Strategies to Accelerate Process Control Adoption in the Pharmaceutical Industry

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MIT NOVARTIS

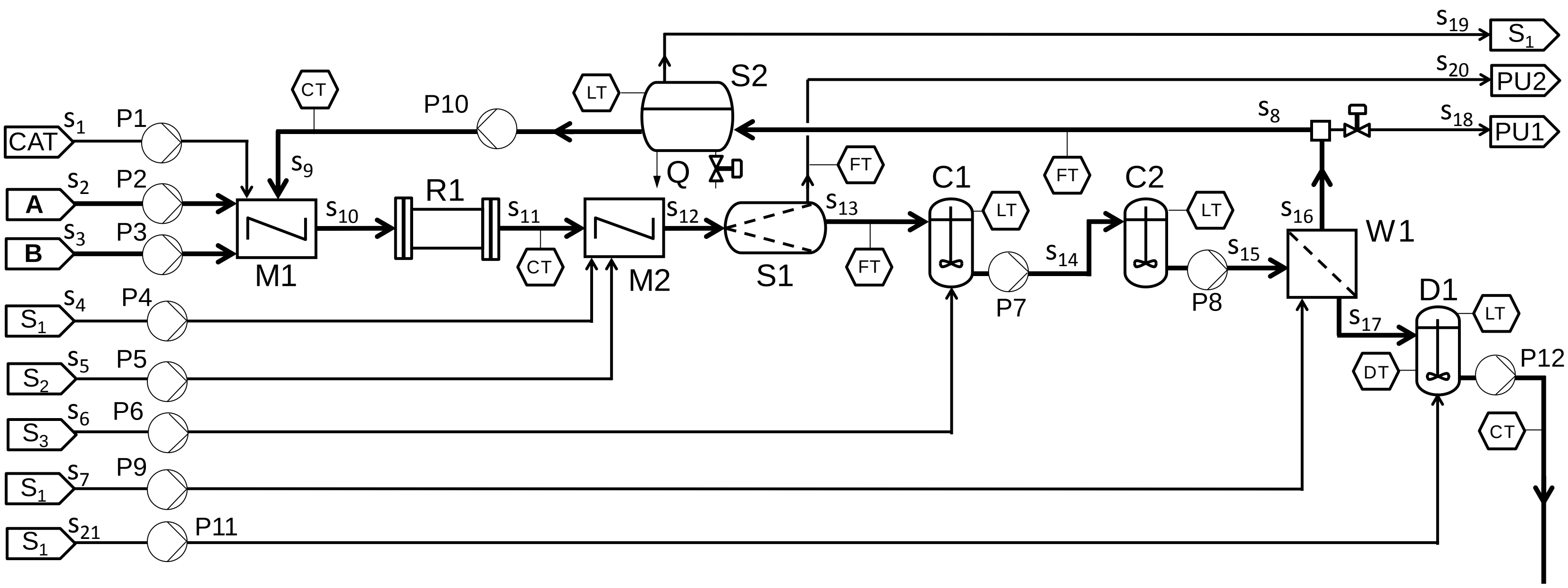
Outline

1. Model-Based Plantwide Control

2. Strategies from the May 20–21, 2014 Continuous Manufacturing Symposium

3. Strategies partly from the October 19, 2015 Promoting Continuous Manufacturing Workshop

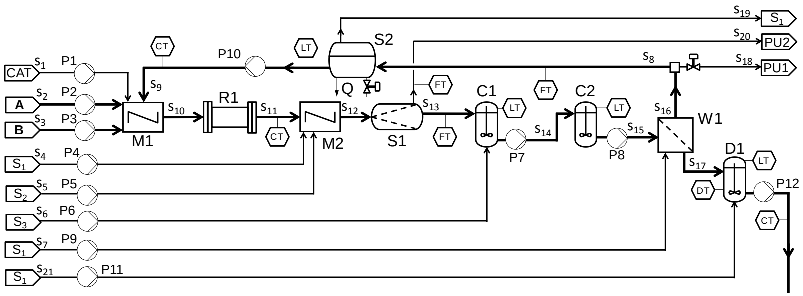
Integrated Control Strategy for Continuous Manufacturing



- Tight integration of operations can result in disturbances propagating downstream, unless their effects are suppressed by an integrated control strategy
- The control strategy must optimize the overall plant operation instead of only isolated units (i.e., need *plantwide control*)

