

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

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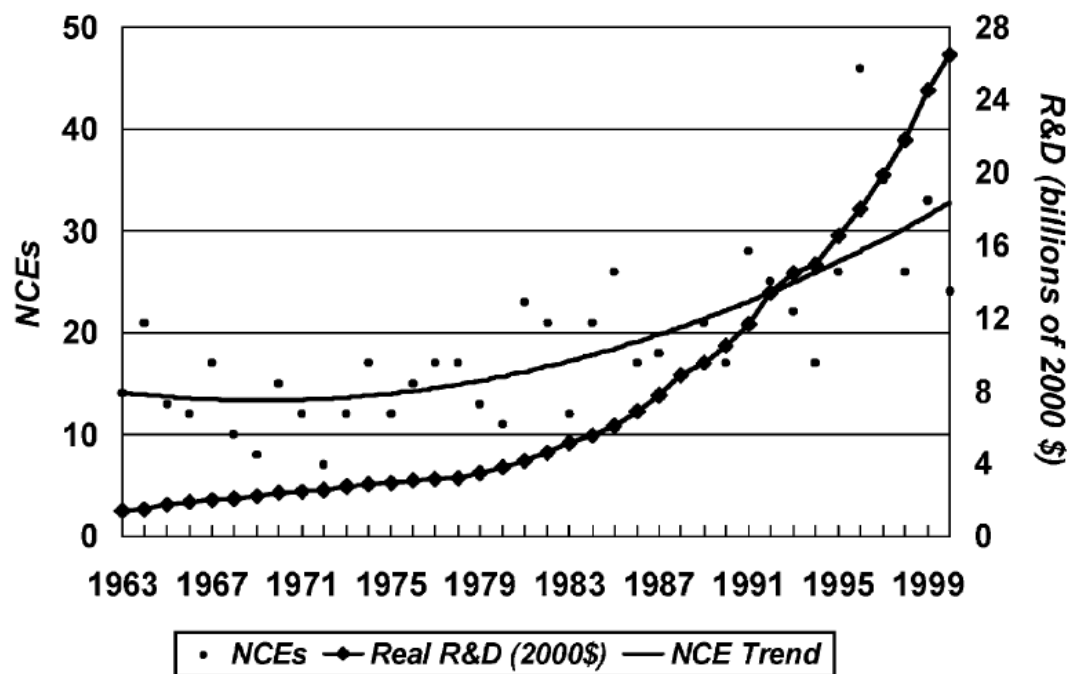
Summary of presentation for QbD/PAT Conference, Heidelberg, 2012



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Motivation

- Development of new pharmaceutical compounds is very expensive¹
- Need for reduction of manufacturing costs
- Moving from batch to continuous can result in significant savings²
- 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 2000¹

