Issue 1, 2018
Friday March 16, 2018

PD2M Newsletter

A quarterly update for the Pharmaceutical Discovery, Development and Manufacturing Forum Members

Note from the chair

John Lepore
Pharmaceutical Discovery, Development and Manufacturing Forum, Chair
QbD and CMC Practices Lead, Merck & Company, Inc.

Happy 2018 to all PD2M Members, and welcome to the relaunched PD2M Newsletter! Restarting the newsletter is one component of a multifocal effort to extend and deepen our interactions with our membership, both current and prospective. With the relaunch, I would like to thank our new newsletter chair, Carla Luciani from Eli Lilly for taking on the responsibility of making this newsletter a reality.

Over the course of the year, we will feature a variety of technical, regulatory, and organizational information that we hope the membership will find of interest. If there are specific topics that you would like to see in the newsletter, feel free to drop us a line to john_lepore@merck.com. Looking forward to hearing from you!

Note from the editor

Carla V. Luciani
Pharmaceutical Discovery, Development and Manufacturing Forum, Newsletter Chair
Future Manufacturing Platforms Leader, Assoc. Engineer Advisor, Eli Lilly & Co.

Dear PD2M members,

We are very excited to relaunch the PD2M Newsletter. With each issue, we will strive to share useful information for PD2M members as well as highlight technical contributions and perspective articles of interest for the PD2M community. If you have suggestions, ideas, or want to contribute with a short article, please contact me.

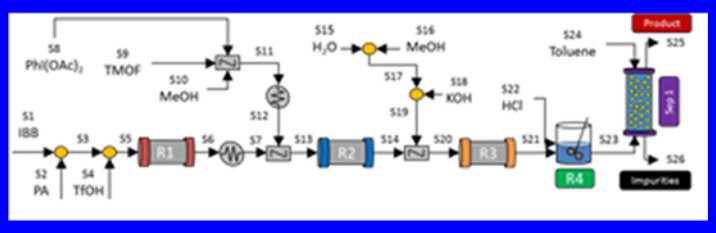
Special thanks to the members who graciously accepted our invitation to share technical contributions and perspectives for this first issue:

- *Thomas O, Connor*, US Food and Drug Administration
- *Jacob Albrecht*, Bristol-Myers Squibb
- *Paul Collins*, Eli Lilly & Co.

Do not miss the organizational updates provided by:

- *Jonathan McMullen*, Programming Chair 2018

PD2M Newsletter issues will be released quarterly. Enjoy the first issue!



Process flow diagram of flow synthesis of ibuprofen.

Abstract

A process model for the continuous manufacturing of ibuprofen was developed as a case study for applying modeling to support the risk assessment of continuous drug substances processes. The process model was used to identify the process parameters with the largest impact on conversion and to evaluate various process control approaches. The project advances the Agency's capability to assess mechanistic modeling studies of flow reactors submitted to the Agency.

Disclaimer: This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies

Acknowledgments

The author would like to thank Nima YazdanPanah, Ph.D. ORISE Fellow U.S. Food and Drug Administration.

