Case Study: The Application of a Plant-wide Control Strategy for a Continuous Pharmaceutical Process at the Novartis-MIT Center for Continuous Manufacturing

Richard Lakerveld[1,2,3], Brahim Benyahia[1,2], Patrick L. Heider[1,4], Haitao Zhang[1,5], Salvatore Mascia[1], James M.B. Evans[1], Richard D. Braatz[1,2], Paul I. Barton[1,2].

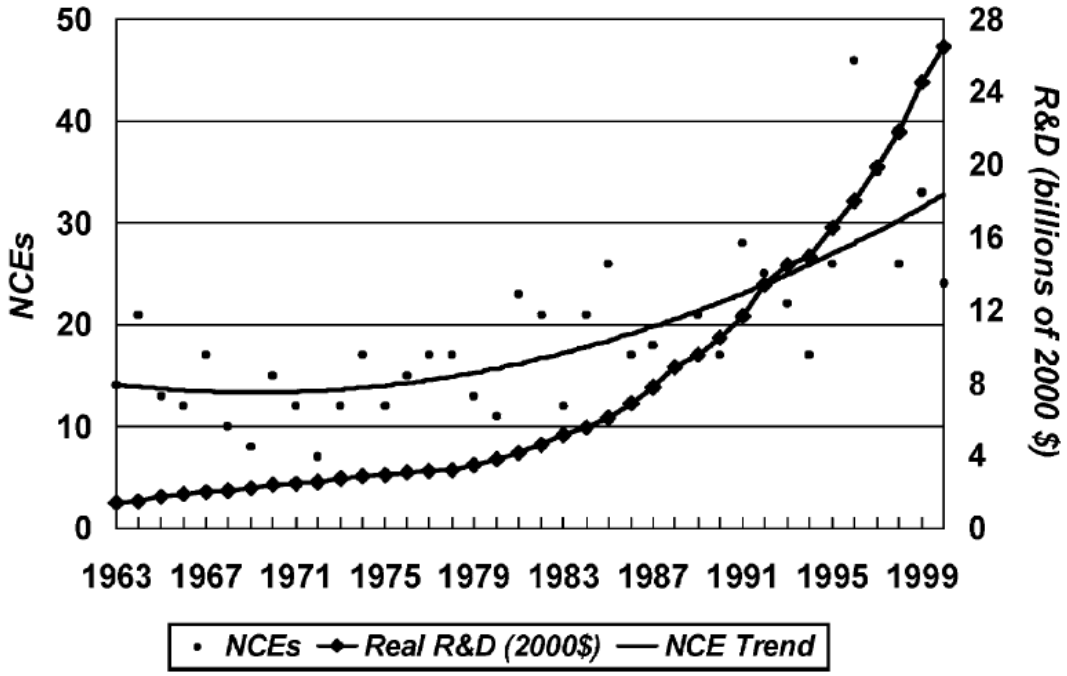
[1] Novartis-MIT Center for Continuous Manufacturing, MIT
[2] Process Systems Engineering Laboratory, MIT
[3] Current affiliation: Delft University of Technology
[4] Jensen Research Group, MIT
[5] Molecular Engineering Laboratory, MIT

Summary of presentation for QbD/PAT Conference, Heidelberg, 2012

Novartis-MIT Center for Continuous Manufacturing

Motivation

- Development of new pharmaceutical compounds is very expensive[1]
- Need for reduction of manufacturing costs
- Moving from batch to continuous can result in significant savings[2]
- Novartis-MIT Center for Continuous Manufacturing founded to develop new technologies



Inflation-adjusted industry R&D expenditures (2000 dollars) and US new chemical entity (NCE) approvals from 1963 to 2000[1]

[2] Schaber et al. (2011). "Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study," *Ind. Eng. Chem. Res., 50, 10083-10092*

[1] DiMasi et al. (2002). "The price of innovation: New estimates of drug development costs," *J. Health Economics, 22, 151-185*

