November 2015

The PD2M Pipeline

Note from the Editor

Shekhar Viswanath

The fall edition of the newsletter focuses on providing a summary of sessions of interest to the AIChE PD2M member. The PD2M forum features 29 sessions from Monday through Friday morning, in addition to the plenary session on Monday morning, an awards session on Monday evening and a poster session on Wednesday evening. The awards session on Monday evening will feature awards for outstanding research in Drug Substance, Drug Product, an Integrated Drug Substance-Drug Product research award, and for the first time, a student award. The PD2M awards committee is happy to announce Dan Hallow (J&J) and Jim Litster (Purdue) as the recipients of PD2M Drug Substance and Drug Product awards respectively. Lastly, PD2M members interested in contributing to PD2M programming content should look to attend the Tuesday programming meeting at noon.

Daniel Hallow

James Litster

Save the date for FDA AIChE Workshop on Adopting Continuous Manufacturing Feb. 29 , to March 2, 2016.

Find us at: http://www.aiche.org/community/sites/divisions-forums/pharmaceutical-discovery-development-and-manufacturing-forum-pd2m/newsletters

Modeling and Simulation

Joe Hannon

From the DynoChem team at Scale-up Systems. In this edition, we highlight application of the scientific method in a preview of the AIChE 2015 Annual Meeting.

Trial and error is not the only way

In the previous edition we took aim at the potential wasted effort of using statistical DOE for development and optimization of drug substance unit operations and the risks that creates for process scale-up. In this edition, we promised to outline a better way. The AIChE Annual meeting always provides several relevant illustrations of a better way to work, that embodies the scientific method, in which fundamental process models are used to produce testable predictions.

AIChE has a good track record

For one fine historical example, BMS (Steven H. Chan, Steve S. Y. Wang, and San Kiang) showed at AIChE 2005 how to design a continuous process using two well executed experiments in batch mode:

Heat Profiles for 30 Minute Dose

$T_{setpoint} = 5°C$ $T_{setpoint} = 15°C$
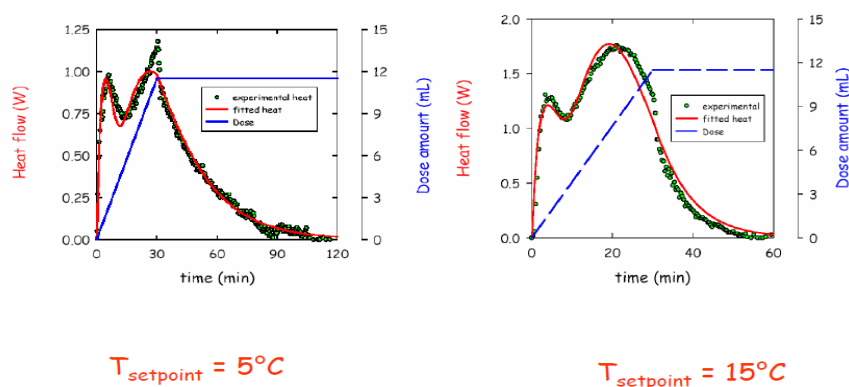
Conclusions

- It is important to perform a thorough hazard evaluation in order to investigate the safety boundaries of a process.
- Designing experiments in conjunction with modeling are important in order to elucidate the kinetics and thermodynamics of the reaction.
- Reactor modeling with experimentally measured kinetics and thermodynamics parameters should be used to assess potential scale-up hazards.
- Scale-up of hazardous chemistry continues to be an engineering challenge but kinetics and predictive modeling can help.

Two other excellent AIChE presentations in this vein were given by Dan Hallow then (2008) at BMS and now at J&J and Jeremy Merritt from Lilly (2011). Congratulations to Dan who is the 2015 recipient of the AIChE Award for Excellence in QbD for Drug Substance, based in part on the work presented at AIChE.