Plantwide Control of Continuous Manufacturing

- System characteristics
  - Many connected unit operations
  - Very fast to slow processes
  - Multi-purpose plants with short development time
  - Alignment with regulatory requirements



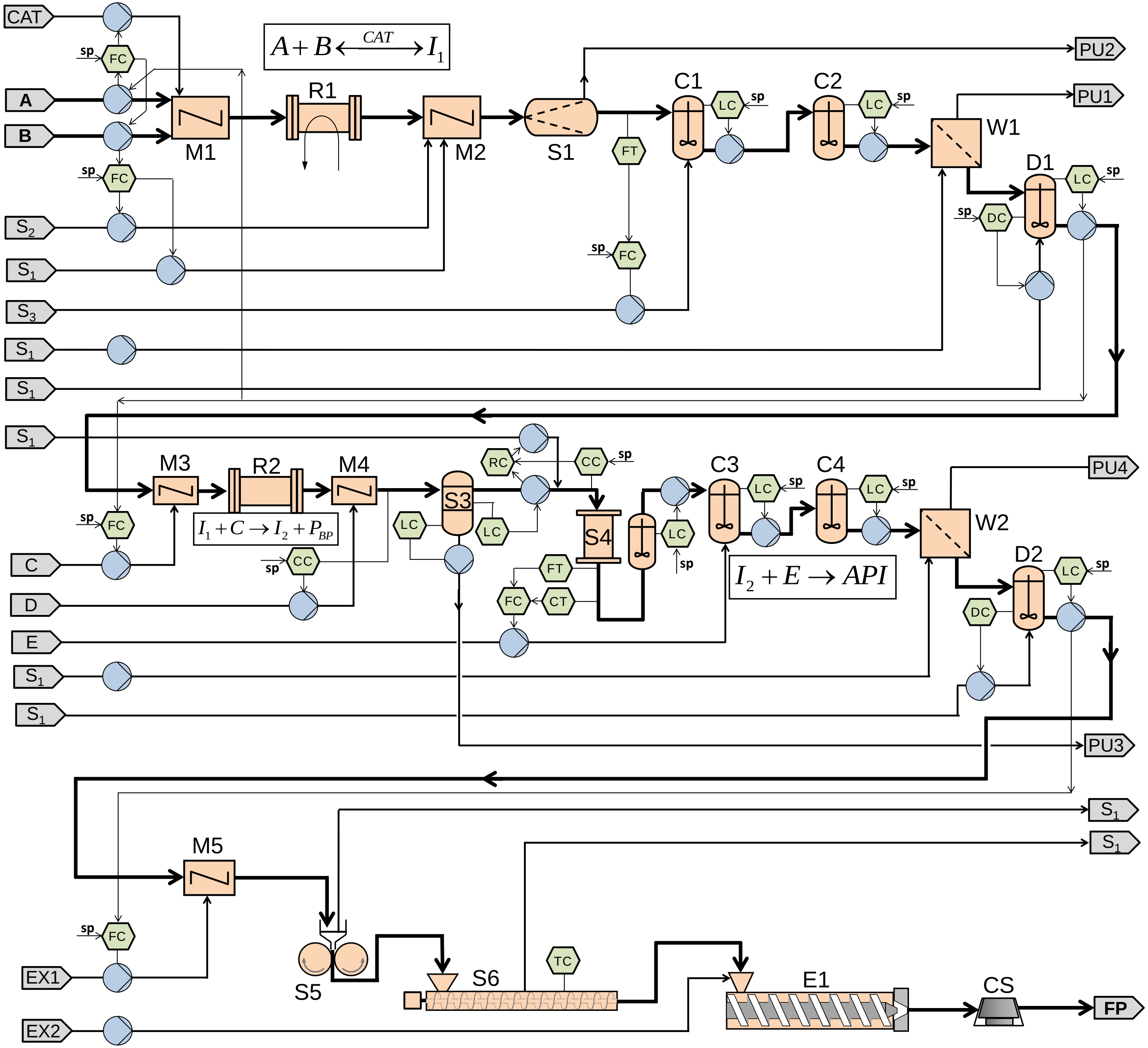
- Approach adapted from the chemical industry
  - Employ systematic and modular design of plantwide control strategies for continuous manufacturing facilities
  - Experimentally demonstrated on continuous pilot plant

R. Lakerveld, B. Benyahia, P.L. Heider, H. Zhang, A. Wolfe, C. Testa, S. Ogden, D.R. Hersey, S. Mascia, J.M.B. Evans, R.D. Braatz, and P.I. Barton. The application of an automated control strategy for an integrated continuous pharmaceutical pilot plant. *Organic Process Research & Development*, 19, 1088-1100, 2015