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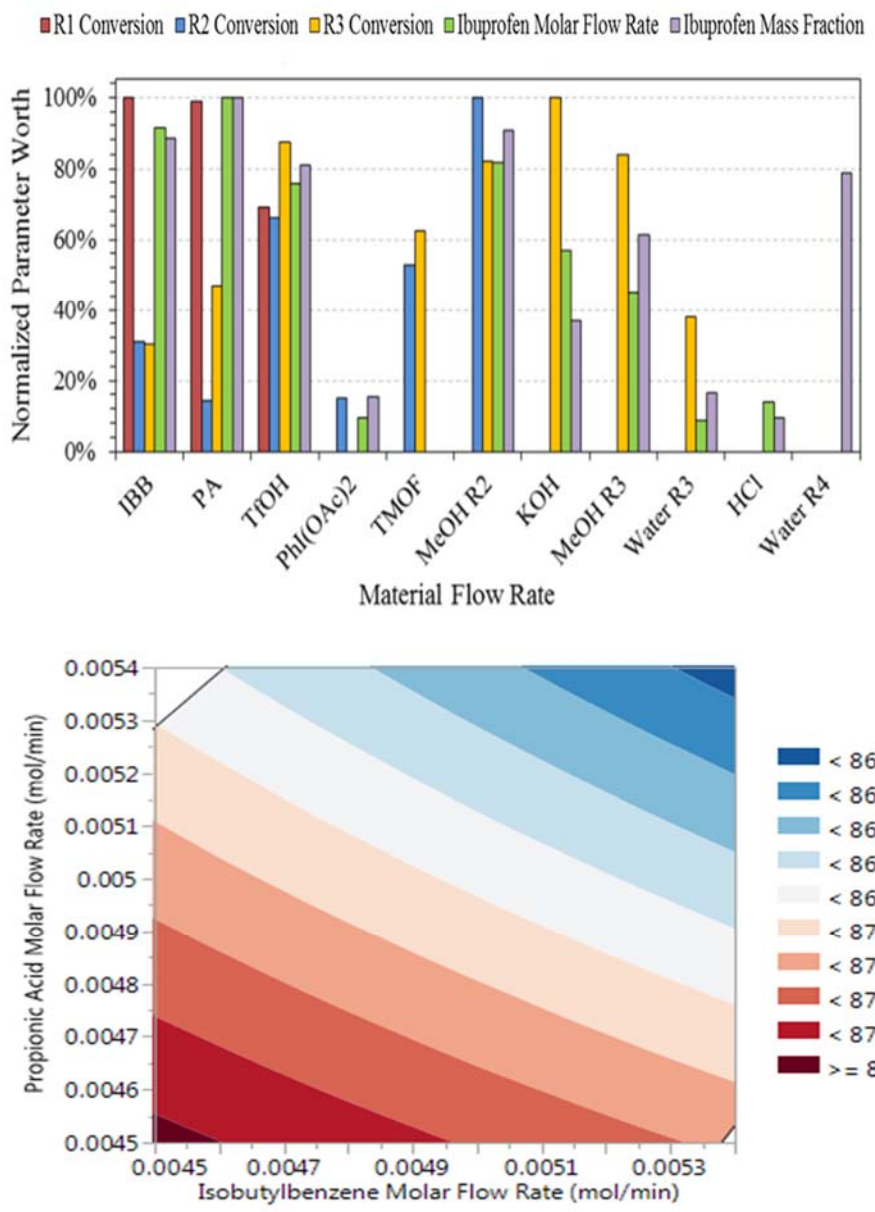
Advancing Process Modeling to Support Quality Risk Assessment for Continuous API Manufacturing

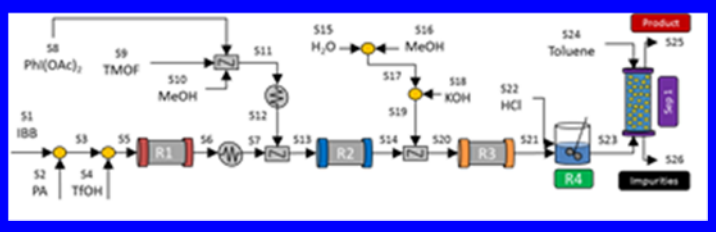
Thomas O'Connor, Ph.D.
Senior Chemical Engineer
U.S. Food and Drug Administration

Through CDER's Emerging Technologies Team (ETT), the FDA has encountered several implementations of continuous drug substance manufacturing. The proposed control strategy approach for these processes is a frequent area of discussion between ETT and the sponsor. As part of justification for elements of the control strategy, sponsors have utilized and submitted data from process models. To support feedback from the ETT, FDA has several ongoing research initiatives on advancing the utilization of process modeling for continuous manufacturing.

As a case study for applying modeling to support the risk assessment of continuous drug substances processes, a flowsheet model for the continuous manufacturing of ibuprofen was developed. The reported telescoped continuous flow synthesis of ibuprofen uses three major reaction steps: Friedel-Crafts acylation, 1,2 aryl migration, and saponification. Literature data was used to develop and validate the process model. The model predicted conversion and ibuprofen mass flow rate at the exit of the process are 65.5% and 512 mg/hr respectively, which is comparable to the experimentally measured values of 68% conversion and a mass flow rate of 534 mg/hr. A Latin Hypercube steady-state simulation design varying the 14 molar flow rates in the process identified that the flow rates of isobutyl benzene (IBB) and propionic acid (PA), the inputs to the first reactor, have the largest impact on reactor conversions and product flow rate. A dynamic model was then developed to simulate the impact of disturbances to the IBB flow rate and to estimate the residence time distribution of the system. To achieve an ibuprofen with uniform quality, the concentration of all the reagents and intermediate components should be regulated in such a way that their stoichiometry remains constant. For this aim, a multi-loop multi-cascade controller was implemented and tuned as part of the dynamic model. Article content here.