Back to the Future – AIChE 2015

If you're travelling to AIChE 2015, try to make some of the following talks that continue in this vein:

Time and Location	Title and Link	Notes
Monday, November 9, 2015: 1:48 PM Ballroom B (Salt Palace Convention Center)	Model-Based Risk Mitigation Strategy for Late Stage Development of a Drug Substance Manufacturing Process	A framework for putting predictive modeling into practise in a project with many unit operations and potential risks.
Monday, November 9, 2015: 4:12 PM Ballroom D (Salt Palace Convention Center)	GSK Design Space Verification Lab Pilot Project	Design and construction of lab facilities to enable development of scalable design spaces
Tuesday, November 10, 2015: 4:00 PM 155D (Salt Palace Convention Center)	Kinetic Modeling and Scaleup Assessment of Seeded Solvent Mediated Form Conversion	Mathematical modeling of form conversion.
Wednesday, November 11, 2015: 4:55 PM Ballroom D (Salt Palace Convention Center)	Development and Demonstration of a Suite of Tools Aimed at Process Development Intensification and Efficient Experimentation Practices	Intelligent usage of lab automation tools to design better experiments.
Thursday, November 12, 2015: 8:50 AM Ballroom B (Salt Palace Convention Center)	Modeling of Drug Substance Manufacturing in a Multi-Purpose Plant	Techniques for scale-up prediction based on lab scale experiments and simulation.
Friday, November 13, 2015: 8:30 AM Ballroom B (Salt Palace Convention Center)	Can R&D be Standardized? Implementation of a Recipe Framework Supporting Lab to Patient Execution and Analytics	Visionary thinking on leveraging data consistently from all scales of operation to improve performance.

The next challenges – previewed at AIChE 2015

A couple of forward-looking talks in the modelling and simulation field this year also caught our eye.

Time and Location	Title and Link	Notes
Monday, November 9, 2015: 4:50 PM 155D (Salt Palace Convention Center)	Unsolved Problems in Crystal Growth: Challenges for the Future	Solution effects on growth may soon be understood, whereas understanding polar crystal growth remains some way off.
Tuesday, November 10, 2015: 5:00 PM 155B (Salt Palace Convention Center)	Building "Body-on-a-Chip" Systems for Drug Development	It's a different type of modeling but nonetheless interesting and potentially valuable for everyone.
Tuesday, November 10, 2015: 8:30 AM Ballroom A/C (Salt Palace Convention Center)	Validation of Models and Procedures in Chemical Engineering	Sounds like some useful pointers towards consistent use of terminology and model testing.
Friday, November 13, 2015: 9:20 AM Ballroom D (Salt Palace Convention Center)	Molecular Modeling to Design and Control (M2DC): A First Principles Approach to Polymorph Prediction and Crystallization Unit Design	Outline of tools that could make solid form more predictable and controllable.

Continuous Processing Highlights

Shekhar Viswanath

There are 4 sessions dedicated to continuous processing at AIChE this year, 2 each in drug substance and drug product, on Tuesday and Wednesday.

Utilizing continuous drug substance reaction systems, reactions involving high energy intermediates can be processed (267b & 328b), and impurity control can be achieved (267c). There is an active research element on the design of flow reactor equipment to handle 3-phase reactions for small volume production (267d), and the design of fouling-free continuous crystallizers (328a). The industry is also developing fully continuous processes (267e) for potent molecules with continuous filtration, washing and dissolve-off deployed to minimize handling. The industry is moving rapidly towards process validation of continuous processes (328c) and articulating the control strategy for continuous processes (328d) while academia is focused on the next appropriate questions of integrating feedback and feedforward process control with control strategy (328e), and plant-wide process simulation (328g)

In continuous drug product processing, a regulatory perspective on the control strategy of continuous processes can be heard (509a). Continuous hot melt extrusion to deliver amorphous dispersions and the best practices to achieve robust manufacturing outcomes will be discussed (509b, 572e & 572f). A rational solution to the ever-ensuing debate between utilizing process data and/or PAT data to ensure a state of acceptable control in a continuous drug product process is discussed (509c). The same question is solved utilizing a non-linear steady state data reconciliation model (509d) for a continuous granulation process. Details of a new continuous tablet coating equipment are shared (509f). The ability to integrate and visualize the process data and PAT layers with adequate system security is the subject of another talk (509g).

Regulatory and Manufacturing

John Lepore, Kevin Seibert, Tim Watson

The PD2M Forum again this year has an exciting blend of industrial, academic and government speakers to round out what should be an interesting week of presentations in Salt Lake City. Several notable presentations with have a focus on regulatory aspects of process development and late phase optimization as well submission strategies.

The Plenary lectures on Monday, November 9th (50) exemplify this mix with presentations from Pfizer and their application of 3-stage validation for content uniformity based on recent guidance withdrawal and emphasis on the existing USP<905> for marketed products rather than release testing, a presentation from the FDA's Office of Process and Facilities, discussing the re-organization of the quality function and the impact to process review and facility inspections, and finally a presentation from Lilly on the Systems Based Pharma initiative with an emphasis on opportunities for academics.