A continuous pilot plant

S. Mascia, P.L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P.I. Barton, R.D. Braatz, C.L. Cooney, J.M.B. Evans, T.F. Jamison, K.F. Jensen, A.S. Myerson, and B.L. Trout. End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation. *Angewandte Chemie*, 52(47):12359-12363, 2013

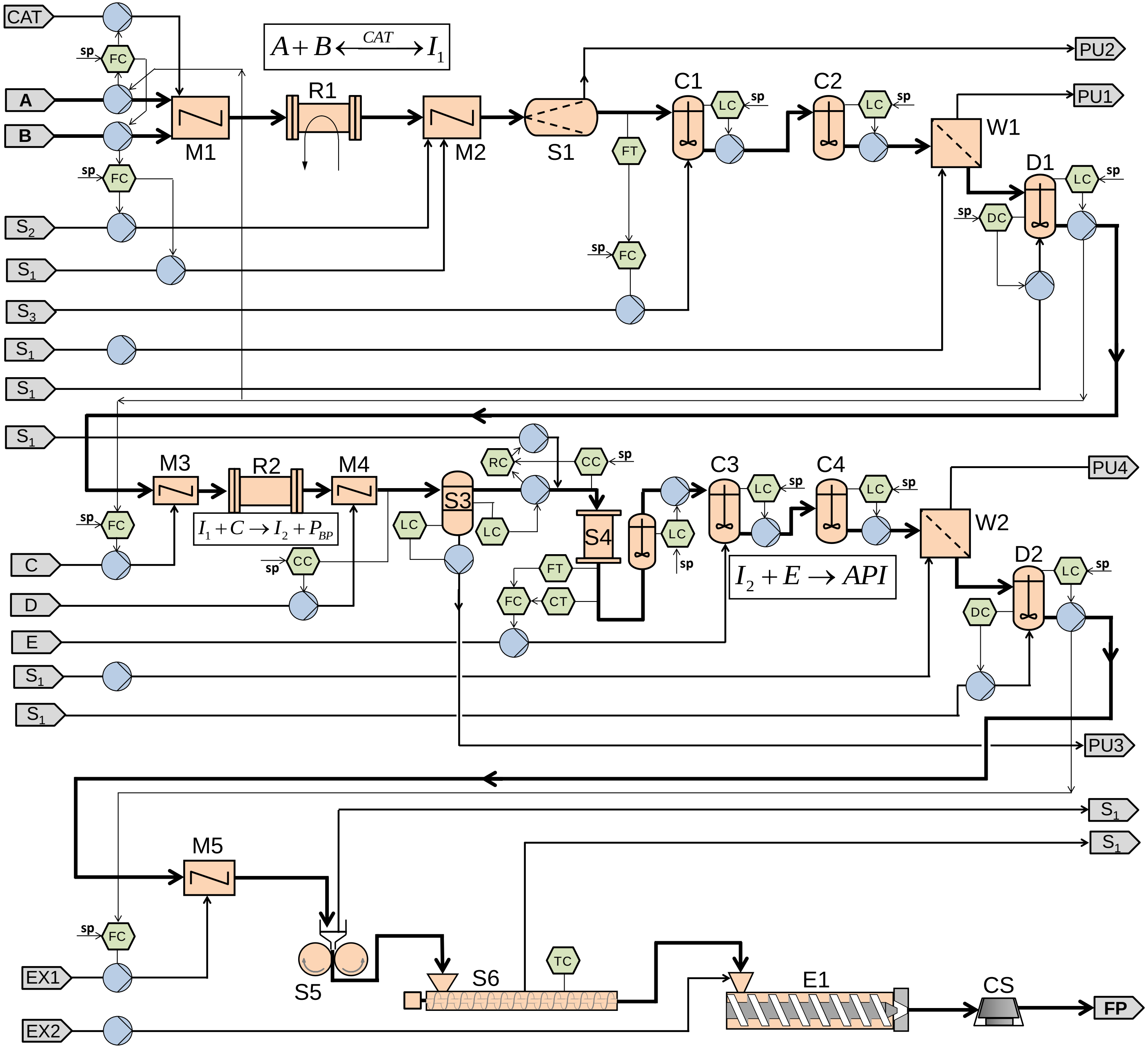
Model-based Plantwide Control



- First-principles dynamic models were built for each unit operation (UO) as they were developed
- Models were validated and then placed into a plant-wide simulation (with uncertainties)
- Plant simulation used to design plantwide control strategy