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

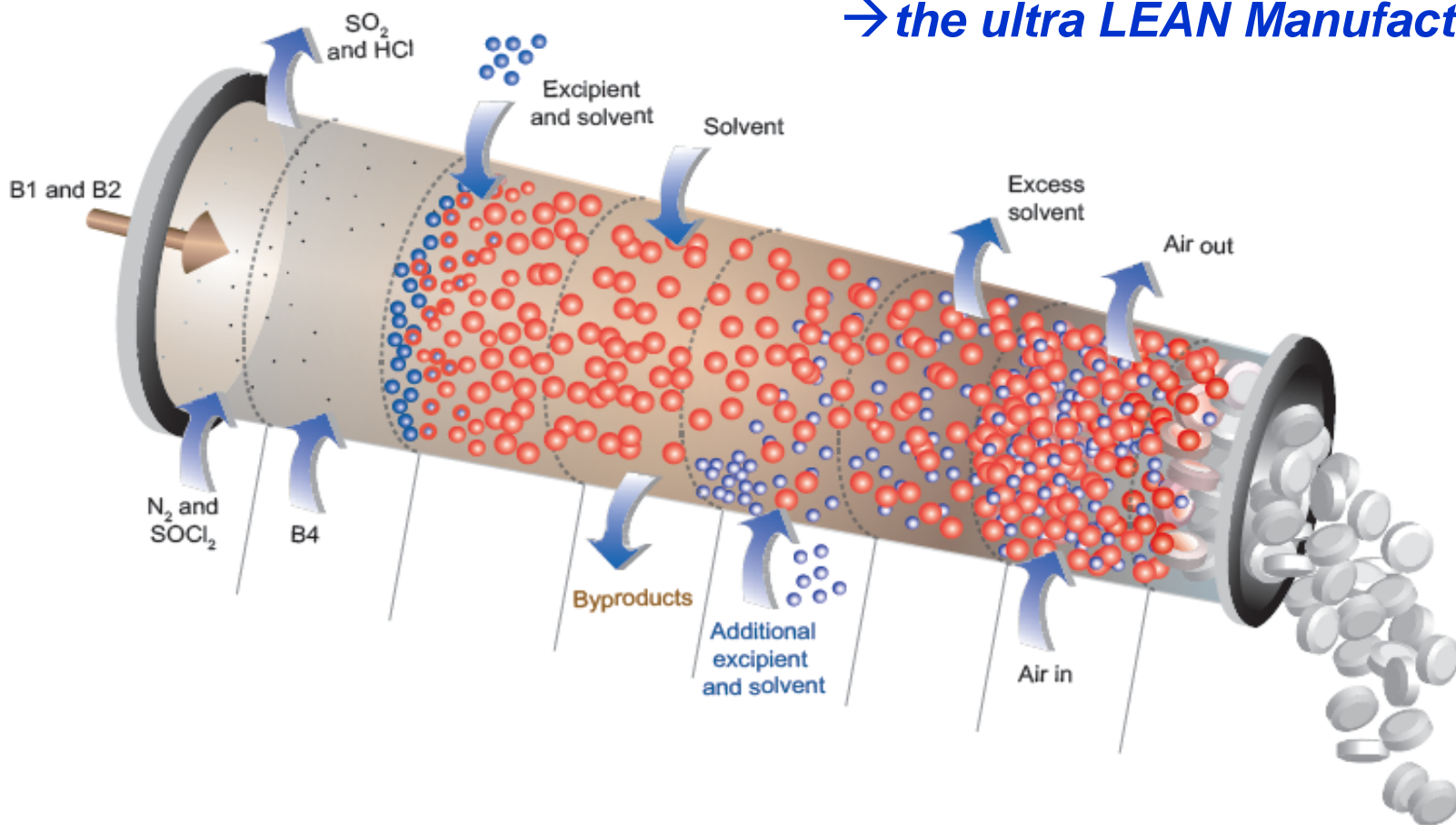
Benefits of Continuous Manufacturing

- 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

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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

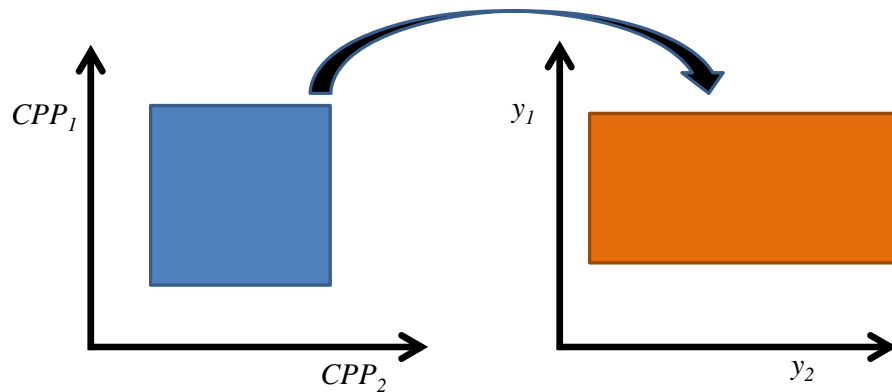
“Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management”¹

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

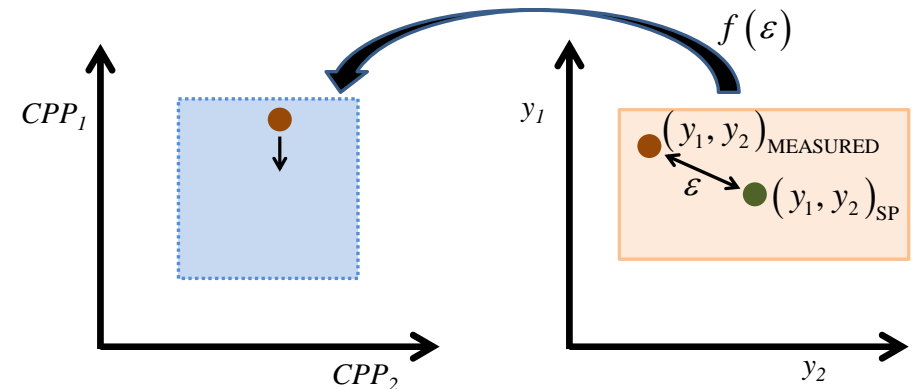
Quality by Design

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

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