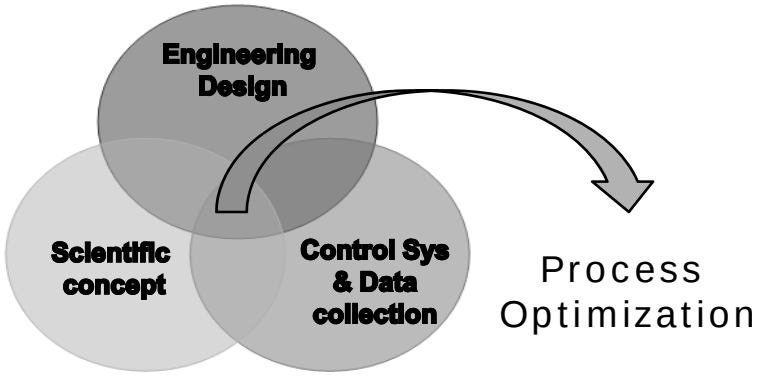
FROM SCIENTIFIC CONCEPT TO ENGINEERING REALITY

UPSTREAM

Anton Renardshaw Edmund, PhD.

Process optimization



Some Potential Failures in Bioreactors

http://en.wikipedia.org/wiki/File:Pg166_bioreactor.jpg

Slow growth
Contamination, bioburden fail
Bioreactor vessel leak
Wrong media
Media precipitation
DO probe
pH probe
Thermal sensor failure
Process control failure
Data acquisition system

Connecting a World of Pharmaceutical Knowledge ISPE

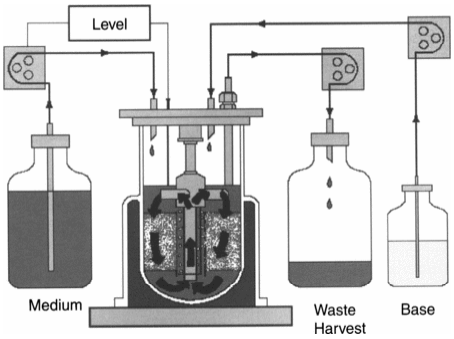
Some Potential Failures in Bioreactors (Cont.)

Loss of back pressure
Excessive foaming
Loss of cooling capacity
No air supply
Power failure
Protein degradation
Feed temperature
Agitation
Process duration

Connecting a World of Pharmaceutical Knowledge ISPE

Industrial Example 1: Base Addition

- Base addition happens during fermentation/ production phase in order to maintain pH in the bioreactor



Schematic representation of the CelliGen Plus packed-bed bioreactor (courtesy of New Brunswick Scientific; www.nbsc.com

Connecting a World of Pharmaceutical Knowledge ISPE

Industrial Example 1: Base Addition (contd.)

- Additionally, the same base (Caustic) is added at the end of fermentation to terminate Cell Culture

•http://www.ferms-and-more.at/en/aboutus/equipment/

Connecting a World of Pharmaceutical Knowledge ISPE

Industrial Example 1: Base Addition (contd.)

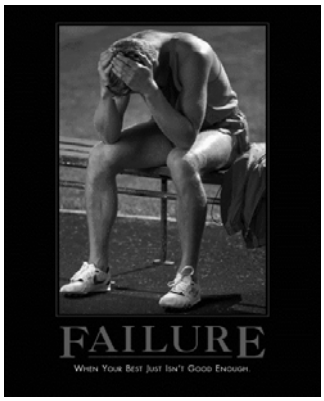
- There were two bioreactors at production phase in the same suite
- One bioreactor was at early stage of production phase
- The other bioreactor was at late state of production phase
- Base addition was designed to be fed automatically when the base addition logic was activated

•http://www.ferms-and-more.at/en/aboutus/equipment/

Connecting a World of Pharmaceutical Knowledge ISPE

Industrial Example 1: Base Addition (contd.)

