Managing Manufacturing Aspects – with process and project orientation.

Jignesh Padia

Agenda

- Areas of Experience
- Process Know-how
- Manufacturing Perspective
- Summary

Areas of Experience

- Understanding of CMO Business
- Process Development
- Technology Transfer
- Project Management
- Facility Design

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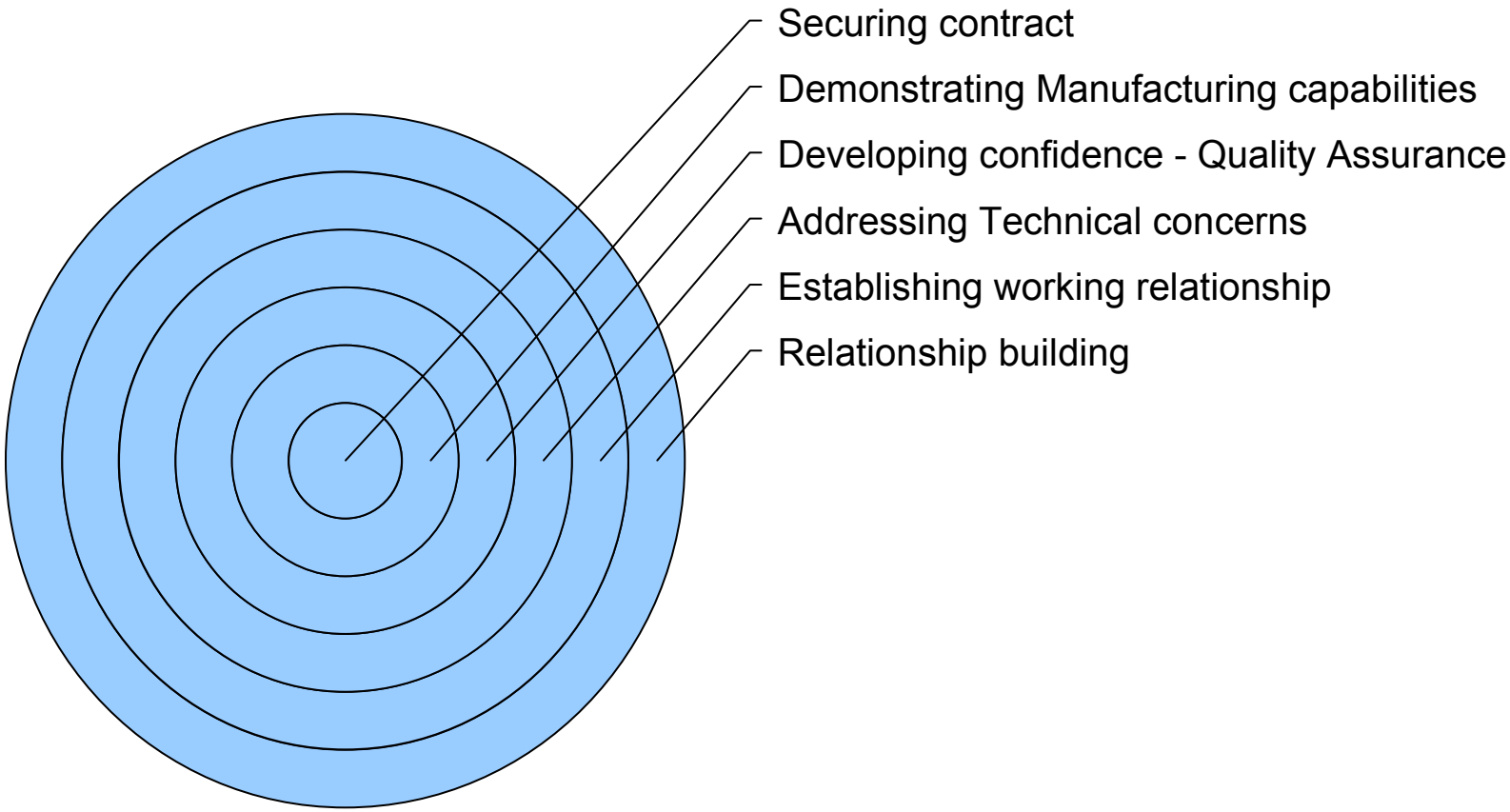
Areas of Experience

Understanding of CMO – Business



Areas of Experience

- Understanding of CMO Business
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Areas of Experience

Process Development

- Fermentation Processes
  - CHO Cells
  - Pichia
  - Saccharomyces
  - E.coli
- Downstream Processes
  - TFF / AKTA platforms / DiscStack Centrifuges
  - NFF / Homogenizer/ Sonifiers
- Scale-down and Scale-up studies
- Process Validation

Areas of Experience

- Understanding of CMO Business
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- Facility Design

Areas of Experience

Technology Transfer

- External: Client → QSV
- Internal: PD → MA
- Issues/ Problems to watch out for
  - Process Changes
  - Equipment
  - Communication Gaps

Areas of Experience

- Understanding of CMO Business
- Process Development
- Technology Transfer
- Project Management
- Facility Design

Areas of Experience

- **Project Management**
  - Deliverables
  - Timelines
  - Budget
  - Risk Analysis & Management
  - Communication
  - Resource management

Areas of Experience

- Understanding of CMO Business
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Areas of Experience

- **Facility Design**
  - **Key Phases**
    - **Scale of Design**
    - **Conceptual Design Phase**
    - **Detailed Design Phase**
  - **Challenges**
    - **Gray Zone Allocation**
    - **Keeping cost of clean rooms and HVAC down**
    - **Buffer Prep and Buffer Hold zones**
    - **Personnel and Equipment Flow**