Top: Analysis of process flow rate impact of 5 major process outputs. Bottom: Contour plots showing the effect of varying IBB and PA molar flow rates on reactor conversions and Ibuprofen production.



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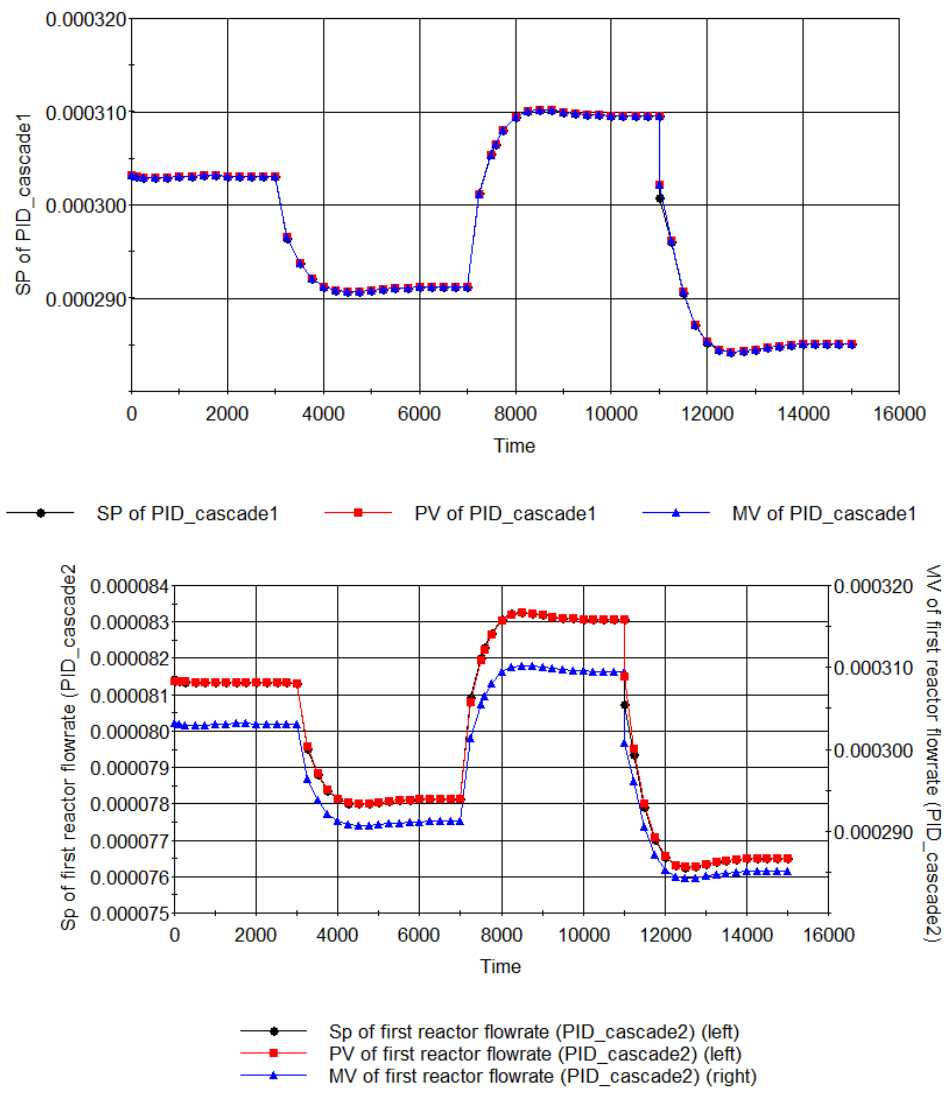

Performance of the PID controllers including the setpoint, process variable, and manipulated variable, as a function of time.

The project demonstrates how process models can be used to support quality risk assessment and advances the Agency's capability to assess mechanistic modeling studies submitted to the Agency. The process and simulation approaches progressed in this project will next be paired with flow chemistry experiments to examine the impact of process parameters on the formation of key impurities in addition to conversion. In addition, a next step that stretches across multiple research initiatives at the FDA is working with various stakeholders on development and application of risk-informed credibility assessment framework for process modeling that takes into account specific role and scope of the model in addressing the question of interest and the impact on final product quality.
For questions related to this project, you can contact me at thomas.oconnor@fda.hhs.gov.

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Abstract

PD2M engineers are making better decisions faster thanks to the explosive growth in enabling technologies for data mining, analysis, and modeling.

