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What is holding the industry back from implementing CBP (Continuous Bioprocessing) more broadly?

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Morten Munk, "What is holding the industry back from implementing CBP (Continuous Bioprocessing) more broadly?" in "Integrated Continuous Biomanufacturing II", Chetan Goudar, Amgen Inc. Suzanne Farid, University College London Christopher Hwang, Genzyme-Sanofi Karol Lacki, Novo Nordisk Eds, ECI Symposium Series, (2015). http://dc.engconfintl.org/biomanufact_ii/69

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Morten Munk
NNE PHARMAPLAN

CONTINUOUS BIOPROCESSING

What is holding the industry back from implementing CBP more broadly

Integrated Continuous Biomanufacturing II

November 1-5, 2015

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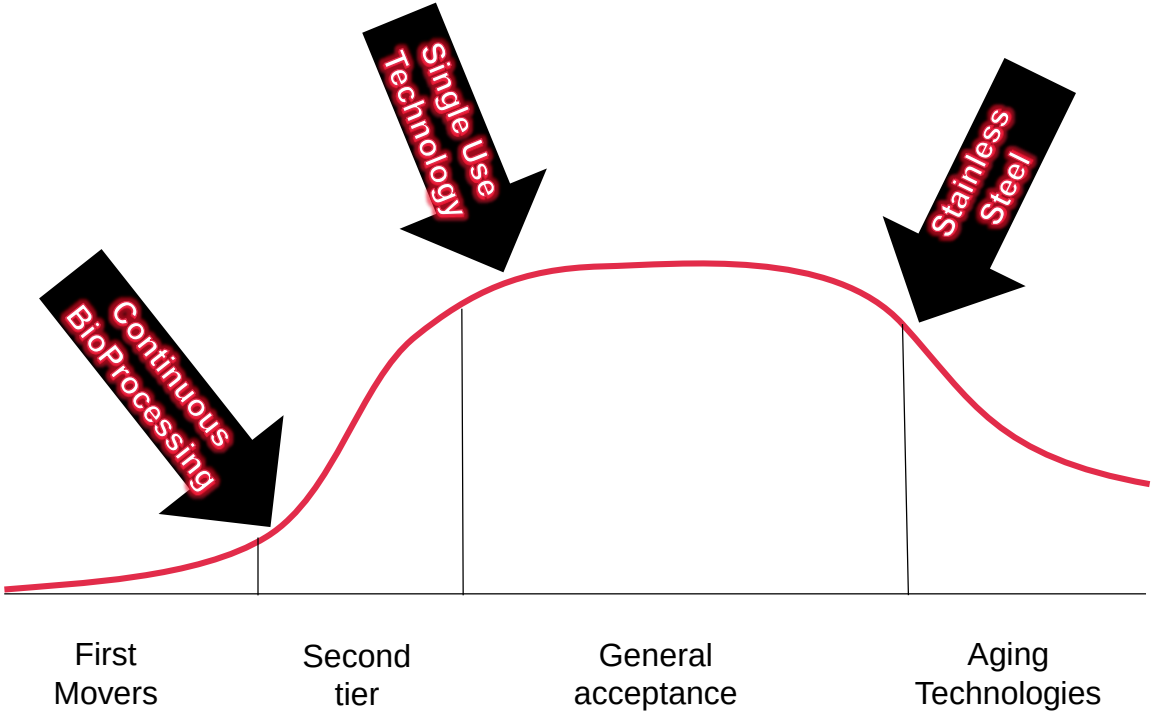
Focused pharma engineering

Agenda

- Introduction of new technologies
- Marked expectations – Results form Continuous BioProcessing survey
- Authorities expectations
- Facility design and operation – Batch vs CBP
- Quality Impact
- Stepwise Approach
- Conclusion

