

# 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<sup>1,2,3</sup>, Brahim Benyahia<sup>1,2</sup>, Patrick L. Heider<sup>1,4</sup>, Haitao Zhang<sup>1,5</sup>, Salvatore Mascia<sup>1</sup>, James M.B. Evans<sup>1</sup>, Richard D. Braatz<sup>1,2</sup>, Paul I. Barton<sup>1,2</sup>.**

<sup>1</sup> Novartis-MIT Center for Continuous Manufacturing, MIT

<sup>2</sup> Process Systems Engineering Laboratory, MIT

<sup>3</sup> Current affiliation: Delft University of Technology

<sup>4</sup> Jensen Research Group, MIT

<sup>5</sup> Molecular Engineering Laboratory, MIT

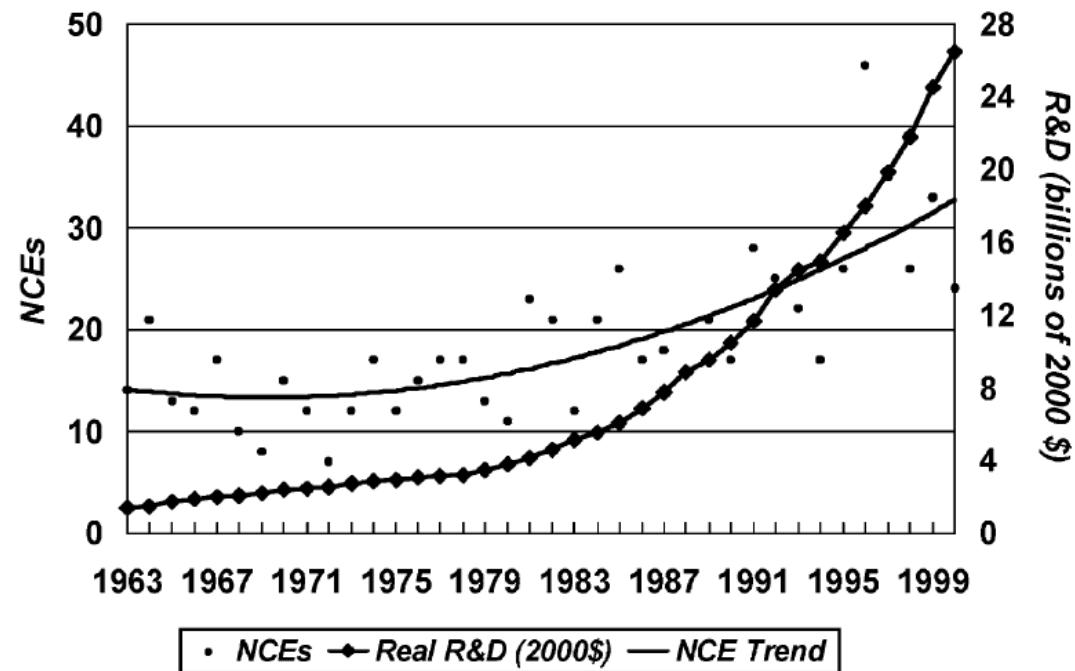


**Summary of presentation for QbD/PAT Conference,  
Heidelberg, 2012**

# Novartis-MIT Center for Continuous Manufacturing

## Motivation

- Development of new pharmaceutical compounds is very expensive<sup>1</sup>
- Need for reduction of manufacturing costs
- Moving from batch to continuous can result in significant savings<sup>2</sup>
- 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<sup>1</sup>

