Issue 2, 2019
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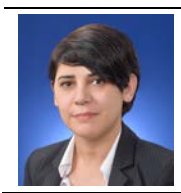
PD2M Newsletter

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

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 members,

The 2019 AIChE Annual meeting is around the corner. The Pharmaceutical Discovery, Development and Manufacturing Forum has an interesting program that features several topics of great interest for our community (e.g., Journey from Industry 4.0 to Pharma 4.0, emerging technologies, regenerative engineering, continuous processing, big data and smart analytics, and machine learning, etc.). We are excited to learn more about the most recent technical advances from practitioners, academics, and regulatory bodies in the chemical engineering field… but also for the opportunity to catch-up with colleagues.

PD2M organized two workshops this year:

- PD2M Advanced Process Control Workshop that took place last September 30 in Bethesda. The workshop was a great success and Thomas O'Connor provides more details in Page 2.
- PD2M Future of Pharmaceutical Manufacturing Workshop that will take place in November in Washing D.C. A summary of the event is discussed in page 3. You still have time to register.

In this issue, Prof. Hirokazu Sugiyama highlights the work of his group in Pharmaceutical Process System Engineering at the University of Tokyo. If you are interested in learning more about Prof. Sugiyama's research group, you can find them at the AIChE Annual Meeting.

Enjoy!

Carla

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Recent PD2M Advanced Process Control Workshop

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

The current state of process control in the pharmaceutical industry is predominantly based on approaches where input process parameters are validated and controlled at fixed set points or tight ranges. While often resulting in acceptable product quality, these control techniques using recipe and PID-based control are unable to adequately adjust the parameters to account for variations from raw materials, process disturbance and environmental conditions, and thus result in variability in quality and productivity. Contrary to traditional process control, the main objective of Advanced Process Control (APC) is to maintain process outputs at predefined set points, by manipulating process inputs within flexible ranges. APC is gaining an increased use in the industry to drive more consistent product quality and maximal economic output such as yield, throughput and reduced cycle time.

APC is a mature field widely used by many manufacturing industries, such as Oil & Gas and Chemicals., however the implementation of APC within the pharmaceutical industry is lagging. There are particular considerations when implementing APC in the pharmaceutical industry due to technical complexity of the products, the need to validate and maintain APC applications within a GMP environment, and existing practices and culture. The intent of this workshop was to bring the community together to have a focused dialogue to better understand the current opportunities, challenges, and best practices for overcoming these barriers.

The topics that workshop addressed were:

- Key terminology: Do we have an agreed definition of APC in the pharmaceutical industry? Are we leveraging, or should we leverage, APC definitions and concepts from other industries?
- Role and relationship of APC with regards to QbD, PAT, and other advanced manufacturing initiatives: How does APC connect to the control strategy? Do advanced manufacturing or complex products create opportunities for the implementation and value of APC?
- Organization readiness and governance for APC implementation/ maintenance: Are there best practices for establishing a governance and organizational structure for APC implementation and maintenance? Strategies for closing any skill gaps.
- Quality Systems for APC Implementation and CMC challenges: What if any is the regulatory impact of APC? Considerations for validating and maintaining an APC application within a GMP manufacturing environment.

The workshop promoted interaction and dialogue; proving attendees the opportunity to learn and to impact the discourse on how stakeholders (industry, academia, regulators) can work together to move the implementation of APC forward in the pharmaceutical industry for the benefits of patients.

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Upcoming PD2M Future of Pharmaceutical Manufacturing Workshop

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

Have you ever wondered how the future of pharmaceutical manufacturing is shaped? Want to be part of it? The PD2M Future of Pharmaceutical Manufacturing Workshop will explore the business, regulatory, and technical aspects associated with adopting novel manufacturing platforms to produce medicines. How innovations and regulations are working together toward the modernization of the pharmaceutical industry.

Together with AIChE and strong attendance from FDA, the workshop will be held in Washington, DC on 21-22 November.

In the plenary session, Mike Kopcha (FDA), Paul Collins (Eli Lilly) and Klvas Jensen (MIT) will discuss how pharmaceutical industry, academia, and regulatory bodies are positioned to adapt to the future of pharmaceutical manufacturing and share their views on: what is the impact of new modalities and personalized medicines? What are the major barriers for technology adoption? Why do regulatory agencies pursue pharmaceutical modernization?

Thomas O'Connor (FDA), Tim Watson (Pfizer), and James Coburn (FDA) will discuss the Regulatory Considerations for QbD of the Future. Why do organizations tend to favor less innovative investments? Are regulatory bodies receptive to novel approaches? Our invited speakers will challenge that perception and share their vision for QbD of the future.