General lifecycle for technologies



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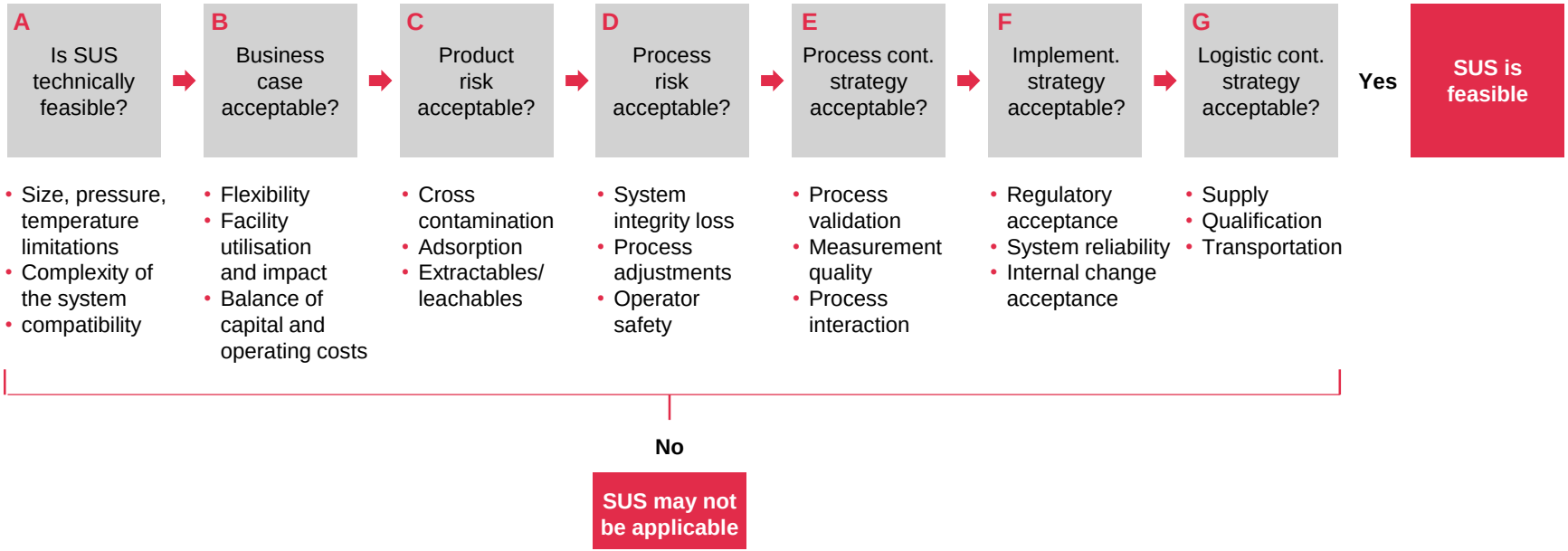
Guided Decision Process for SUS

- Example from the PDA Technical report on implementation of Single Use Systems (SUS)



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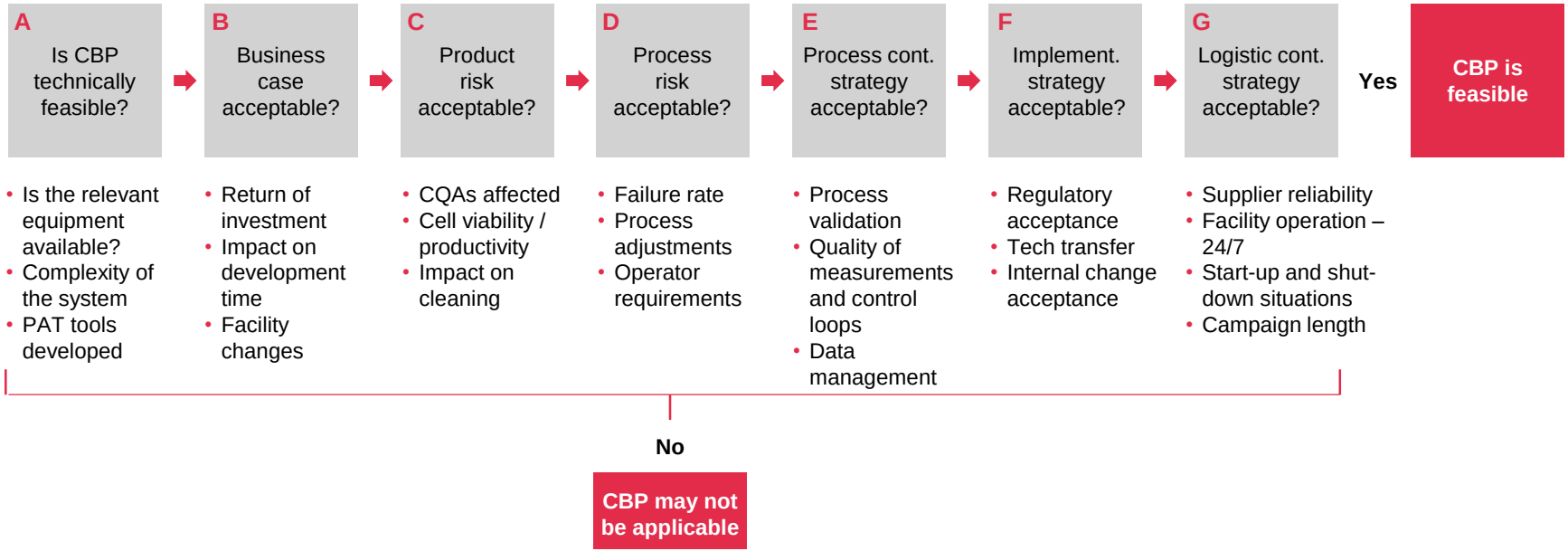
Guided Decision Process for CBP



