity (%)	mg/ml
Fraction A	60	0,01
Fraction B	50	0,04
Fraction C	72	0,28
Fraction D	92	2,78
Fraction E	94	3,74
Fraction F	95	1,84
Fraction G	92	0,69
Fraction H	86	0,38
Fraction I	85	0,23
Fraction J	76	0,06



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•Data courtesy of SynCo BioPartners

Summary

Unit Operation	Scaleability	Comments
Pre-culture I/II	Good	Ratio of medium to flask volume is an issue for OTR. Additional pre culture phase for at scale applications needs to be tested during verification runs
Fermentation	Good	Process simplicity is the key with batch processes being most reproducible.
Centrifugation	Poor	Comparison of batch centrifuge vs continuous centrifuge is a challenge
Cell disruption	Excellent	Highly reproducible. Defining reduction in optical density allows differences at scale to be compensated
Depth Filtration	Good/ Excellent	Scale up on basis of surface area usually means larger margins at scale but are acceptable if load studies not executed.

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•Data courtesy of SynCo BioPartners

Summary

Unit Operation	Scaleability	Comments
Ultra filtration	Good/ Excellent	Surface area and trans membrane pressure should be monitored
Chromato-graphy	Good/ Excellent	Establish binding capacity (for binding steps) early and test expected final bed height during development phase. Consider volumes of pools at scale when developing model – collection and storage issues Consider flow rate effects at scale leading to pressure

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•Data courtesy of SynCo BioPartners

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Thank you

Susan Dana Jones
BioProcess Technology Consultants

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