Areas of Experience

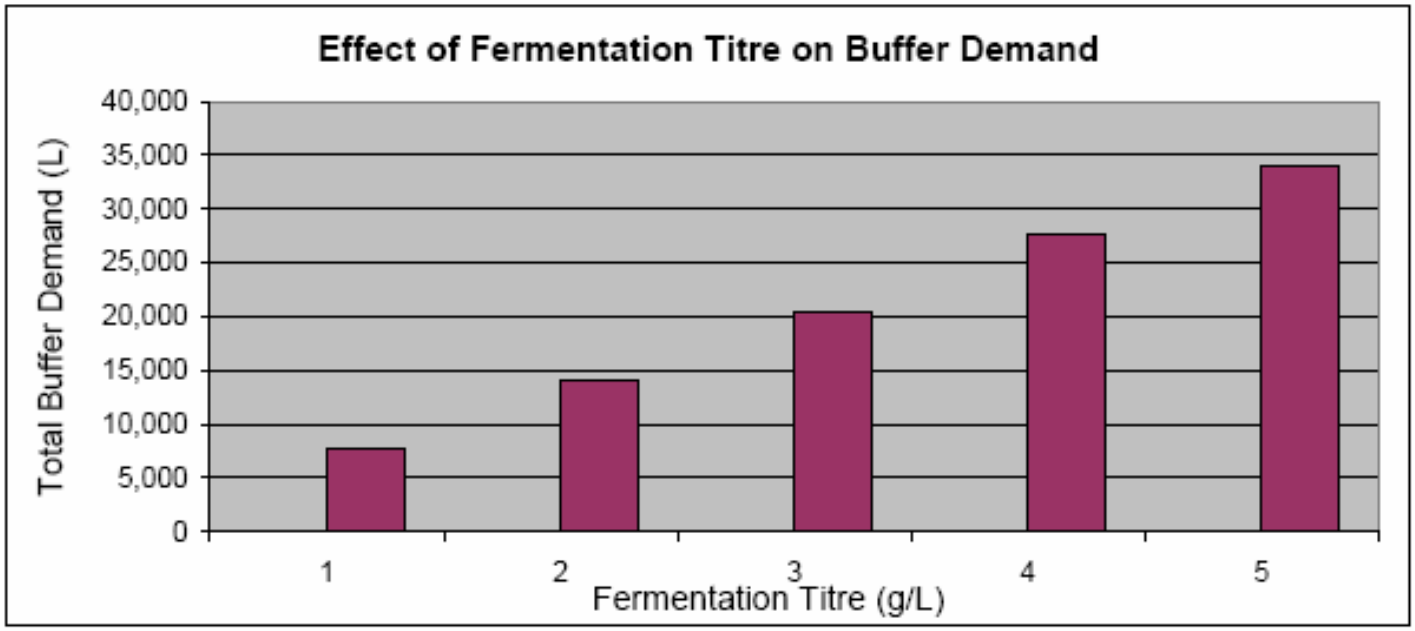
- **Facility Design: Example: WFI Usage (sensitivity analysis)**

	Fermenter Volume	Productivity	Total Protein	IB Solubilization	HIC (Post Viral Column)	IEX #1 (Post Viral Column) **Parallel Processing**
Case # 1	7500	10 g/L	53 Kg		200 cm	2 X 200 cm
Processing Tme (H)	3 days			5	15	18
Total Cycles	1			1	3	3
WFI Requirements	5250			26250	143000	284000
Case # 2	7500	5 g/L	27 Kg		200	200
Processing Tme	3 days			5	11	18
Total Cycles	1			1	2	3
WFI Requirements	5250			26250	94000	143000
Case # 3	7500	1 g/L	6 Kg		80	80
Processing Tme	3 days			5	7	16
Total Cycles	1			1	2	4
WFI Requirements	5250			26250	15000	30000
Case # 4	1500	10 g/L	10.5 Kg		200	250
Processing Tme	3 days				5	7
Total Cycles	1				1	1
WFI Requirements	1050			5250	47000	74000
Case # 5	1500	5 g/L	6 Kg		80	80
Processing Tme	3 days				7	16
Total Cycles	1				2	4
WFI Requirements	1050			5250	15000	30000
Case # 6	1500	1 g/L	6 Kg		60	80
Processing Tme	3 days				4	4
Total Cycles	1				1	1
WFI Requirements	1050			5250	5000	8000

Note: Timing are process time only and it doesn't include CIP, Prep & SIP
Note: WFI requirement is only based on crude assumptions and doesn't include the WFI requirement for Other unit operations

Areas of Experience

- **Facility Design: Example: Buffer Usage (sensitivity analysis)**



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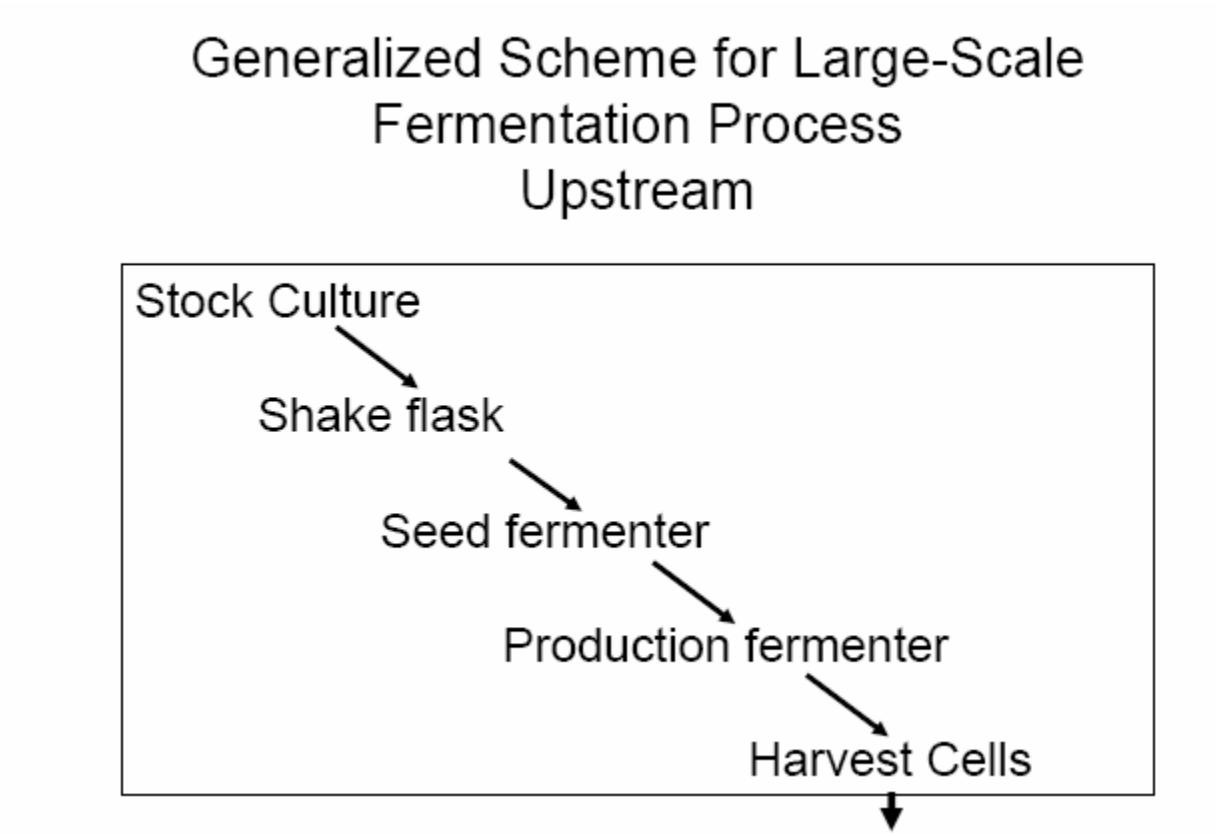
Process Know-how