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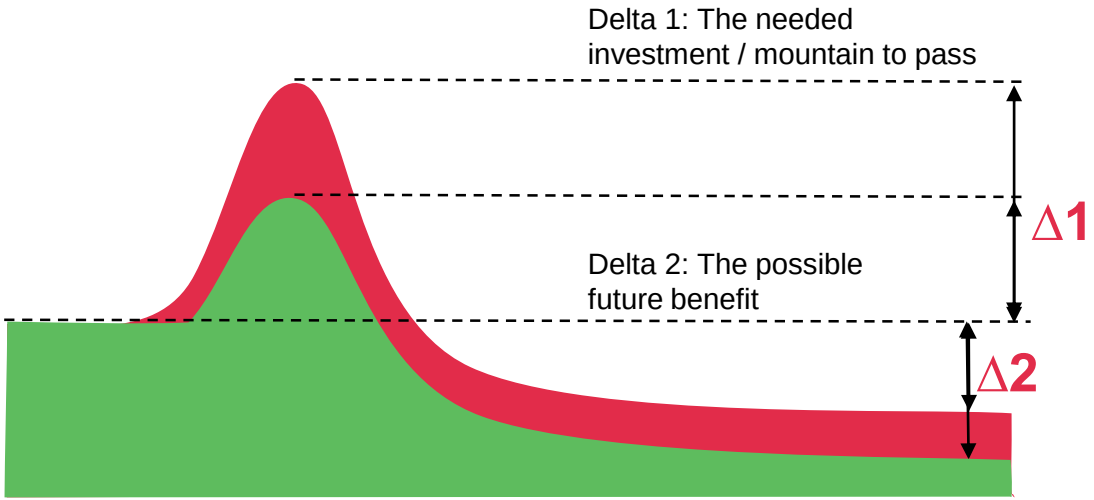
General lifecycle for implementation of changes