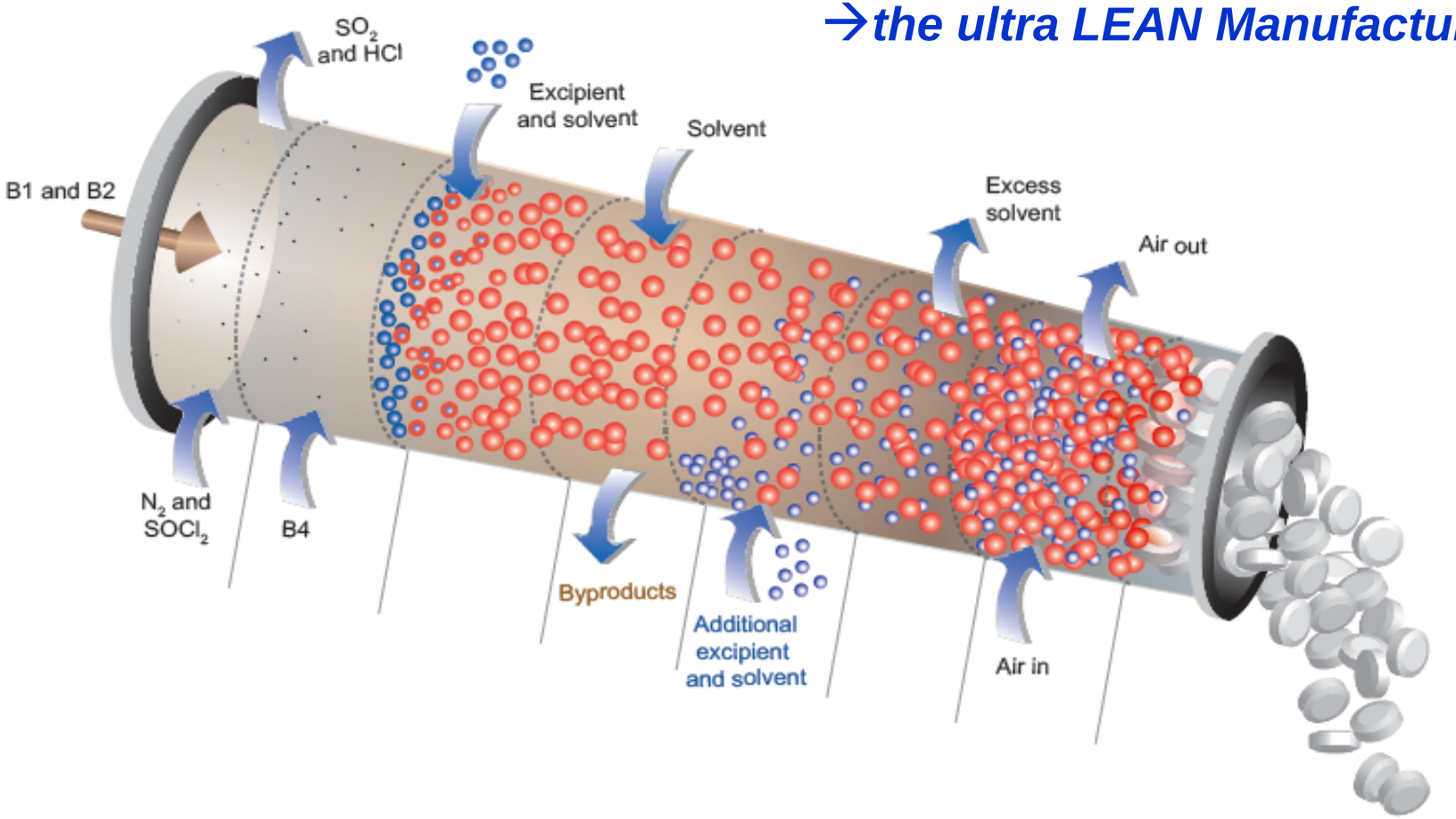
Benefits of Continuous Manufacturing

- Recycle streams to increase yield
- Enables chemistries not suitable for batch
- Simplified scale-up
- Decreased footprint of equipment
- Reduced process and transit time
- Simplified real-time process control
- Increased product uniformity
  – eliminates batch-to-batch variation

Novartis-MIT Blue Sky Vision

Integrated Continuous Manufacturing: A radical transformation

→the ultra LEAN Manufacturing



From start of chemical synthesis through final pharmaceutical dosage form

 Trout, B., Bisson, W., Continuous Manufacturing of Small Molecule Pharmaceuticals, NVS-MIT CCM (2009)

Novartis-MIT Center for Continuous Manufacturing

Integrated pilot plant

- Demonstrate end-to-end continuous pharmaceutical process
- Investigate integration and control
- Case study for process modeling and continuous QbD