- **Upstream / Fermentation**
- **Downstream**
- **GMP**

Process Know-how

- **Fermentation**
  - Generalized Scheme - Upstream
  - Mammalian & Microbial Processes
  - Process Variables & Scale-up Parameters

Process Know-how



Process Know-how

Mammalian & Microbial Processes

- **Mode of Operation**
  - **Batch**
  - **Fed-batch**
  - **Perfusion**

Vial → T-Flasks → Spinner Flasks / Small Reactors → Large Reactor

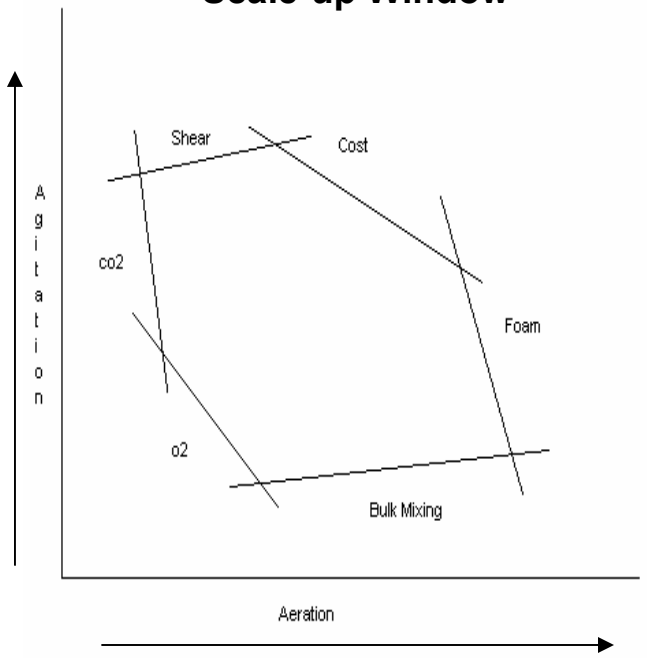
Vial → Shake Flasks → Small Reactors → Large Reactor

Process Know-how

Process Variables

- **Inoculum Development**
  - Strain stability
- **Sterilization**
  - Impact of scale
- **Environment Parameters**
  - pH
  - Temperature
  - DO
  - Shear
  - Mixing time

Scale-up Window



Power per unit Volume
$K_L a$
Tip speed & Heat Transfer
pO_2

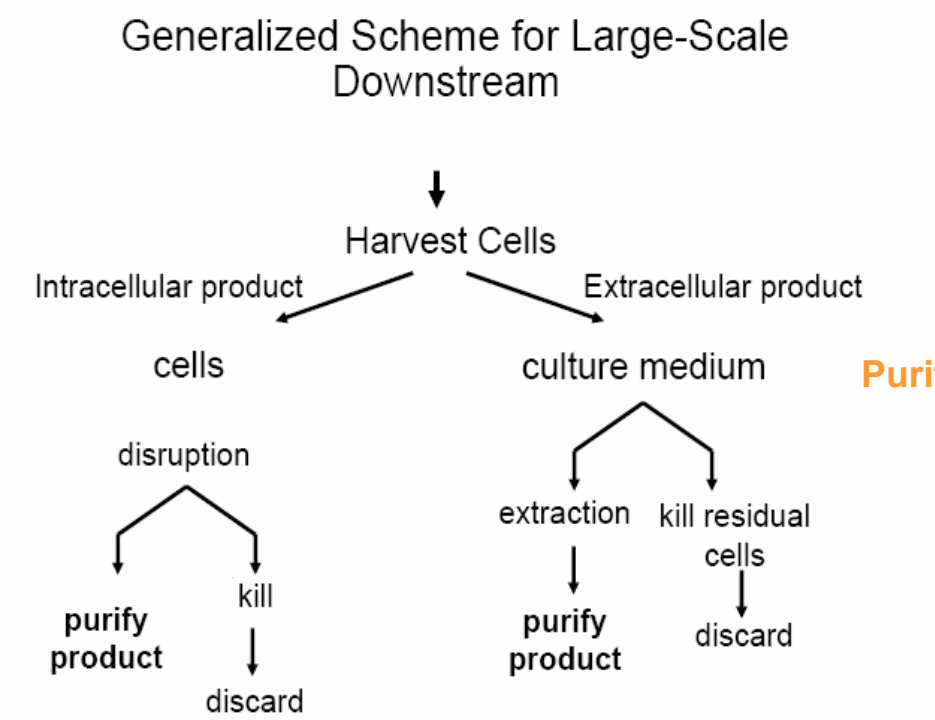
Process Know-how

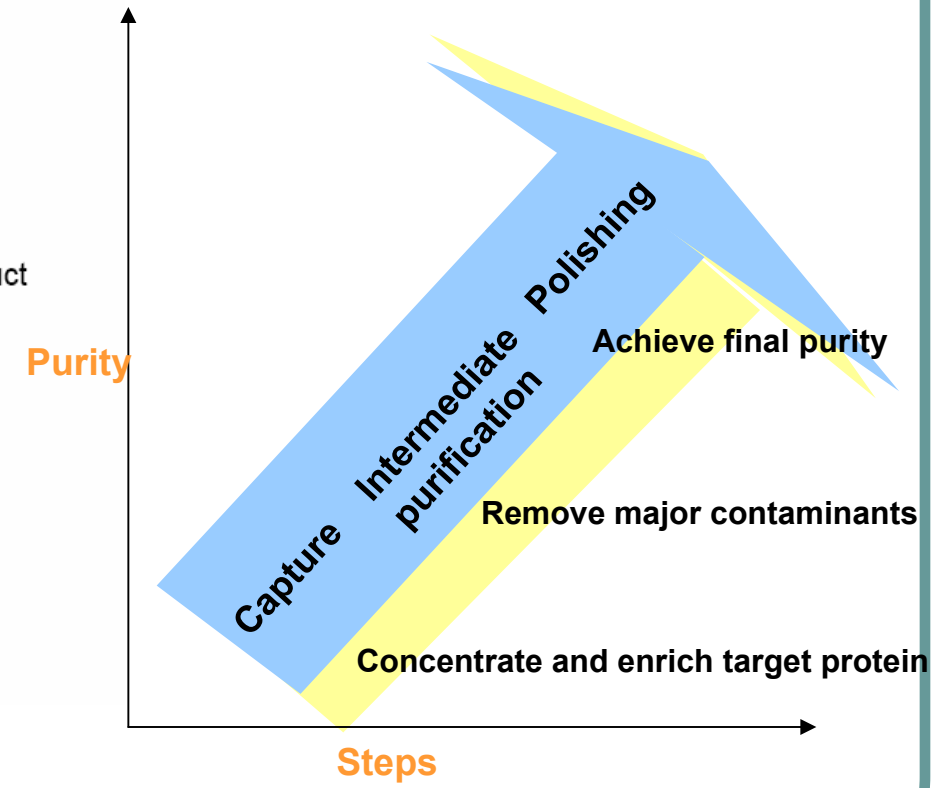
- **Upstream / Fermentation**
- **Downstream**
- **GMP**