- pH went too low in early stage bioreactor on 3rd shift
- Programmed base addition did not initiate base addition
- Base was added manually and then program kicked in as well
- Too much base addition caused → high pH → End of Run



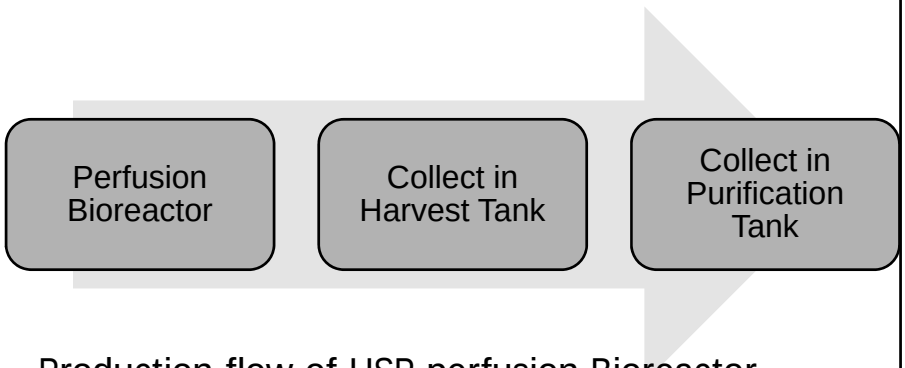
http://www.dennis-yu.com/wp-content/uploads/2012/01/failure.gif

Connecting a World of Pharmaceutical Knowledge ISPE

Industrial Example 1: Base Addition (contd.)

- As early stage bioreactor was terminated accidently, additional base (Caustic) need to be added to terminate the culture (end of run)
- At Shift Change, 1st shift took over the transition
- Caustic was added to the wrong Bioreactor accidently
- 2nd bioreactor was terminated

Industrial Example 2: Product volume



Production flow of USP perfusion Bioreactor

Industrial Example 2: Product volume

- Harvest material was transferred from harvest tank to purification tank.
- The Harvest Volume was higher than normal
- The Transferred Material Volume in the purification tank was ~200 L higher than the volume had been in the Harvest Tank

Industrial Example 2: Product volume- Investigation

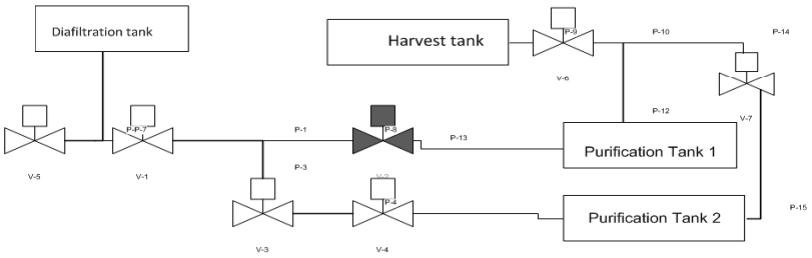
- Initial thought was tank level algorithm was wrong as each tank had unique linear and nonlinear portion algorithm
- Metrology was called in, and the calibration algorithm was rechecked.
- There wasn't any abnormal algorithm on top portion of the tank.
- Where did the extra 200L came from ?

nodabrewing.com

Harvest Tank

Purification Tank

Industrial Example 2: Product volume-Investigation



- One Diafiltration tank was being shared for both Purification tanks (PT)
- PT1 had higher harvest volume
- PT2 Diafiltration line was WFI rinsed during harvest transfer
- One of the block valves stayed open during this process

Engineering Design (Scaleup)

- Optimize Cell density during inoculation from seed to production reactor
- Control Media Delivery
- pH control- Base addition
- DO Transition from growth to production
- Sweep Temperature with culture growth
- Harvest transfer- Controlled Agitation

  (perfusion Bio-reactor)
- End of run-product Transfer

Any Questions??

Connecting a World of Pharmaceutical Knowledge ISPE

Connecting a World of Pharmaceutical Knowledge ISPE