R. Lakerveld, B. Benyahia, …, R.D. Braatz, and P.I. Barton. *Organic Process Research & Development*, 19, 1088-1100, 2015

Model-based Plantwide Control



Met all purity specs in Summer 2012

S. Mascia, P.L. Heider, H. Zhang, R. Lakerveld, …, A.S. Myerson, and B.L. Trout. *Angewandte Chemie*, 52, 12359-12363, 2013

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Key Control-related Messages (from the May 20–21, 2014 Continuous Manufacturing Symposium)

- The main objective of continuous operations should be on being "in control" rather than being at steady state
- Continuous operations require a plant-wide control strategy that ensures that all CQAs are satisfied
- A monitoring system needs to track material as it moves through the manufacturing facility, using PAT and RTDs
- Systematic approaches are needed to manage constraints, disturbances, nonlinearities, uncertainties, and risk
- Regulatory bodies need to ensure that regulations and regulatory practices promote and do not derail continuous

Allan S. Myerson, Markus Krumme, Moheb Nasr, Hayden Thomas, and Richard D. Braatz. Control Systems Engineering in Continuous Pharmaceutical Manufacturing. *J. Pharm. Sci.*, 104, 832–839, 2015

Special Control-related Technical Needs (from the 2014 CM Symposium)

1) Design of optimal startup and shutdown procedures
2) Design of process monitoring and control systems that collectively provide high quality assurance
3) Control strategies for specific new unit operations
4) Development of systems integration methods that respect the higher quality assurance needed in pharmaceuticals
5) Understanding the integration of design spaces and quality assurance with design of overall plant-wide control strategy
6) Design/tuning of control systems for each unit operation to take into account disturbances, nonlinearities, dynamics, constraints, and uncertainties
7) The quantification of the technical risks of failures or delays that occur anywhere in process development

Suggested strategies for accelerating widespread adoption of process control (from the CM Symposium)

- Generate more graduates with expertise in pharmaceutical process control
  - Federal support for pharmaceutical manufacturing is very low in most countries, and university pharma centers rarely hire control engineers
  - Can industry and regulatory bodies work together with other federal agencies to create funding mechanisms that are competitive with high-money areas like biomedical engineering?

- Speed the correction of misconceptions about continuous pharmaceutical process control/operations, e.g.,
  - Steady state vs. "in control"
  - Artificially defined batches vs. residence time distribution functions
  - Understanding the value of feedback vs. feedforward control

Suggested strategies for accelerating widespread adoption of process control (from the CM Symposium)

- Regulatory bodies have a challenge in training the individuals who directly interact with companies on filings
  - Could financially support the development of high quality training materials in pharmaceutical process control for joint use by students, company employees, and regulatory staff
  - Could enhance training of their technical staff by supporting joint research projects with universities in continuous manufacturing and the associated process control technology
  - Could encourage other federal agencies to support research in pharmaceutical process control

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Suggested strategies for accelerating widespread adoption of process control

- Develop first-principles models and simulation techniques to support robust process design and control*
- Consider developing a modeling toolbox in a collaboration among government agencies, academia, and industry; then make available to stakeholders*
- Develop integrated automated control systems to facilitate straightforward deployment**

* *Promoting Continuous Manufacturing in the Pharmaceutical Sector*, The Brookings Institution, Washington, DC, October 19, 2015, http://www.brookings.edu/~/media/events/2015/10/19-continuous-manufacturing-pharmaceutical-sector/meetingsummary_101915_continuousmanufacturing.pdf

** Z.K. Nagy and R.D. Braatz. Advances and new directions in crystallization control. *Annu. Rev. Chem. Biomol. Eng.*, 3, 55–75, 2012

Extra slide

Approach takes into account the four strategies for ensuring that a particular CQA spec is satisfied

1. Direct measurement of the CQA
2. Prediction of the CQA based on a first-principles model that is fed measurements of related variables and is running in parallel with operations
3. Prediction of the CQA based on an empirical or semi-empirical model (e.g., response surface map, PLS model) that is fed measurements of other variables

(1–3: Can use in closed-loop feedback control strategy)

4. Operation of the CPPs to lie within a design space, that is, some specified set shown in offline studies to provide assurance

(4: Open-loop strategy)

The smaller the number, the higher the quality assurance