Process Know-how

- **Downstream**
  - Generalized Scheme - Downstream
  - Mammalian & Microbial Processes
  - Process Variables & Scale-up Parameters

Process Know-how





Process Know-how

Mammalian & Microbial Processes

- Centrifuge/MF
- UF/DF
- Chromatography
  - IEX
  - Affinity
  - Gel-Filtration
  - HIC
- Viral Clearance
- Sterile Filtration

Process Know-how

Process Variables & Scale-up Parameters

Scale-UP parameters to consider	
Filtration	**Chromatography**
Loading per membrane area	Loading per resin volume
TMP, ΔP, Cross flow	Linear flow rate
Feed channel length, lumen diameter	Bed height
Pore size - cutoff	Binding capacity, Bead porosity

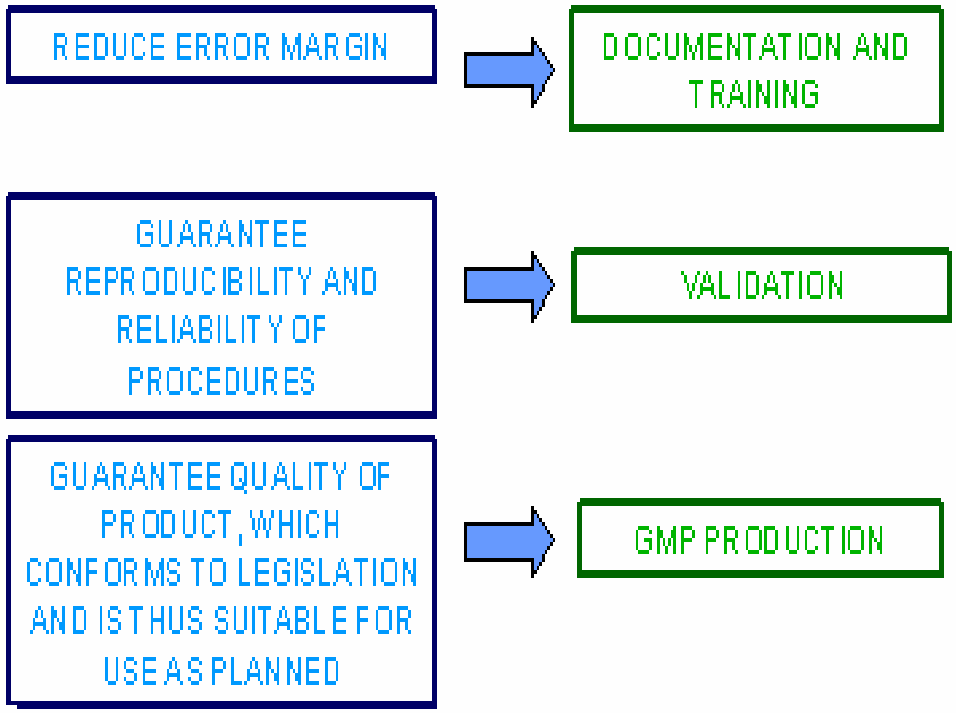
Process Know-how

- **Upstream / Fermentation**
- **Downstream**
- **GMP Consideration**

Process Know-How

GMP Consideration

- Documentation
- Training
- Process Validation
- Process Changes
- Process Automation



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Manufacturing Perspective

- Manufacturing Overview
- Gantt Chart
- Technology Transfer
- Process Management
  - Materials
  - Personnel
  - Equipments
  - Validation
- Facility Utilization
- Lessons Learned

Manufacturing Perspective

Manufacturing Overview

- **Project**
  - Consider the time lines, budget, training, facility limitation etc.
- **Tech Transfer**
  - Step forward toward the manufacturing
  - Optimize if you can
- **Manufacturing**
  - Validate the process and facility
  - Prepare for Campaigns
  - Monitor the yield and the cost. Implement any changes made by regulatory authorities.

Manufacturing Perspective

Manufacturing Overview

- Optimise capital
  - Maximise utilisation of facility and equipment
- Optimise production
  - Production strategies
  - Evaluate alternative technologies
  - Plan production schedule
  - Investigate effect of unscheduled events
  - Identify & remove bottlenecks
  - Increase throughput

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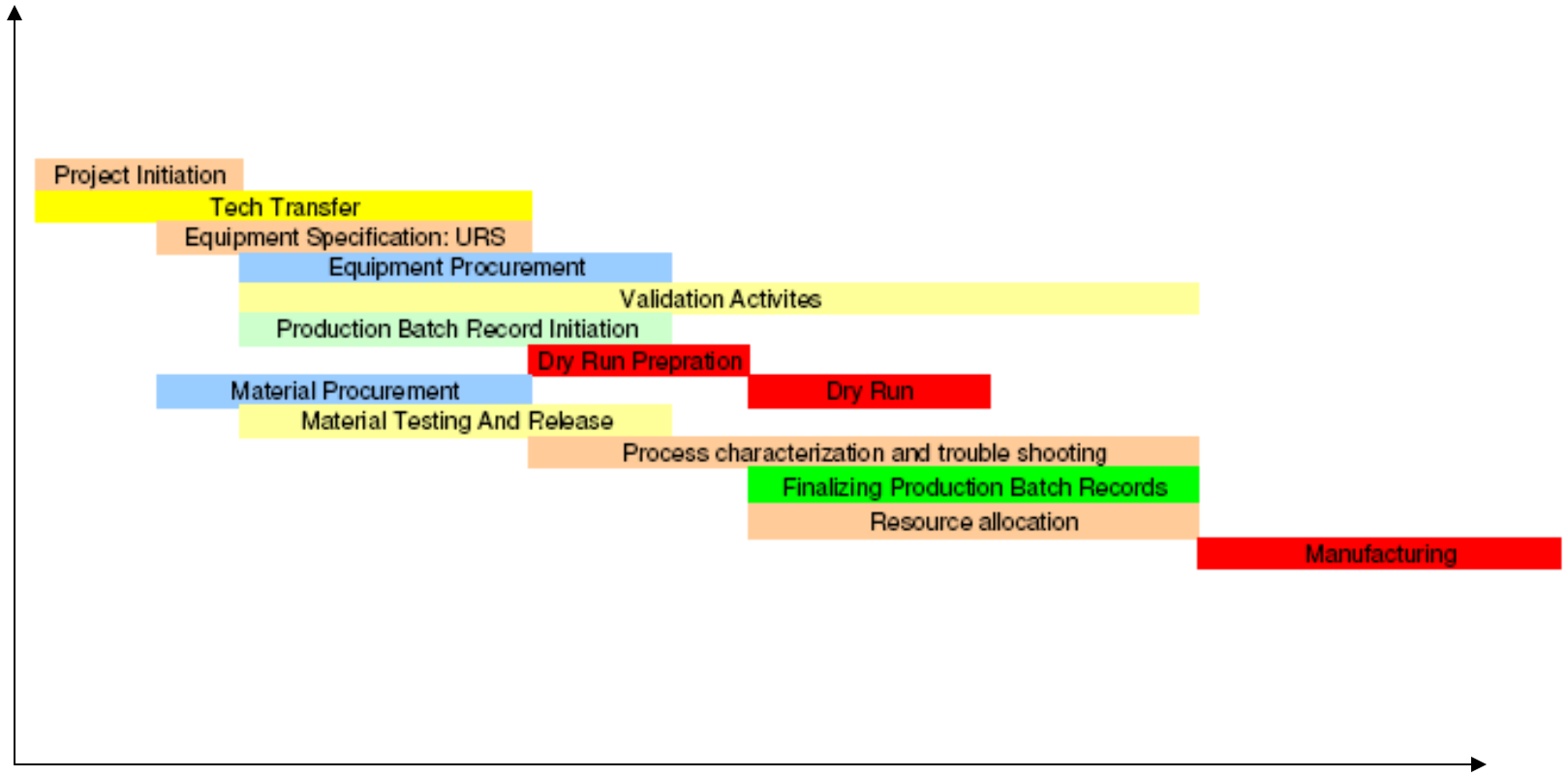
Manufacturing Perspective