Reduce the activation energy



The aim is to reduce Δ1 and increase Δ2

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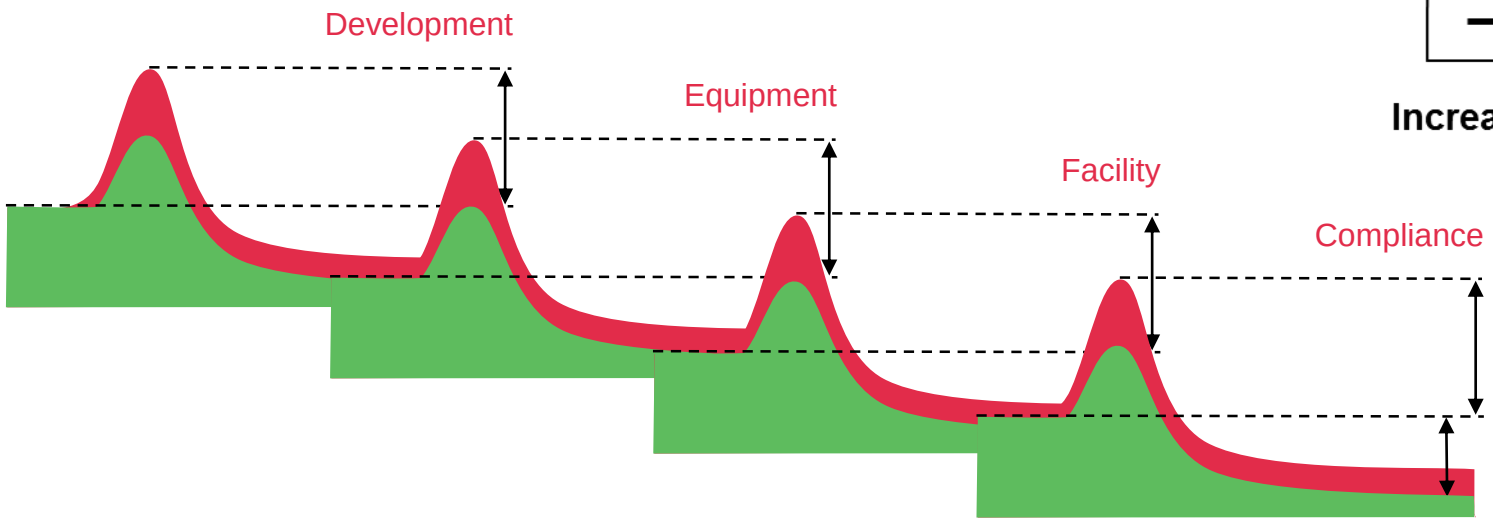
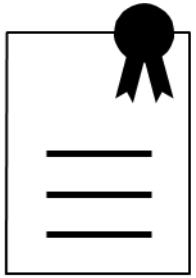
Manufacturing cost elements



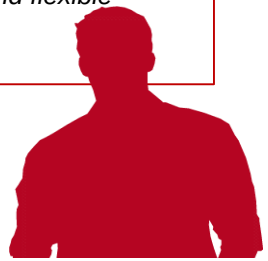


Increased quality

Marked requirements to pharma engineering

AGILE AND FLEXIBLE OPERATIONS

"Help us ensure we can always deliver to demands in more agile and flexible ways



Sites need to ensure they can always adapt and deliver to changing demands

SEAMLESS GMP COMPLIANCE

"Help us build and maintain quality systems and solutions that can ensure the right level of compliance