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

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

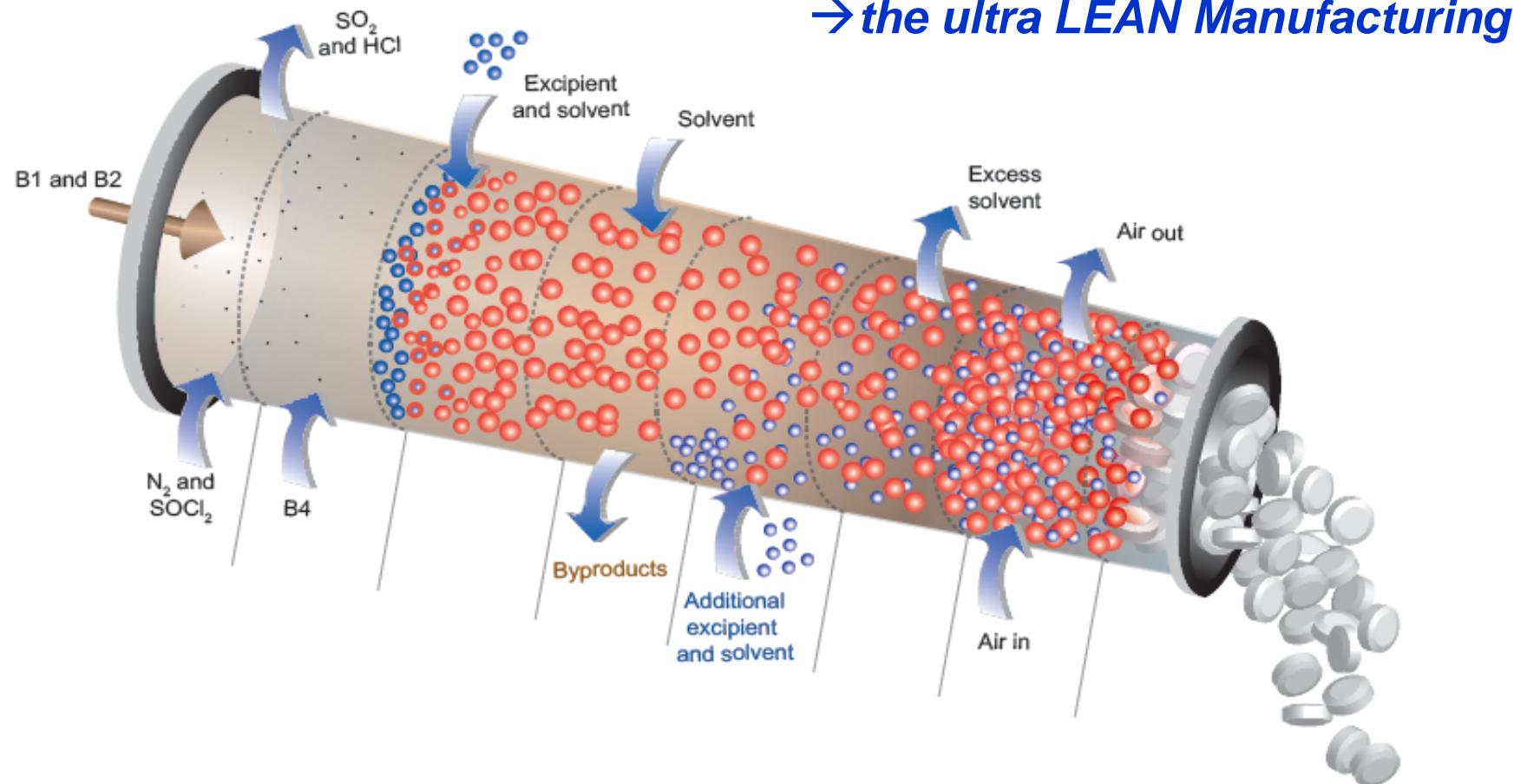
# Benefits of Continuous Manufacturing

---

- 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



From start of chemical synthesis through final pharmaceutical dosage form

# 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

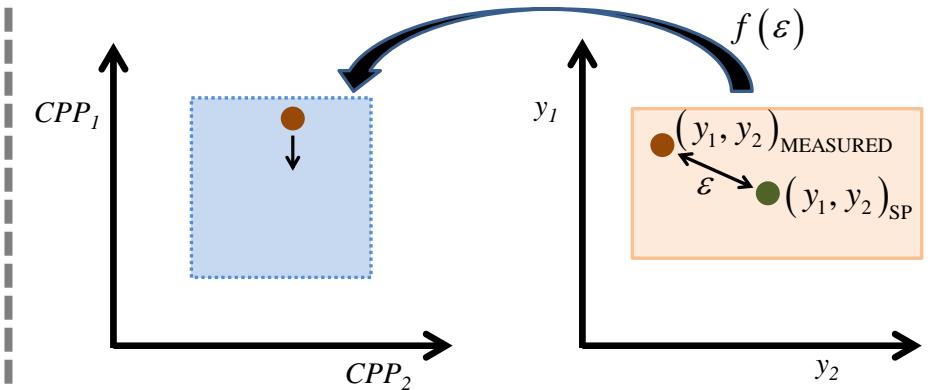
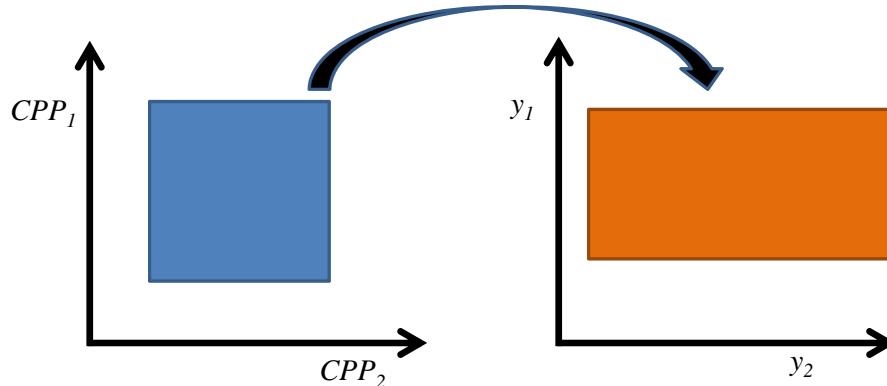
*“Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management”<sup>1</sup>*

## Pharmaceutical development includes<sup>1,2</sup>

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