Gantt Chart for Manufacturing New Product



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Manufacturing Perspective

- **Transferring the technology**
  - Form a team
  - Get the process information
  - Crunch the information
  - Pick individual unit operation
  - Prepare the list of equipments and raw materials
  - Try it at pilot scale
  - Tech Transfer Report

Manufacturing Perspective

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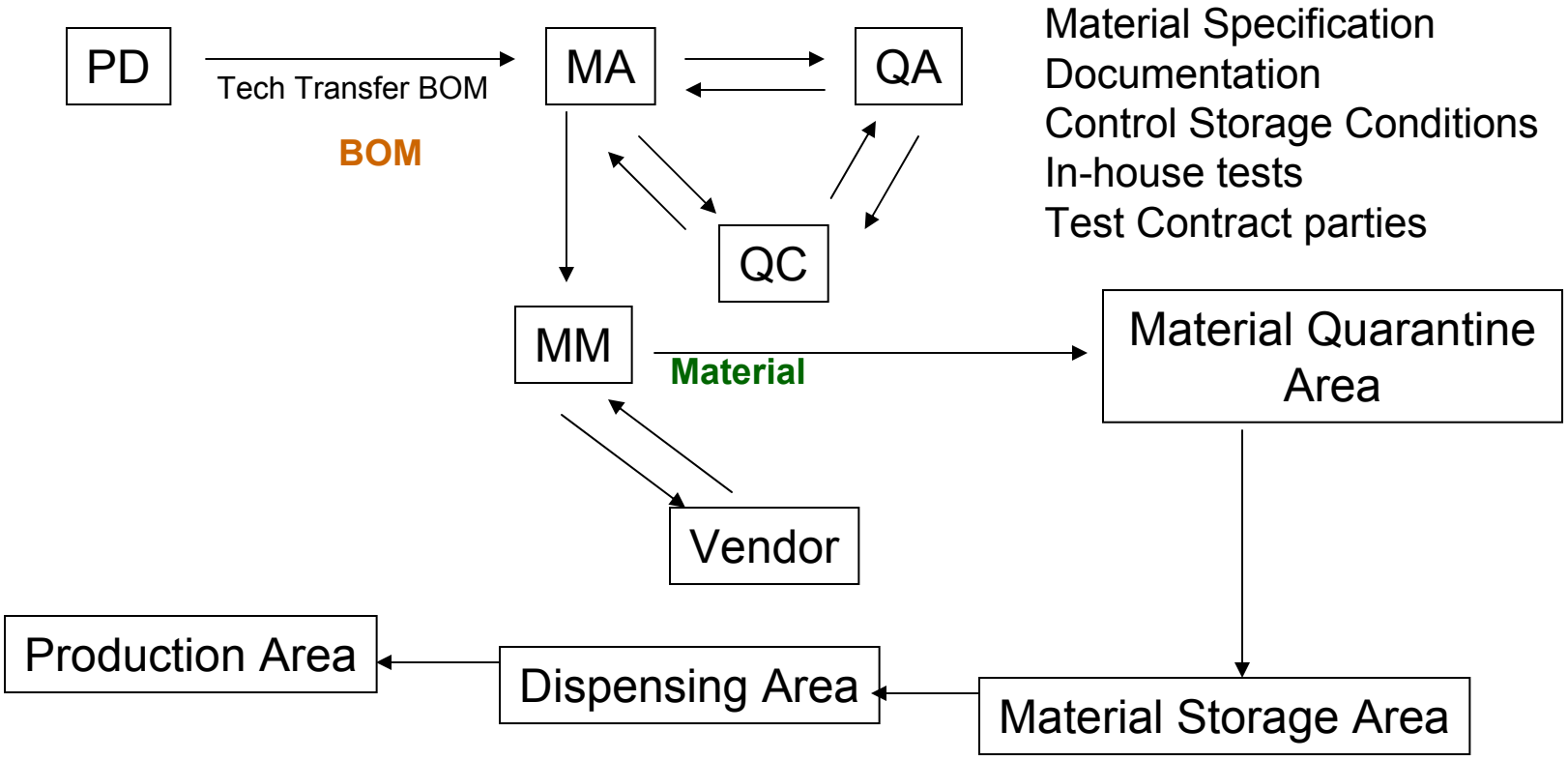
Manufacturing Perspective

- **Material Management Process**



Manufacturing Perspective

Material Management

- **Mass balances**
  - **Media**
  - **Buffer**
  - **CIP Chemicals**
- **Consumables**
  - **Filters**
  - **Resins**
  - **Membranes**