On Monday afternoon, the Application of QbD in Drug Substance Process Development highlights several important regulatory topics including the incorporation of models into control strategy development from GSK, and two talks from Lilly, highlighting strategies for developing and sharing model output in regulatory filings (119).

Continuing the QbD theme on Monday, several presentations (183, 223) will be devoted to regulatory concepts. QbD and drug product development includes topics from the FDA's perspective on QbD and how the pharma industry can continue to benefit from the initiative, as well as talks from BMS on predicting process capability from a roller compaction process and API properties and the impact to a HSWG formulation, and design space mapping and optimization with DOE from Lilly. This session is rounded out with a presentation on a regulatory perspective of a dry powder inhalation capsule's control strategy.

Of course, Monday of AIChE would not be complete without the PD2M Forum Awards Ceremony (258).

On Tuesday and Wednesday several sessions are devoted to continuous manufacturing (267, 328), with several notable presentations touching on regulatory initiatives. On Tuesday a presentation from APC and UCD in Dublin will be focusing on case studies and the technical and regulatory challenges associated with continuous processing. Wednesday's continuous manufacturing sessions open with a presentation from the FDA and the regulatory implications of running a process in a continuous fashion, and continues with several exciting presentations covering topics ranging from process control, CQA selection, control strategy development and PAT data management (509, 605).

To end the week, several sessions will have presentations with potential regulatory implications, including several focused on the integrating of modeling, process development, and optimization into the development of a process control strategy,(652, 661). Overall it looks to be an exciting week with many opportunities to engage in some stimulating discussions with industry, academia, and regulatory authorities on a variety of topics.

Looking forward, AIChE and FDA will be co-sponsoring a workshop: Adopting Continuous Manufacturing: Overcoming the Perceived Obstacles, on February 29 to March 2, 2016 in Bethesda, Maryland. This will present many opportunities for industry, academia, and regulators to engage and help drive appropriate use of continuous processing forward.

Look to an upcoming issue for a progress update on the ICH Q11 Q&A document.

We look forward to seeing you in Salt Lake.

Discovery

Jeff Varner

Despite early promise and many example models in the literature, computational systems biology has yet to fundamentally impact the development of new therapies for cancer, cardiovascular diseases, or the treatment of acute events like thrombosis during surgery (1). Biological model uncertainty, reticence on the part of biologists to embrace mathematical modeling, and perhaps most significantly lack of understanding of the biological processes at play in complex disease such as cancer have all been cited as issues restraining progress (2-3). However, as the field of systems biology and biological network modeling matures, new developments in how we model biology, as well as our ability to experimentally interrogate disease systems, could allow us to make good on the earlier promises of systems biology.

Simulating complex diseases such as cancer requires much more than isolated models of gene expression or signal transduction and metabolic processes. Rather, it requires holistic multiscale approaches which integrate molecular networks with changing environmental cues (4). Unfortunately, such holistic approaches quickly become infeasible. Thus, one of the most promising recent developments has been the reemergence of effective or logical models of biological networks. Small yet predictive network models could be integrated with multiscale tools to give more predictive multiscale simulations. Gene expression models based upon boolean logic have been prevalent in the developmental biology community for nearly twenty years (5). Boolean logic has also effectively captured metabolic regulation in constraints based metabolic models (6). Other promising approaches to limit model complexity such as data-driven systems approaches (7,8) or logical model formulations such as contained fuzzy logic (9,10) are also emerging paradigms that constrain model complexity by data availability. Another promising approach is the use of model ensembles. Sethna and coworkers showed that complex model behavior is often controlled by only a few parameter combinations, a characteristic seemingly universal to multi-parameter models referred to as sloppiness (11). Thus, reasonable model predictions are often possible with only limited parameter information using potentially uncertain models. Model ensembles have been interrogated using tools such as sensitivity or robustness analysis (12,13) to estimate fragile or robust network components that also reflect cell-to-cell (14,15) or even patient-to-patient heterogeneity (16).