PDM2: Pharmaceutical Data Mining and Modeling Yields Benefits

Jacob Albrecht

Pharmaceutical Discovery, Development and Manufacturing Forum, Treasurer

Chemical & Synthetic Development Technologies Group, Bristol-Myers Squibb

e-mail: jacob.albrecht@bms.com

In pharmaceutical process development, common challenges arise again and again for different programs as they advance. With the benefit of experience, engineers can better anticipate and solve these issues before they become costly. But how can researchers best extract the vast historical experience that is often contained in internal records?

At the 2017 AIChE Annual meeting, I had the privilege to present the work done with Jun Qiu at BMS to aggregate and mine our internal solubility screening data at my presentation titled “Solubility Data Mining and Predictive Modeling: AI+ChE”. Solubility data is important for developing reaction and crystallization processes, but experimental measurements are difficult for early-phase programs. Our solubility data set was collected as part of an automated solubility screening workflow spanning a decade, and contained measurements for over 700 small molecule compounds each in dozens of different solvents and solvent mixtures. In all, nearly 65,000 data points were collected and analyzed. The analysis of such a data set allowed us to rapidly test hypotheses related to solvent selection, such as correlations and synergies between solvent pairs and temperature effects. But we were interested in extracting even more value from the data, using modern data science tools.

Access to the raw data, combined with recent advances in data-oriented programming languages and cloud computing capabilities allowed us to perform analyses such as unsupervised clustering and predictive modeling. The clustering confirmed that the solvents coalesced into groups familiar to any expert (aliphatic, polar aprotic, alcohol, water, etc.), but with some surprises (e.g. MIBK behaves most like an acetate). A structure-property model was also developed from the data and then deployed as an internal web application to allow any researcher to rapidly estimate solubility by providing a solute’s molecular structure. An example of a step-by-step workflow to create a predictive model for solubility measurements is available here. This story from BMS is just one example of how historical data can be leveraged to aid pharmaceutical development. As the barriers to data mining and analysis continue to drop, expect to learn more about exciting developments in this area.

Coming up at the 2018 AIChE Annual meeting, Shekhar Viswanath from Lilly and I have proposed a session titled “Data Analytics in Pharmaceutical Discovery, Development, and Manufacturing”. Our vision is that the session will serve as a forum to share the many proven and emerging ways that data analysis, from data visualization to Artificial Intelligence, can benefit pharmaceutical development. We hope that you can join us!

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Top 10 Career Derailers for Engineers in Pharma

Paul C. Collins
Pharmaceutical Discovery, Development and Manufacturing Forum, Past Chair
Sr. Director, Small Molecule Design and Development, Eli Lilly & Co.

Abstract

Dr. Paul Collins, AIChE Fellow and Sr. Director at Small Molecule Design and Development- Eli Lilly & Co., was the 2017 recipient of the Industry leadership award. Paul received this award for his successes and leadership in AIChE and in the pharmaceuticals industry, including initiatives that have enabled continuous manufacturing, developed scientists, and driven pharma success at AIChE

PD2M Newsletter asked him to share his experience with career derailers for engineers in pharma. Enjoy Paul's blog!

So our newsletter editor asked me if I could write a blog on "Top 10 Career Derailers for Engineers in Pharma." I don't know that I'll come up with 10 derailers, but I do have some thoughts on things you shouldn't do. Most of them come from personal observation over the years.

(1) Choosing the wrong department – you need to be somewhere with good balance of abilities and people that can help you in your career. I have seen people that choose jobs based on location alone, or salary alone. That's a choice that might work in the immediate short term. But, eventually it will limit or derail you. You need to find a place that fits your personality and career interests. Companies, and departments within companies, have their own distinct personality and culture. You can usually figure that out during an interview day. People will volunteer all kinds of information to you about their department. Pay attention to what you are hearing and to whether or not something seems "off" to you. Pick a place that seems consistent with you as a person. This can apply to new or experienced people, obviously.

(2) Don't let yourself be insulated – Pharma is a business that has the potential to be isolated. There hasn't always been a lot of cross pollination between pharma and other chemical industries. But, there is a lot of commonality between engineering applications across industries. Be external – find out how other engineers do their work and think how you can apply that within pharma.

(3) Related to the insulation category – the regulatory interface makes pharma different than many chemical industries. Don't let yourself be insulated from those groups. There are many conferences and interaction opportunities with groups such as the FDA. You should try to make use of those. Those are great opportunities to learn what those groups want to see from people like you. If you don't know about the regulatory world, you can get off track pretty easily.