Quality by Design

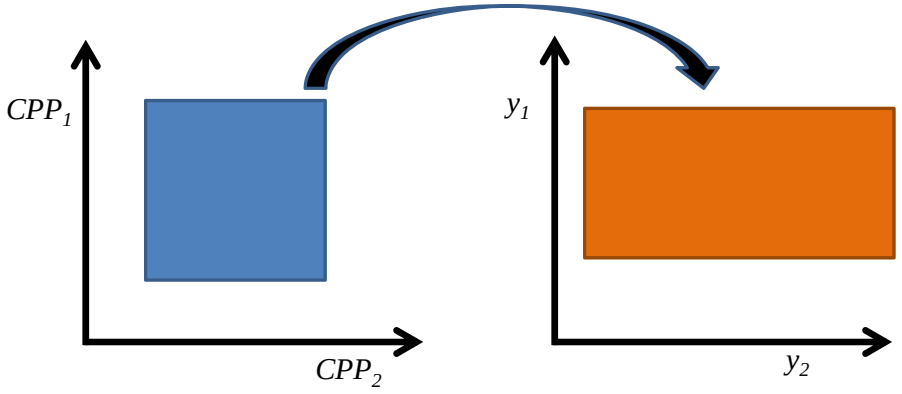
"Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"[1]

Pharmaceutical development includes[1,2]

1. Defining the target product profile
2. Identifying critical quality attributes
3. Selecting an appropriate manufacturing process
4. Identifying a control strategy

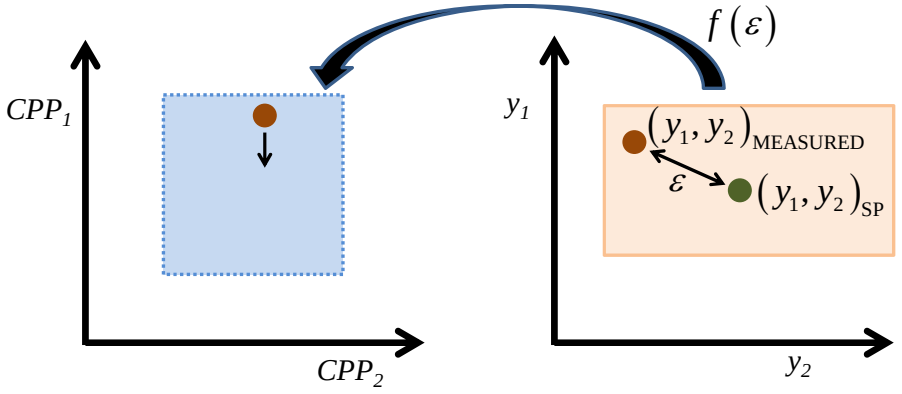
1 Lionberger, Lee, Lee, Raw, & Yu, *AAPS J*, *10*, 268-276, June 2008
2 ICH Consensus Guideline Q8, Pharmaceutical Development, 2007

Quality by Design
Design space ('passive') vs. feed-back control ('active')



Design-space methods:

- Control strategy based on operation within fixed parameter space
- Difficult to scale up
- Lacks flexibility
- Validated design space can be small fraction of the 'real' design space
- Complicated for continuous manufacturing



Feed-back methods:

- Control strategy based on feed-back to parameter space
- Straightforward to scale up
- Flexible
- Design space does not need to be exhaustively validated a priori
- Promising for continuous manufacturing

Lionberger, Lee, Lee, Raw, & Yu, *AAPS J*, *10*, 268-276, June 2008

Agenda

- Pilot plant
- Design of a feed-back/feed-forward control strategy
  - The role of process modeling and hierarchical decomposition
- Application of control strategy on pilot-plant scale: examples and lessons learned
  - Mitigate disturbances to protect key intermediate CQAs
  - Feed-forward & feed-back control
  - Using PAT in feed-back control
  - Use buffering to prevent off-spec material
  - Plant-wide control loops
- Conclusions & Discussion

Conclusions

- Continuous manufacturing offers opportunities to the pharmaceutical industry
- Challenging questions for control strategy
  - Design-space methods vs. feed-back methods
- Model based on a pilot plant for a continuous pharmaceutical process used to:
  1. Systematically evaluate sensitivities of CQAs with respect to CPPs
  2. Synthesize a control structure using feed-back to maintain CQAs within limits

Conclusions

- Implementation at pilot-plant scale demonstrates key lessons learned:
  - Mitigate disturbances such that key intermediate CQAs are protected
  - Feed-forward & feed-back control
    - Both methods can contribute to control strategy
    - Combination very effective
  - Using PAT in feed-back control
    - Real-time measurement of key intermediate CQAs is essential for success of control strategy
  - Use buffering to prevent off-spec material
  - Plant-wide control loops