The rapid advancement of experimental and computational techniques are closing the gap between the promise and reality of computational systems biology. Next generation sequencing technologies have enabled an unprecedented view of the genetic basis of many cancers including pancreatic, and breast cancers (17,18). RNA-sequencing (RNA-seq) methods are also greatly expanding our knowledge of the dynamic nature of the transcriptome, including the regulatory role of small RNAs (19). High-throughput upgrades to traditional biochemical methods, such as micro-western arrays, have enabled the quantitative assessment of protein abundance and modifications for tens or perhaps even hundreds of proteins in the future (20). At the metabolite level, new *in-situ* Forster Resonance Energy Transfer (FRET)-based sensor technologies are changing the way we interrogate cellular metabolism, and especially our knowledge of critical metabolites such as Lactate (21). These techniques when combined with traditional approaches borrowed from metabolic engineering such as flux balance analysis (22), are enabling the analysis of cancer metabolism at an unprecedented scale (23). Taken together, advancements in experimental measurement technologies will be critical to our understanding of the origins of complex diseases like cancer, and to our ability to construct and validate better mathematical models.

Consortia Update: Precompetitive Collaboration Continued

Steve Baric

As many AIChE PD2M members know, there is a growing development across pharmaceutical companies around the establishment of precompetitive collaborations on technologies for process development.

And as avid readers of the *PD2M Pipeline* are no doubt aware, there are a number of organization giving momentum to this development including the Innovation & Quality (IQ) Consortium, a pharmaceutical and biotechnology association which aims to advance innovation and quality in the biopharmaceutical industry; the Allotrope Foundation, an international association of pharmaceutical and biotech companies dedicated to the building of a "Laboratory Framework" to improve efficiency in data acquisition, archiving, and management; CMAC (Continuous Manufacturing and Crystallization), part of the Technology and Innovation Centre at the University of Strathclyde, with a vision to accelerate the adoption of continuous manufacturing and crystallization processes, systems and plants for the production of high-value chemical products; CPAC – Center for Process Analysis & Control, established at the University of Washington, a consortium of industrial, national laboratory and government agency sponsors addressing multidisciplinary challenges in PAT and process control through fundamental and directed academic research; and, last but by no means least, SSPC – The Synthesis and Solid State Pharmaceutical Centre, a unique collaboration between industry partners, research performing organizations and international academic collaborators that aims to deliver relevant solutions that ad-

dress the manufacturing needs of the pharmaceutical industry and in-turn lead next generation drug manufacture.

We are lucky to have again at this year's AIChE Annual Meeting a session within the PD2M Forum dedicated to the discussion of these types of collaborations, with presentation by some of the key organizations driving this important initiative.

The session, "*Pre-Competitive Collaborations in the Pharma Industry: Perspective and Opportunities*" (228), Chaired by Jean Tom (BMS) and Peter Clark (Scale Up Systems) is being held in Ballroom D at the Salt Palace Convention Center on Monday, November 9th and runs from 3:15 to 5:45. Mark your calendars!

Building on the success of last year's session, the program features presentations and a panel discussion about opportunities and success stories involving pre-competitive collaboration in the pharmaceutical industry.

(228a) IQ Consortium Enabling Technologies for Pharma

Jean W. Tom, Srinivas Tummala and Margaret Faul

(228b) Precompetitive Collaboration for Pharmaceutical Crystallization Processing

Aaron Cote

(228c) Allotrope Foundation: Collaborating to Deliver an Innovative Framework for Laboratory Data Based on Open Standards

James M. Vergis

(228d) GSK Design Space Verification Lab Pilot Project

Robert E. Yule

> *This presentation describes the implementation of a Design Space Verification (DSV) lab for GSK drug substance process development and the key learning outcomes. The DSV Lab is a pilot-scale project to develop and deploy reaction and crystallization platforms at lab and intermediate scale that enable faster, more efficient scale-up verification. GSK aims at sharing the progresses made with respect to scale-up verifications and lab informatics amongst pharmaceutical manufacturers and regulators. The DSV project is expected to further the discussions related to data standards (S88) and open data formats, as proposed by Allotrope (see 228c, above).*

(228e) Challenges for Academic and Industrial Partners in Major Research Collaborations - a Case Study

Brian Glennon

(228f) Erc-Sops - a Pre-Competitive Model for Strategically-Driven Research and Technology Development and Commercialization

Fernando J. Muzzio, M. Sebastian Escotet-Espinoza, Zilong Wang and Marianthi Ierapetritou

(228g) The Role of Ncats, SBIR to Support Precompetitive Collaboration

Asaf Alimardanov

Speaking for the entire PD2M community, we look forward to see you at this important session and encourage you to actively participate in the talks, the panel discussion and the follow-up actions to drive this initiative forward.

American Institute of Chemical Engineers

Pharmaceutical Discovery, Development, and Manufacturing Forum (PD2M)

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