Jake Albrecht (BMS), David Slade (PSE), John Thomas (M-Star) and Jon Dieringer (Eli Lilly) will walk us through Industry 4.0, the so-called new industrial revolution. Speakers will discuss readiness, maturity, vulnerabilities, and opportunities for the implementation of IoT, digital twins, cloud computing, V.Rand A.I. in pharmaceutical manufacturing.

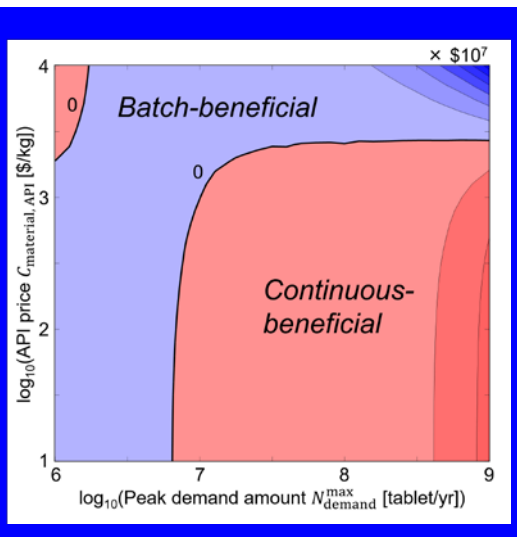
Martin Johnson (Eli Lilly), Martin McLoughlin (BMS), Ken Ford (Novartis), Rich Osifchin (Merck), Laura Crowell (MIT), and Jose Tabora (BMS) will describe emerging technologies that will propel flexibility, efficiency, and speed. A discussion of the advances in continuous manufacturing for small, medium, and large molecules, new technologies/platforms/devices, modeling and simulation, and the future of pharmaceutical processing adapting to a rapidly-changing environment will be highlighted.

As a follow up of the previous workshop, Nima YazdanPanah (FDA), Salvador Garcia (Eli Lilly) and Rex Reklaitis (Purdue university) will discuss how to overcome the fear of advance process control.

It is impossible to discuss the future of pharmaceutical manufacturing without discussing innovation. Fred Parietti (Multiply labs), Luke Rogers (On Demand Pharmaceuticals), and William Grieco (RAPID) will discuss innovation engines and outcomes as it applied to the future of pharmaceutical manufacturing highlighting novel technologies, innovation processes and implementation.

More details about the program can be found here.

If you are interested in attending, you still have time to register!



Example of decision-support information for the choice between continuous vs batch in tablet manufacturing (Matsunami, *et al.*, *Ind Eng Chem Res*, 2018, Open Access)

Abstract

The goal of our research is to develop methods and tools that can support decisions in the design and operation of pharmaceutical processes. This short article aims to introduce briefly the recent achievements, and also to give a preview to the presentations in the upcoming AIChE annual meeting in Orlando.

Acknowledgement

I would like to acknowledge the financial supports from the Japan Society for the Promotion of Sciences (JSPS), Japan Agency for Medical Research and Development (AMED), Nagai Foundation Tokyo, and the industrial collaborators. Experts in the Community of Practice on Pharma PSE in ISPE Japan are appreciated. Lastly, I would like to thank the members of Hirao-Sugiyama Laboratory at The University of Tokyo.

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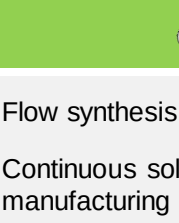
Pharma PSE Research at The University of Tokyo



Hirokazu Sugiyama
Associate Professor
Department of Chemical System Engineering
The University of Tokyo

Having worked for biopharmaceutical manufacturing at Roche in Switzerland for over 5 years, I moved (back) to The University of Tokyo in 2013, and launched a research activity on pharmaceutical process systems engineering: Pharma PSE. My ambition was (and still is) to explore the evolution of pharmaceutical processes with novel approaches to move away from the conventional empirical methodologies to systematic and comprehensive development of optimal solutions. The pharmaceutical industry spans a wide range of applications, each with specific obstacles and challenges. Our research frontier has been expanding to cover academically and industrially relevant topics in small molecules, biopharmaceuticals, and regenerative medicine (see Figure 1). The group has been growing, and today has 1 assistant professor (Sara Badr), 6 PhD students, and 9 master/bachelor thesis students. Last year we celebrated the first PhD commencement from the group (Gioele Casola, now with Roche). This short article aims to introduce briefly the recent achievements, and also to give a preview to the presentations in the upcoming AIChE annual meeting in Orlando.