Sites need well-integrated and balanced quality solutions

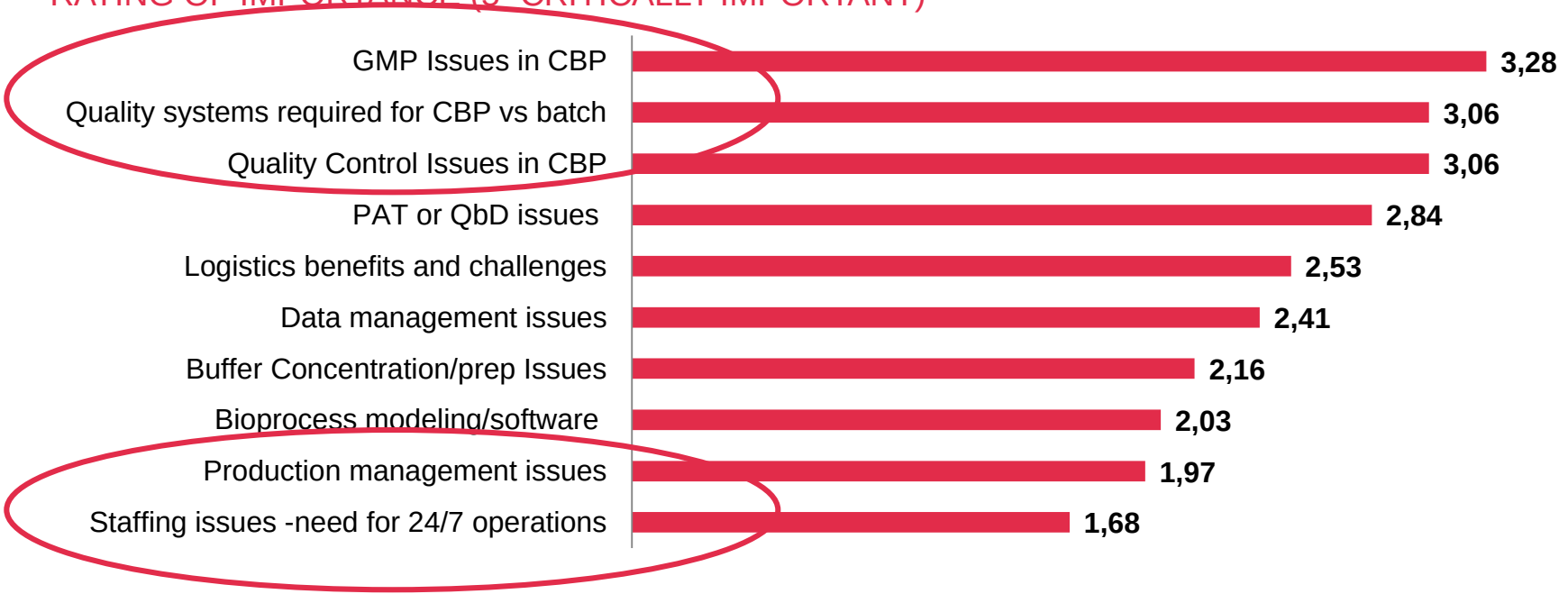
FUTURE PROOF SOLUTIONS

"Help us build the expertise required when introducing new drug categories or technologies

Sites need to quickly absorb knowledge to implement new practises

Operational Issues Associated with CBP

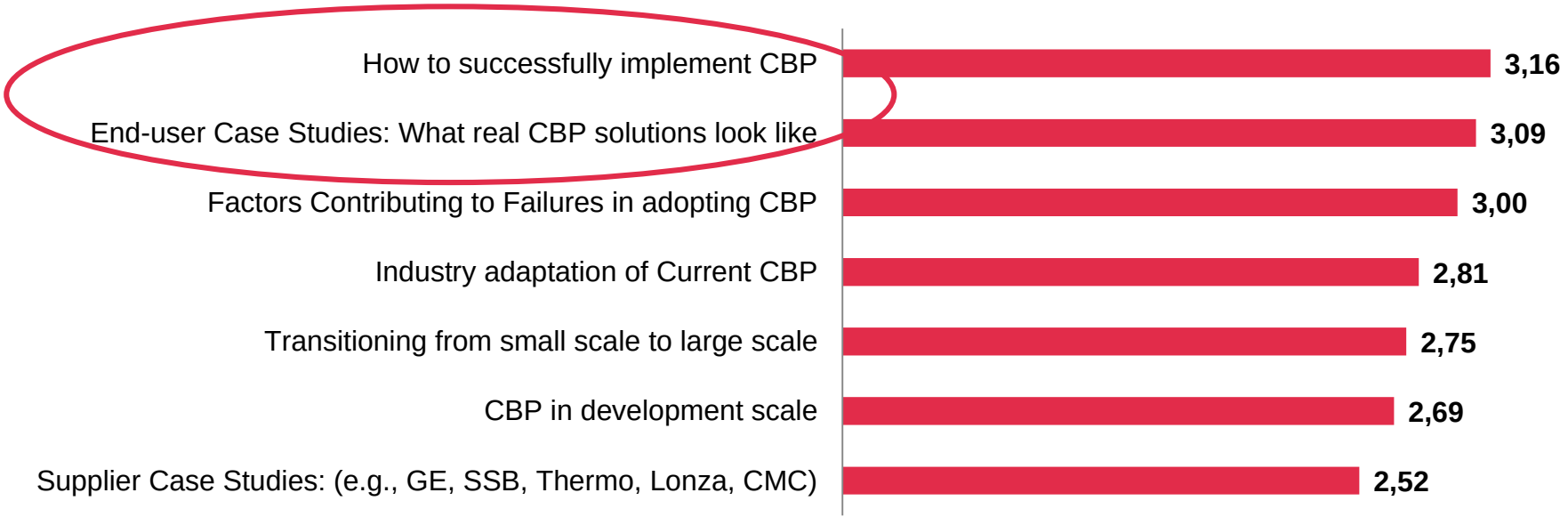
RATING OF IMPORTANCE (5=CRITICALLY IMPORTANT)



Survey performed by BioPlan Associates, for NNE Pharmaplan

Need for CBP Case Studies

RATING OF IMPORTANCE (5=CRITICALLY IMPORTANT)



Survey performed by BioPlan Associates, for NNE Pharmaplan

What is currently holding back implementation of CBP?

