Next generation process & Capacity planning…

… in a new Biotech facility

Foto: Johan Steensland

Scope of presentation

- Introduction of subject
- Next generation of process
  - Balancing of processes
  - Case study
- Capacity and resource utilization
  - Bottleneck identification
  - Case study

Introduction or It all comes back to cost of production!

- A new facility means a substantial investment (150 M€ → ??) which gives a large “locked” depreciation costs to go into the production cost

- For biotech; materials are less expensive (exceptions; special media components, some resins etc) therefore the potential of impacting production cost is limited

- Simplification of processes could have a great impact on cost e.g.
  - Creating “one batchness” minimises administration, QC costs etc
  - Getting rid of unnecessary steps
  - Creating similar processes to go into a multiproduct facility

- Staffing; this is a large contributor to the production cost and it is probably here one can make the largest impact if there is a clear philosophy when starting the design of a facility

Next generation of process

Foto: Johan Steensland

Balancing up and down stream capacity

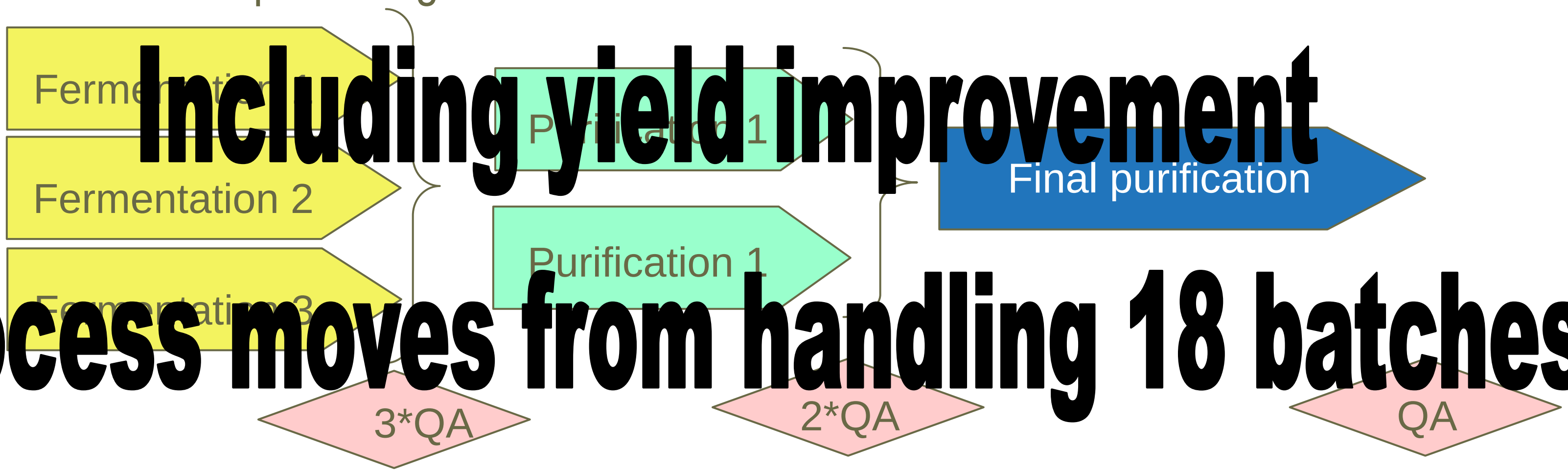
- Is a high fermentation titre everything?

- From a production practical perspective the answer is definitely NO
  Equally or more important is:
  - The match of upstream output to downstream capability
  - The tact which the facility is running at; e.g. if downstream is capable of processing one batch of certain size every 24 h it might be best to get those quantities out of fermentation at the same phase
  - Large batches also equals larger cost at risk when something goes wrong
  - Scaling up downstream has practical limitations (e.g. column sizes)

- Although; a high titre could help by decreasing the scale of fermentation which in turn could affect investment costs

Case study: Using process balancing to develop next generation process

- Introducing one-batchness
  - Current process generation



Including yield improvement process moves from handling 18 batches to 1 batch with the new process

  - Next process generation

Case study: Impact on Value added and lead times

Existing process

Process Time	Total Lead Time
18 days	157 days
%VA	11,5%

New process

Process Time	Total Lead Time
11 days	44 days
%VA	25%

68% improvement

Capacity and resource utilization

Foto: Johan Steensland

Methods for discovering potential bottlenecks

Utilities
•Generation
•Distribution

Control system design

Shift patterns

Fermentation cycle times

What is a bott...?

A phen... an entire syst... component (Wikipedia)

How to overcome them?