Purification/Recovery			Purification				
			Step 1	Step 2	Step 3	Step 4	Step 5
	Type		Thaw	Filter	Protein A	UF/DF	Q Seph
	Step efficiency		95%	98%	95%	98%	90%
Input	Mass	g	36760	34922	34224	32512	31862
	Volume	L	7352	7352	7720	13547	7302
	Concentration	g/L	5.00	4.75	4.43	2.40	4.36
Output	Mass	g	34922	34224	32512	31862	28676
	Volume	L	7352	7720	13547	6638	14603
	Concentration	g/L	4.75	4.43	2.40	4.80	1.96
Output dilution	Dilution factor		0	0	0	0.1	0
	Volume	L	7352	7720	13547	7302	14603
Timing	setup	hr	2	4.00	4.00	4.00	4.00
	loading	hr			0.21		0.76
	Process	hr	24.00	24.00	1.5	8.00	1.5
	Cleaning	hr					
	Sanitisation	hr	2.00	4.00	0.00	4.00	0.00
		hr	**28.0**	**32.0**	**5.7**	**16.0**	**6.3**
Labor timing			**28.0**	**32.0**	**34.3**	**48.0**	**12.5**
Column	No.	No.	1	1	6	3	2
	Cycles	No.			1		1
	Loading	g/l			15		50
	Loading	%					
	Height	cm			15		15
	Total Volume	L			2709		717
	Volume	L			452		358
	Diameter	m			1.96		1.74
	Cross Sectional area/column	m^2			3.01		2.39
UF	Diafiltration Ratio					5	
	Concentration Factor					2.0	
	Flux Rate	$L/m^2/hr$		108		11	
	Flux Rate	L/hr				5012	
	Filtrate calc	L				40099	
	Filtration Area	m^2		2.85		466	
		ft^2		31		5015	

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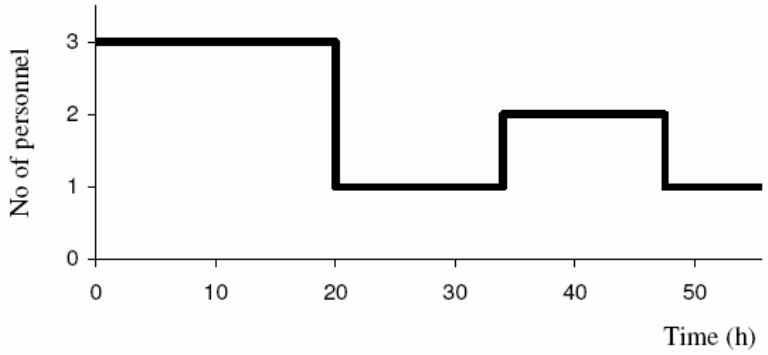
Manufacturing Perspective



Personnel Management

Why have 3 people per shift per day, if you don't need them?

Shifts

Activity	Time (h)	No of 8-hour shifts required.	No of staff in each shift.
A (Fermentation)	20	3	3
B (MF)	6	1	1
C (UF/DF)	8	1	1
D (Protein A & UF/DF)	8	1	2
E (IEX & DF)	5.5	1	2
F (Virus Filtration)	8	1	1

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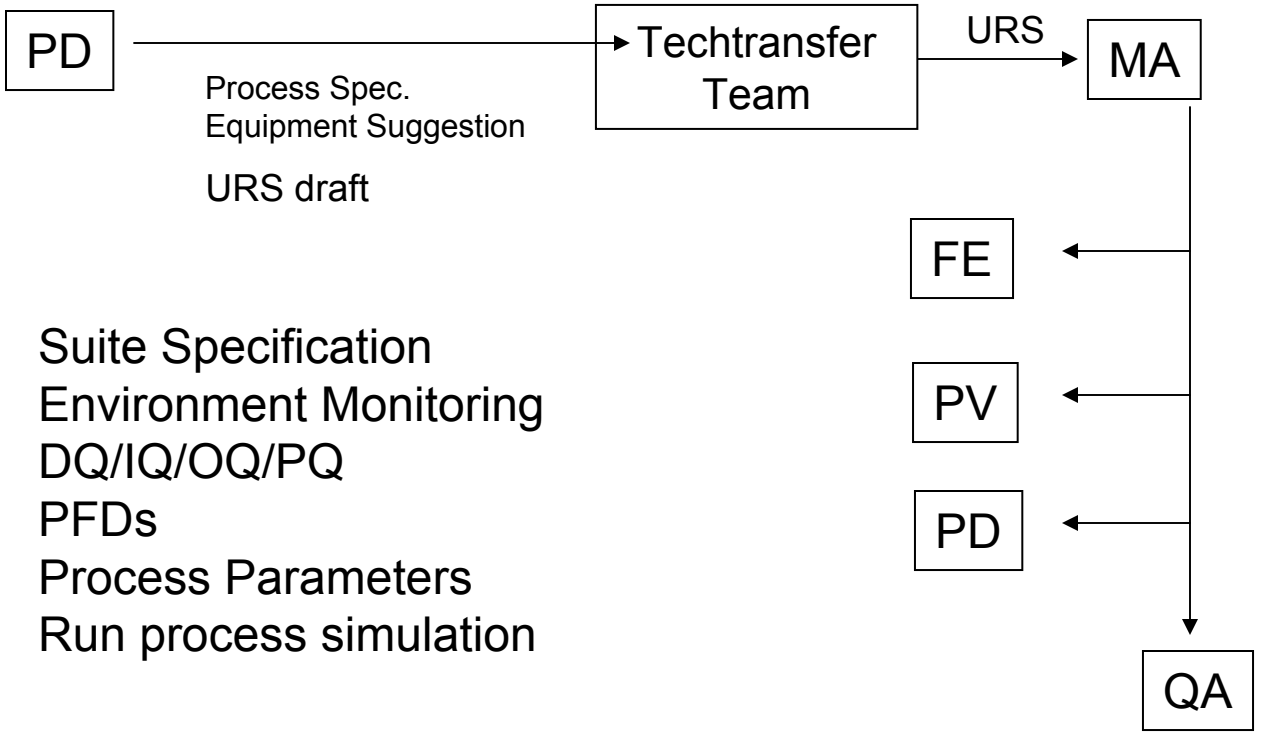
Manufacturing Perspective

- **Equipment & Process Specification**



Suite Specification
Environment Monitoring
DQ/IQ/OQ/PQ
PFDs
Process Parameters
Run process simulation

Manufacturing Perspective

EQUIPMENT LIST: XXX DSP Process:

Unit-Operation	Tanks/Flexboys	Pumps	Systems
DSP – 001	T-001:Harvest/Feed/Retentate Tank: 80 L T-002:Permeate Tank: 200 L	P-001:NCSRT P-002: For continuous wash	NCSRT - MF
DSP – 002	T-002:Feed/Retentate Tank: 200 L T-003:Buffer Tank: 150 L	P-001:NCSRT P-003: For continuous buffer exchange	NCSRT - UF
DSP – 003	T-004: Filtrate Tank: 50 L	P-004: For NFF filtration	N/A
DSP – 004	T-004: Filtrate Tank: 50 L T-005: Buffer A Tank: 100 L T-006: Buffer B Tank: 100 L T-007 : Peak collection Tank: 20 L	P-005: For loading onto the column.	Bioprocess system BPG 200/500
DSP – 005	T-007 : Peak collection/Feed/Retentate Tank: 20 L T-008: Buffer Tank: 100 L	P-005: For Millipore TFF P-006: For continuous buffer exchange	Millipore Pellicon 2 Maxi
DSP – 006	T-007: Feed Tank: 20 L T-009: Retentate Tank 10 L	P-005/006: Millipore TFF / Sartocon System Pumps	Millipore 2 Maxi / Sartocon system with Millipore Holder
DSP – 007	T-009: Retentate Tank: 10 L	N/A	N/A
DSP – 008	T-009: Feed / Retentate Tank 10 L	P-006: Sartocon System Pump	Sartocon system with Millipore Holder
DSP – 009	T-010: Filtrate Tank: 5 L	P-006: Sartocon System Pump	Sartocon system with Millipore Holder
DSP – 010	N/A	P-004: For NFF filtration	N/A

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Manufacturing Perspective

Process validation

Documentation
Validation Master plan
Process Validation Master plan
Responsibilities
Process Definition
Flow Chart & Decision Points
Process Methods
Forms
Process development reports
Documented experimental results
Master batch records/change control etc
Process flow diagrams
Scale-up summary report
Process Validation Summary Report

Activities
Raw material testing
Method development
SOP
Assay development
Training
Identification of the process to be validated
Identification of critical process parameters
Impurity characterization
Consistency of batches
Process monitoring and trending
Defining Validation master plan
Development of process validation protocol
Execution of process validation
Preparation of process validation report
Change control/revalidation
Worst case scenario evaluation

Manufacturing Perspective

Process validation

Objective and measurable criteria for a successful validation
Length and duration of the validation
Shifts, operators, equipment to be used in the process
Identification of utilities for the process equipment and quality of the utilities
Identification of operators and required operator qualification
Complete description of the process
Relevant specifications that relate to the product, components, manufacturing materials, etc
Any special controls or conditions to be placed on preceding processes during the validation
Process parameters to be monitored, and methods for controlling and monitoring
Product characteristics to be monitored and method for monitoring
Any subjective criteria used to evaluate the product - Definition of what constitutes non-conformance for both measurable and subjective criteria.
Statistical methods for data collection and analysis
Consideration of maintenance and repairs of manufacturing equipment
Criteria for revalidation

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Manufacturing Perspective

Facility utilization

Bacterial Suite	
Sterilization - Media Hold	2 days
Preculture	1 days
Bacterial Fermentation	1 days
CIP-Product Hold	5 days
Total	9
Total possible batches in a month	3

Mammalian Suite	
Sterilization -Media Hold	1 days
Preculture	18 days
Mammalian Fermentation	16 days
CIP-Product Hold	5 days
Total	40
Total possible batches in a month	

Set Shutdown/Booking/Working days
Result of this simulation
Check suite occupancy %

Previral Suite	
Chromo	15 hours
TFF - I	8 hours
NFF - I	8 hours
Viral filters	8 hours
pH-HOLD	5 hours
Chromo -I	15 hours
Other Hold- processing time	15 hours
CIP - Downtime	2 days
Total	6 Days

Post Viral + Bacterial Processing	
Centrifugation	8 hours
Homogenization	5 hours
Refold	48 hours
TFF - I	5 hours
Chromo - I	15 hours
TFF - II	5 hours
NFF - I	8 hours
Chromo - II	15 hours
TFF - III	5 hours
Chromo - III	15 hours
Other Hold- processing time	15 hours
Sterile Filtration	5 hours
CIP - Downtime	2 Days
Total	9 Days
Total possible purification batches	3 /month
Maximum Bacterial (only) a year	23 bacthes

Chromo - II	15 hours
TFF - II	8 hours
NFF - II	8 hours
Chromo -III	15 hours
TFF - III	8 hours
Sterile Filtration	5 hours
Other Hold- processing time	15 hours
CIP - Downtime	Days
Total	4 Days

Operational Set-up	
Days for long bathces	5 days
Add Plant shutdown days	30 days
Add % booking	65 %
Working Days in a year --------->	215

Manufacturing Perspective

Facility utilization

Mammalian batches purified		
Bacterial batch purified	3	
Combination of batches purified	3	/month

Mammalian Batches ---->	7	/Year
Bacterial Batches ---->	20	/Year
Combination of batches =	27	/Year

Maximum possible bacterial batches	23	In combination maximum bacterial	20	with 7 mammalians
Maximum possible mammalian	7			
We want bacterial bathces	16			
We want mammalian batches	7			

Days in FCR	144 days
Efficiency of FCR	67 %
Days uses for BTS 1 (only)	214.00 days
Efficiency of PCR	100 %
Days occupied for PCR (combined)	172 days
Efficiency of PCR	80 %

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Manufacturing Perspective

Lessons Learned: Material Management

- Sodium Citrate vs. Citrate (Citric Acid)!
- Approved specifications only! USP/BP
- When using disposables for storage consider pH, Leaching, compatibility etc.
- Ensure that material MSDS are available and being circulated to avoid any handling / Hazardous situations.
- Watch out for lot to lot variations!

Manufacturing Perspective

Lessons Learned: Equipment Specs!

- Objective: Maintain and control critical parameters
- Understand Equipment LIMITATIONS
- Transfer-lines: hold-up from seed reactor to production reactor
- Chillers cooling capacity: Temperature control
- Set-up of systems
- Pump specifications: Feed additions, Harvest, UF/DF
- Pressure limitations: AKTA
- Turnaround time
- PLAN B! Risk Management

Manufacturing Perspective

Other Potential Process Issues

- Non-Scalable methods/operations used by client (examples)
  - Dialysis Kits
  - Gel filtration column with 150 cm tall!
  - Rotary Vacuum filter / evaporator
  - Lab scale centrifuge
  - Chemicals for cell lysis process
  - 3 VVM of Air flow during fermentation process

Manufacturing Perspective

Other Potential Process Issues

- Equipments not compatible
  - i.e. Client has been using Millipore Membranes with Millipore Holder.
  - PD has Millipore / Sartorius / Pall Holders
  - MA has Sartorius Holder – Not compatible with Millipore/Pall
- No QC data available from client
  - Client has been outsourcing the QC work but don't have any documentation.
  - Client was using techniques/equipment not available with internal PD/QC/MA (i.e. Mass Spec)

Manufacturing Perspective

Potential solutions/approach

- Evaluate the potential issues beforehand.
- Check the availability of MA / PD slots to perform the feasibility tests.
- Ensure that PD/MA/QC/QA/BD agree with the proposed plan.
- If required perform a small scale study for feasibility of changed equipments/methods.
- Outsource QC – work if needed.
- Ensure that process steps are scalable between PD/MA
- Prepare a list of items, which are not included/assumed in the process description / Tech-Transfer report, to clarify and avoid any misunderstanding.