- Precedence - someone else needs get it through the FDA/EMA first
- Robust PAT tools, defined regulatory path, robust single use technology
- Comfort level and lack of PAT and control tools
- CBP doesn't easily fit into existing infrastructure / facilities / Quality systems
- Economic justification and adaptation of current Quality/Regulatory programs
- Unit operations not fully developed for continuous processing; not a standard platform

Lack of experience and concern of authorities point of view

Survey performed by BioPlan Associates, for NNE Pharmaplan

Advantages of Continuous Manufacturing (CM)

- Integrated processing with fewer steps
  - No manual handling, increased safety
  - Shorter processing times
  - Increased efficiency
- Smaller equipment and facilities
  - More flexible operation
  - Reduced inventory
  - Lower capital costs, less work-in-progress materials
  - Smaller ecological footprint
- On-line monitoring and control for increased product quality assurance in real-time
  - Amenable to Real Time Release Testing approaches
  - Consistent quality

Potential for reduced cost

8

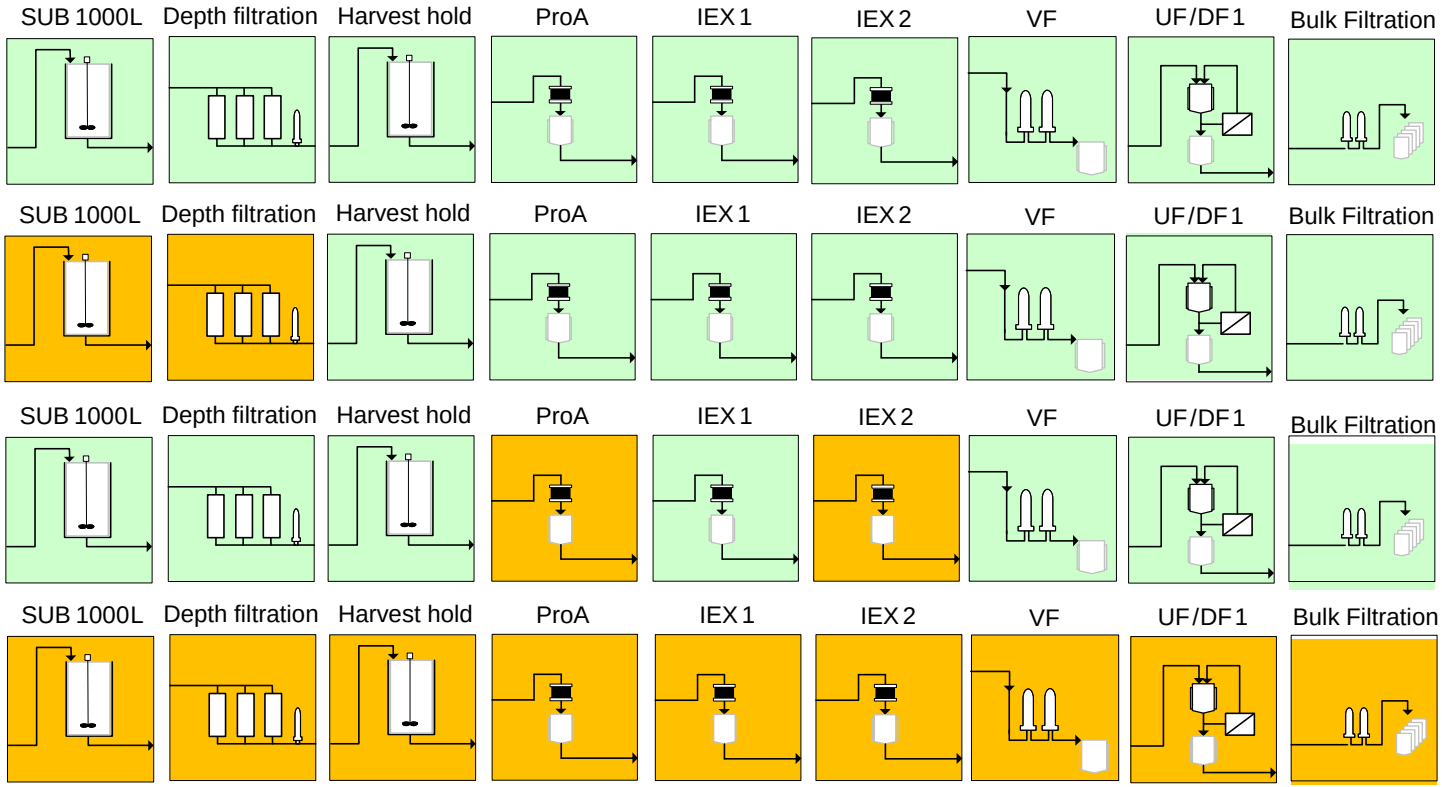
FDA Perspective on Continuous Manufacturing