Chromatography cycle times

Filter test equipment

CIP

Intermediate storage

Off line testing

Methods for discovering potential bottlenecks

- By default all bottlenecks can not be removed so a conscious decision should be made based on:
  - Operational philosophy
  - Projected future capacity need
  - Process knowledge

- Facility design should then accommodate the inputs from above

- This should be done at an early stage in design and an outcome should be a plan for future de-bottlenecking so that it is clear what happens when 1st in line bottle neck is removed and so on

Avoiding bottlenecks by design and production planning

- When to start planning?
  - When the process is defined at least down to unit operations
  - When the design is still not frozen so that potential issues could be mitigated

- How to do planning?
  - There is off-the-shelf software to help out with simulations
  - But there is no help in getting to know your process in these
  - Therefore be very careful in trusting “generic” operations

“The  is in the details”

Case study 1; A recent biotech facility project

Operational philosophy

- No night shifts although process runs 24/7
- Minimise weekend work
- Critical steps as chromatography pooling to be overseen by personnel
- Redundancy for fermentation to avoid complete shut down in case of foreign growth problems
- Minimise movement of material by personnel

Capacity

- Initial output needed 2 batches / week

Case study 1; Process knowledge

- Block flow diagrams developed for each process step

CV	FLOW		LIN VEL		INPUTS (SOLUTIONS)	PROCESS STREAM	
X	Y	L/h	Z	cm/h	Sanitise		
X	Y	L/h	Z	cm/h	Rinse		
X	Y	L/h	Z	cm/h	Equilibrate	**Chromtography**	
X	Y	L/h	Z	cm/h	Load	**XYZ**	
X	Y	L/h	Z	cm/h	Wash		
X	Y	L/h	Z	cm/h	Gradient Buffer A	**X**	
X	Y	L/h	Z	cm/h	Gradient Buffer B	**Cycle(s)**	
X	Y	L/h	Z	cm/h	Regen		
X	Y	L/h	Z	cm/h	Cleaning	UV Gates:	
X	Y	L/h	Z	cm/h	Condition	Front: Y	
X	Y	L/h	Z	cm/h	HETP Spike	Back: Z	
X	Y	L/h	Z	cm/h	Measure HETP		
X	Y	L/h	Z	cm/h	Bacteriostat storage		

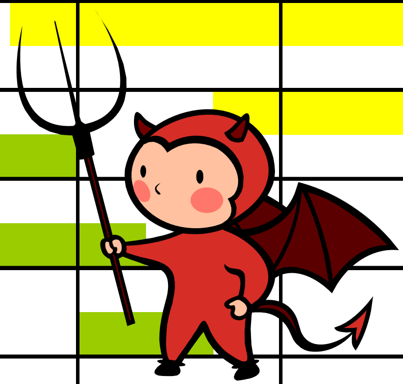
Case study 1

- With the knowledge from process and desired operational philosophy a design was made including:
  - Buffer and media preparation close to warehouse and dispensary to minimise personnel intense solids transport
  - Hold area for prepared solutions
  - Hold point in process introduced to be able to minimize e.g. week end work

Case study 1, production output model (high level)

Day	1	2	3	4	5	6	7
Process area	am pm ni	am pm ni	am pm ni	am pm ni	am pm ni	am pm ni	am pm ni
Seed Lab							
Fermentation							
Harvest							
Midstream							
Purification 1							
Purification 2							
Purification 3							
Purification 4							
Formulation							
Filling							

But remember



Case study 1, production output model (example details)

		Day 1																		Day 2																
Seed Fermenter		7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
CIP	2																																			
Calibration of electrodes	0.5																																			
Mount electrodes and septum	0.5																																			
Filter test pre-use	2																																			
Pressure hold	0.5																																			
SIP	1																																			
Filter test post use	1																																			
Transfer in	0,5																																			
Media SIP	2																																			
Additatives	0.5																																			
Inocculum in	0.5																																			
Process	7																																			
Transfer out	0.5																																			
CIP	2																																			

Case study 1, staffing requirements

Operation	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
Buffer/Media prep	2		2	1	2	2	2	2	1	1	1	1		
Seed lab	1		1	1	1			1	1				1	
Fermentation			1	1	1		1		1		1	1	1	1
Cell harvest	2	2						1	2	1	2	2	1	1
Midstream	1	1	2								1	1	1	1
DSP 1			2			1	2							
DSP 2		1			2	1		1	2	1		1	1	1
DSP 3	2	1							1	1	2	1		
Final fill			2										2	
Total	**8**	**5**	**10**	**3**	**6**	**4**	**5**	**5**	**8**	**4**	**7**	**7**	**7**	**4**
Total/day	**13**		**13**		**10**		**10**		**12**		**14**		**11**	

Case study 1; summary

With the described approach the following were achieved:

- Conscious decision made on limiting capacity
- Actions to increase capacity when required already identified
- Staffing adapted to actual process need reducing the numbers by at least 50% compared to traditional 24/7 coverage

Case study; CIP and SIP

		Day 1																		Day 2																
Seed Fermenter		7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
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CIP	2																																			

CIP philosophy

- Define a worst case model based on most potent drug thus rendering lowest allowable residue to be carried over to the next product.
- Extensive FMEA risk analysis to make bracketing/grouping possible
- Risk analysis also used to justify that there is no need for soft part change out between campaigns/products
- Hardest to clean parts of the process e.g. TFF's and resins to be dedicated per product
- All sampling done with the aim to be able to validate rinse samples only.
- No product specific residue testing all protein and other contents tracked back to TOC
- Ability to monitor TOC on-line

SIP philosophy

- Design started with a fully steam able facility

- Risk analysis performed to indicate where SIP were necessary:
  - It was concluded that there was no major benefit in doing SIP from a cleaning/bioburden perspective from midstream to end of process.

- The only parts of the process where SIP where kept was:
  - Fermentation to ensure a monoculture
  - After the last bioburden reduction filter before final fill to ensure a minimal bioburden load to the final formulation operations.

Thank you!