(4) Don't be dogmatic – I've met many engineers over the years that believe engineering is supreme in pharmaceutical process development. Ironically, those engineers are the same ones that can't stand the perceived arrogance of organic chemists and other more basic scientists in process development. Many backgrounds can be used in pharmaceutical process development. And should be used. Be open to what all the backgrounds bring to the table. Engineering is about application of science. Apply broadly…

(5) As a subset of dogma – not everything has to be modeled. I know lots of engineers that think everything HAS to be modeled. You know the old saying "you don't really understand your process if you can't model it." Whatever. I like modeling and support it. But it is not the answer to everything, and I'll go out on a limb and say "you really don't understand the overall business if you believe you have to model everything."

(6) Don't worship equipment – that probably sounds odd to you, but I know people that always boil down the solution to a piece of equipment. We USE equipment quite often, but the value is always in the engineering approach. Not the equipment. I actually knew an engineer that would pet a slurry mill like it was a dog and say stuff like "Good Old Urschel has never let us down." Good grief. Don't let yourself get pushed into the equipment corner and defined as the keeper/user of large equipment.

(7) Don't try to flowchart your career - believe it or not, your career is not a flowchart of YES/NO, IF/THEN decisions. I think some people like to pre-plan their moves. But that is limiting to you. A sometimes unpopular fact is that other people will usually have really good career ideas for you. But if you have planned things out on your own, you will miss a lot of really good ideas. Some of the best jobs I ever had were the ones I thought I didn't want. They weren't my idea. They were the ideas of other people. But, you know, they were really good roles. I'm glad I did what they suggested.

(8) Failing to recognize the future – this isn't exclusive to engineers, but is relevant to us just as it is to everyone in pharma. There tends to be a belief that the world in which we live never needs to change. As an example, the long-standing batch infrastructure in pharma is an outgrowth of this phenomenon. But, I think the reality is that there is always change expected. Sometimes it is acute and short term – and we recognize that. Sometimes change is slow and the "apparent" rate constant looks like zero. That's an illusion. Don't get stagnant in your career. It's possible that you can go 10+ years without big changes in the field, but that won't buy you a career. Eventually you will have to change in some way. Be ready. Look for trends and look for things regulatory agencies keep asking for over time. I'm willing to bet that you will find predictors of the future in those things.

OK. I only came up with 8. I'm sure you can think of your own set of derailers and I'd be interested in hearing those from you sometime!

Reminders

2018 AIChE Annual Meeting, Pittsburgh Oct 18 to Nov 2
Call for abstracts is open until April 18, 2018 (link)

Visit the PD2M Website

https://www.aiche.org/community/sites/divisions-forums/pharmaceutical-discovery-development-and-manufacturing-forum-pd2m

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Programming Update

Jon McMullen
Pharmaceutical Discovery, Development and Manufacturing Forum, Programming Chair 2018
Reaction engineering Lab Leader, Merck & Company, Inc.

The Call for Abstracts for the 2018 AIChE Annual Meeting is open! Chemical engineers from across the world will converge on beautiful Pittsburgh, PA from October 28 through November 2 to share their research and learn more about recent trends in the fields. This year PD2M is sponsoring sessions in a variety of technical areas related to pharmaceutical research, development, and manufacturing. Similar to last year, we expect to see strong presentations that discuss the recent advancements in continuous processing, particle engineering and material science, and process control strategies. Sessions on the integration of product and process design will give us a better sense of how we can combine our experimental knowledge with first principles to rapidly develop robust processes in the lab and manufacturing environments.

The PD2M program also looks to highlight potential disruptive technologies that may have significant impact on the way we develop syntheses and products for our customers and patients. Sessions on innovative technologies to accelerate and enhance drug discovery, development, and manufacturing will discuss how automation, data rich experimentation, and other novel engineering tools are improving our process knowledge and efficiency. A session on data science and analytics will highlight tools and approaches that capture key information from big data, and how to use that information to drive decisions. These sessions, along with talks in other areas related to computational solid state pharmaceutics, enabling and advanced formulations, and the development of oral biologics will give us a better sense and appreciation for how are industry is progressing.

Please consider showcasing your work at this year's annual meeting. Encourage your colleagues and those in your professional and academic networks to submit an abstract. And don't forget about submissions for poster presentations. This is a great way for you to present your work and establish new network connections across the industry. Submissions can be made from https://www.aiche.org/conferences/aiche-annual-meeting/2018
Please feel free to email Jon McMullen if you have any questions or would like to be more involved with this year's PD2M AIChE program.