IFPAC Annual Meeting
Baltimore, January , 2012

Sharmista Chatterjee, Ph.D.
CMC Lead for QbD
ONDQA/CDER/FDA

12 http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341197.pdf

Degree of Continuous Bioprocessing (CBP)



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Facility design and operation – Batch vs CBP

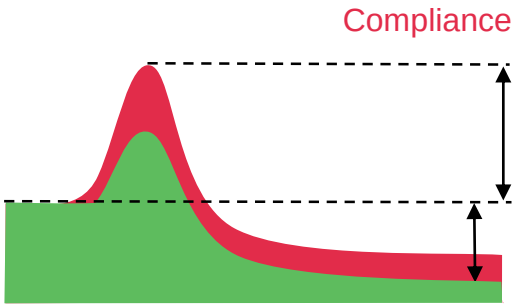
Batch

- Possible to be operated in 1 or 2 shifts, 5 days
- Can be based on manual operation
- Separate USP and DSP teams
- Some advantage of PAT
- Possible re-use of equipment in different steps
- Large vessels for hold steps
- Large buffer vessels and process equipment
- Process steps independent
- Less impact due to delay or failure in one step
- Manufacturing can be separated from Dev, QC and QA
- Facility designed based on scale up
- X productivity per m^2 facility area
- Product quality and process reproducibility

CBP

- Need 24/7 operation
- High level of automation required
- One team
- PAT a requirement
- All equipment dedicated to each step
- No or limited hold steps needed
- Smaller equipment both USP and DSP
- The process steps need to be in synchronized
- The whole process stops if one step stops
- Dev, QC and QA need to be close /integrated in the manufacturing facility
- Facility designed based on scale out
- 5 to 15 X productivity per m^2 facility area
- Product quality and process reproducibility improved

Quality Advantages

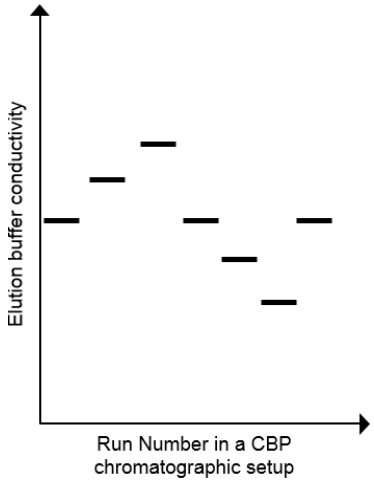


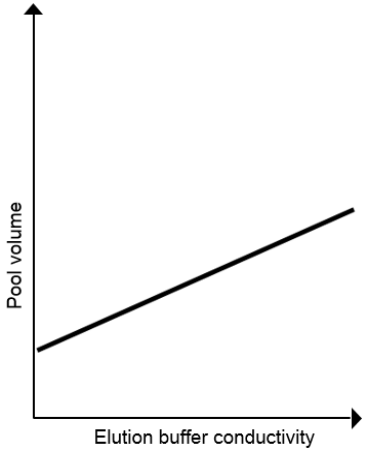
- Shorter contact time
  - Time at 37°C in complex media – 14 days vs 3 days
  - Protein/resin interaction – hours vs minutes
- Shorter processing time
  - Less/shorter intermediate hold times
- Real time process control
  - Fast response time to process drifting and deviations
- Generation of large amount of data
  - Option for increased process understanding → Increased Process Control
- Option for real time release
  - Build in quality vs testing in quality
- Increased reproducibility and control
- Aim for a state of “in control” rather “steady-state” conditions

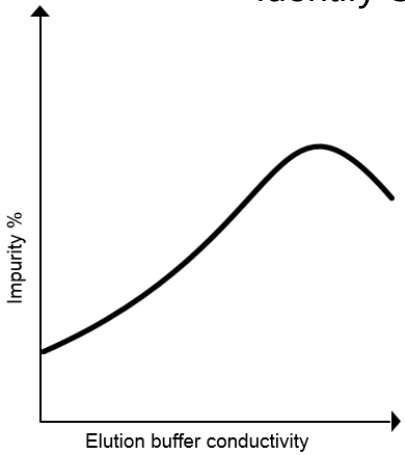
Stepwise Approach - Start in the development lab!

