Eighth Annual

THE BIOPROCESSING SUMMIT

Practical Solutions for Today's Bioprocess Challenges

August 15-19, 2016 | Westin Boston Waterfront , Boston, MA

SPEAKER Q&A SERIES

Cambridge Healthtech Institute's Kent Simmons recently spoke with Richard D. Braatz about his upcoming presentation "Plant-Wide Process Control Model for Biological Manufacturing," to be held August 19 in Boston as part of the Process Characterization, Qualification and Control conference at the 8th Annual Bioprocessing Summit.

Q: Define a "plant-wide" strategy for the control of critical quality attributes.

The attributes of any material produced by a manufacturing unit operation is affected by variations in feed compositions and operations. As the material from one unit operation is fed into the next unit operation and so forth through a manufacturing plant, the variations in material attributes are coupled in their effects on the critical quality attributes (CQAs) of the final drug product. A plant-wide strategy systematically takes all of the unit operations and their interconnections into account when designing the control systems to ensure that all of the product CQA specifications are satisfied.

Q: What approaches are used to ensure that all of the CQA specifications are met?

For each CQA, the four approaches to consider for its control are: (1) direct measurement of the CQA, (2) prediction of the CQA based on a mechanistic 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 semiempirical model (e.g., response surface map, chemometrics model) that is fed measurements of other variables, and (4) operation of the related variables known as critical process parameters (CPPs) to lie within a design space, that is, some specified set shown in offline studies to provide quality assurance. While at least one approach is needed for each CQA, employing multiple approaches can provide further quality assurance.

Q: What was the first implementation of plant-wide modeling and control to a continuous manufacturing plant?

The Novartis-MIT Center for Continuous Manufacturing completed the design and implementation of the first end-to-end integrated continuous manufacturing plant for a pharmaceutical product in 2012. The plant started from a chemical intermediate and performed all of the intermediate reactions, separations, crystallization, drying, and formulation to form final tablets in one tightly controlled process. A mathematical model of the entire plant was used to design the control systems to ensure that the critical quality attributes were satisfied.

Q: How does plant-wide modeling and control differ from small-molecule to biologic drug manufacturing?

Although the details of the unit operations are different, the overall strategy is the same. First mathematical models that include process dynamics, disturbances, and uncertainty estimates are constructed and validated for each unit operation. Mechanistic models are preferred although sometimes (semi)empirical models are required. The second step is to apply the models to design and verify the control systems for each unit operation to satisfy local material attributes. The third step is to combine the models into a process simulation platform to create a plant-wide model for the entire manufacturing chain. Then sensitivity analysis is applied in the virtual plant simulations to design and evaluate the effectiveness of the plantwide control system in meeting the product CQA specifications.

Richard D. Braatz is the Edwin R. Gilliland Professor of Chemical Engineering at MIT. His expertise is in process systems and control (BS 1984, Oregon State University; MS 1991 and PhD 1993, California Institute of Technology). After a postdoc at DuPont, a faculty position at the University of Illinois at Urbana-Champaign, and a Visiting Scholar position at Harvard University, he joined the faculty at MIT where he does research in (bio)pharmaceutical manufacturing. He leads the Quality-by-Design and control systems activities in the Novartis-MIT Center for Continuous Manufacturing and in the development of the Integrated and Scalable Cyto-technology (InSCyT) Platform for Biopharmaceutical Manufacturing on Demand. He has consulted or collaborated with more than 20 companies including Novartis, Pfizer, Merck, Bristol-Myers Squibb, Biogen, and Abbott Laboratories. His pharmaceuticals research has been recognized by the AIChE PD2M Award for Outstanding Contribution to QbD for Drug Substance, the ISA Technical Innovation Award, IEEE Control Systems Society Transition to Practice Award, and the AIChE Excellence in Process Development Research Award.