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Control Systems Engineering in Continuous Pharmaceutical Manufacturing

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Paper Outline/Sections

1. Introduction to Continuous Manufacturing & Control Systems
2. Current State and Needs
   - 2.1 Steady-state and Dynamics in Continuous Manufacturing
   - 2.2 Process Monitoring and Control
   - 2.3 Systems Integration
   - 2.4 Disturbances, Nonlinearities, Constraints, Uncertainties, & Risk
3. Challenges
   - 3.1 What Can Universities Do?
   - 3.2 What Can Industry Do?
   - 3.3 What Can Regulatory Bodies Do?
4. How to Meet the Challenges, Including Future Technologies

Key Messages

- 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, & risk
- Universities should consider developing an open-source standardized software for systems and control
- Universities & industries should jointly invent new processes
- Regulatory bodies need to ensure that regulations and regulatory practices promote and do not derail continuous

Key Messages: Specific Technical Needs

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 an 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

Questions/Points for Discussion

- How can universities have more faculty and graduates with expertise in pharmaceutical process control engineering?
  - 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?
- Control vendors use proprietary codes that slow the transfer of systems and control solutions from universities to companies, between universities, and between companies
  - Can or should companies band together to force control vendors to create open-source standardized software for systems and control?
  - Should universities be the place to develop such software?
  - Can the success of linux and other open-source software be copied?

Questions/Points for Discussion

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

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