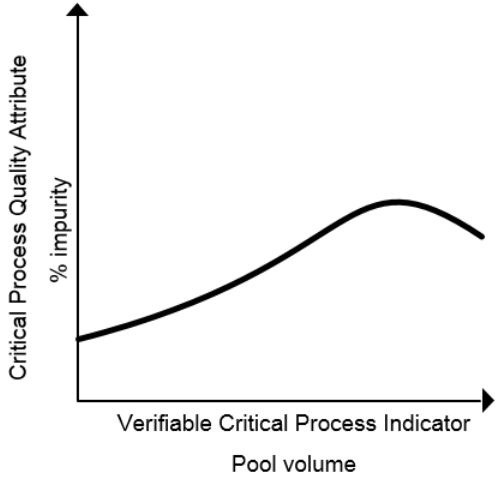
- Taking advantage of CBP in development do not require to run manufacturing in CBP mode
  - Column life time studies
  - Testing parameter ranges in one set up

- Generate knowledge of relationship between CQA's and CPP's
- Basis for feed-forward and feed-backward controls
  - Perfusion rate impact on viable cell conc, Elution conductivity impact on pool volume
- Identify Critical Process Indicators (CPI)









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Are others considering CBP ?

Sanofi's Genzyme looking hard at continuous manufacturing

Biotech has faster, compressed process working for months

January 31, 2013 | By Eric Palmer

Other companies also are evaluating continuous processing. In fact MIT's research is done at something called the Novartis-MIT Center for Continuous Manufacturing, born of a $65 million collaboration between the university and the Swiss drugmaker. Other companies are looking at other processes to make manufacturing faster and more efficient.

GSK commits to continuous processing

Witty says it could be used on up to half of the company's drugs

February 19, 2013 | By Eric Palmer

With the new technology, a plant of only about 100 square meters is required, compared to the 900-square-meter facilities needed for current methods, he said. "So you are talking about a massive reduction in capital deployment and space occupancy obviously, you will see something like a 50% reduction in carbon footprint insolvent use up to a 50% reduction in cost," he said. And this will not be a rarity, Witty said. He went on to explain that between a third and half of the company's current portfolio of drugs could be made using continuous processing.

FiercePharma Manufacturing

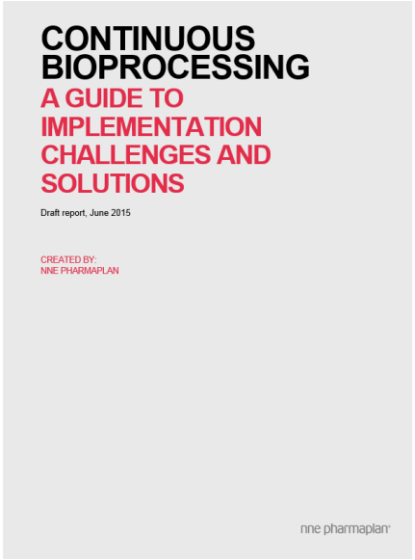
GSK doubles down on Singapore continuous processing plant

June 29, 2015 | By Eric Palmer

Several years ago, GlaxoSmithKline committed $50 million to set up an antibiotics facility in Singapore to do continuous processing, a radically different manufacturing approach that has a much smaller footprint, and so much lower operating costs and less environmental impact, than traditional batch processing. The drugmaker now says it is ready to embark on a £38 million expansion there.

Conclusions

- The science exists to enable continuous manufacturing of pharmaceuticals
  - Still specific scientific and technical challenges to be addressed
- There shouldn't be unmanageable regulatory hurdles precluding implementing continuous manufacturing
  - However, there is a lack of experience both in industry and within the regulatory authorities
- FDA supports the implementation of continuous manufacturing using a science and risk-based approach
- Advisable to use a structured and stepwise approach
- Develop processes using and a QbD and PAT approach, as this will benefit both a batch and a CBP manufacturing model



Thank you

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