Manufacturing Perspective

- **Example of Cooling Capacity Determination**

Assumption

Total Heat Produced by Organism: 12705 Kcal/h ~ 4.2 Tones

Practical Experiment

Time (h)	T(in)	T(out)	T(F)

Plot Temp(F) vs. Time

Determine the dT/dt

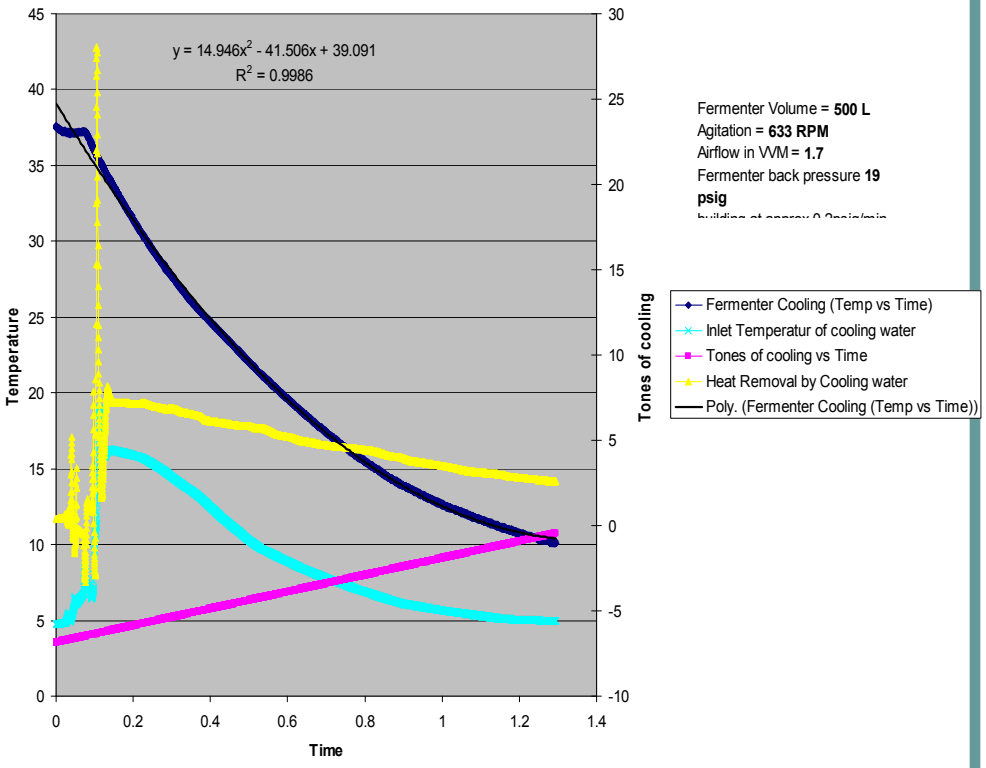
Calculate

M = Mass flowrate of cooling water

Cp = Heat Capacity of water (at T(F))

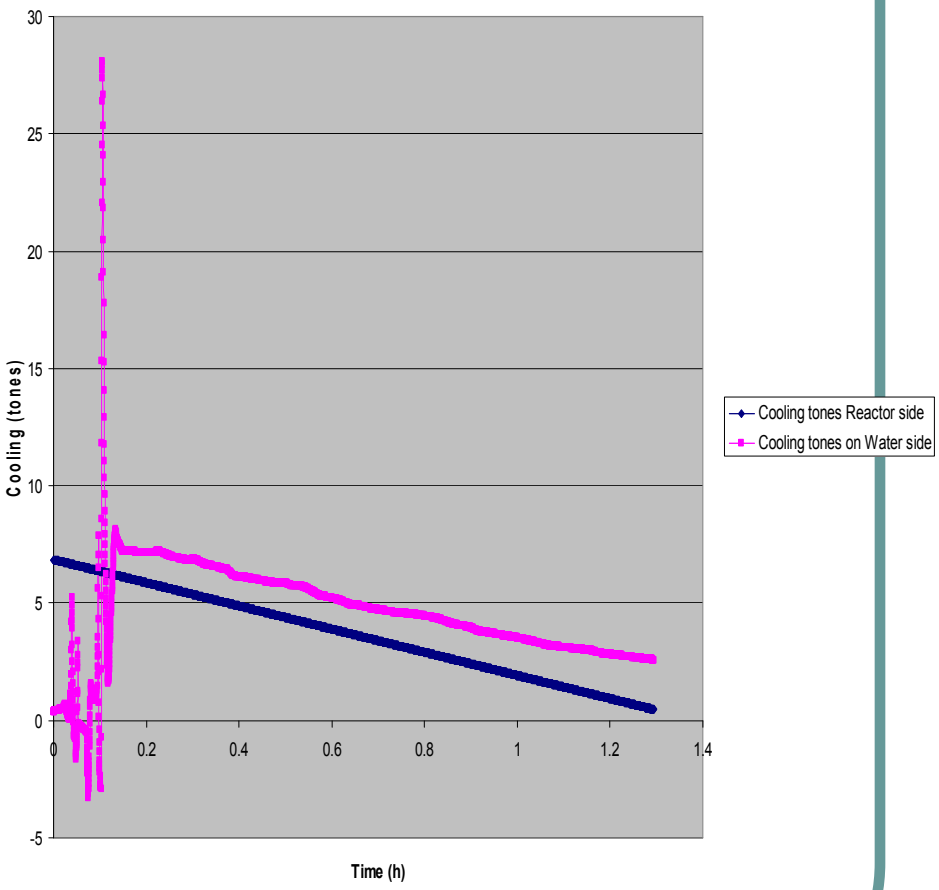
U = Q / A / (((2 TF - (Tin+Tout)) / 2)

Q = M Cp dT/dt



Manufacturing Perspective

- Calculate average Q from available data
- Verify that the Cooling Q achieved on the fermenter is > total heat produced by organisms.
- In this case (6.9 tones) Q max cooling is > (~ 4.2 tones) Q max heat generation by organism.



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Summary

- Strong interest in Bio-Manufacturing Processes
- Strong technical skills to support the improvement of process development / manufacturing.
- Exposure to CMO – business model / working environment
- Ability to handle technical issues
- Keen to learn and adapt to new strategies and to manage manufacturing processes.

- Skills:
  - Focused and result oriented thinking
  - Process related risk assessment
  - Ability to understand the impact of process options on project budget and timelines
  - Adaptability and Flexibility to work with multi-cultural and cross-functional teams
  - Self-confident and personnel management skills