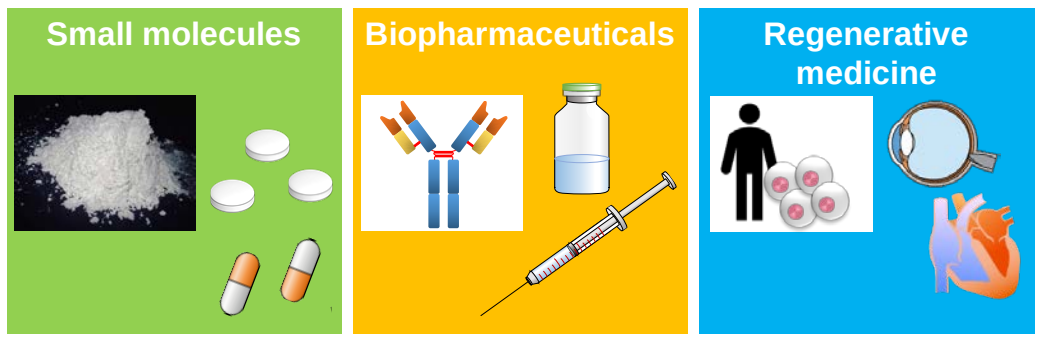


Figure 1: Our domain of interest and research topics

1. Small molecules

The major development of small molecule has been the introduction of continuous manufacturing. The main challenges involve standardization, operation, and control. In our group, models with different resolutions are applied to topics in flow chemistry and continuous solid drug manufacturing. Additionally, experimental approaches are taken with industrial collaborators to further understand the impact of different powder processing technologies on product quality [1]. A model-based economic assessment approach was proposed to support decision-making on batch and continuous technology selection [2]. We are now applying a superstructure approach to cover as many options in mixing, granulation, and compaction as possible, in order to enable holistic economic evaluation. A MATLAB-based software is in development that can support key decisions on, e.g., batch vs continuous, wet vs dry granulation, or formulation strategy, from Phase II on. On WED in a PD2M session, Kensaku Matsunami will give a talk on the latest development.

2. Biopharmaceuticals

The market of biopharmaceuticals will experience rapid expansion of new products in the next years. This will necessitate more production capacity and efficiency through implementation of highly productive processes and reduction of non-value adding time, e.g., changeover, in both drug substance and drug product manufacturing. In our group, we launched a project on monoclonal antibody (mAb) production processes, where pilot facility data are used to model integrated continuous manufacturing as a design alternative. Three presentations will be given in the annual meeting. On TUE in a CAST poster session, Haruku Shirahata will present an approach of systematic alternative generation and assessment. On WED in a PD2M session, Kozue Okamura will give a talk on dynamic simulation and process assessment of mAb cultivation modes using pilot-scale experimental data. And on FRI in a CAST session, Sara Badr will present design of integrated monoclonal antibody production with highlighting opportunities for continuous manufacturing.

Changeover operation are investigated in detail, both in drug substance and drug product manufacturing. The impact of deploying single-use technology in sterile filling operation and the optimal choice of equipment technology have been studied through a framework for comprehensive multiobjective assessment [3, 4]. We are now implementing the developed models and algorithms as a software named “TECHoice” for ease of industrial application. A free online prototype version [5] is available under http://www.pse.t.u-tokyo.ac.jp/TECHoice/. Cleaning and sterilization were also tackled by data-driven approaches and uncertainty-conscious performance assessment [6, 7]. Furthermore, combined modeling and experimental approaches have been implemented for H2O2 decontamination of sterile isolators to determine optimal conditions regarding sterility and productivity [8]. Currently, machine learning and data-driven approaches are applied for predictive monitoring and operation support for H2O2 decontamination. On THU in a CAST session, Anicia Zeberli will talk about the latest work regarding this topic.

3. Regenerative medicine

Following the recent successes of clinical trials of human induced pluripotent stem (hiPS) cells, one of the remaining major obstacles towards industrialization is the cryopreservation process. We have been working on the filling, freezing, and thawing processes. For the filling process, a conceptual model for lot-sizing has been proposed considering the cell quality change during filling [9]. For freezing, a set of mechanistic models was developed that can determine optimal conditions considering both productivity and cell quality, given the target cell numbers required to produce the organ [10]. On TUE in a PD2M session, I will give a talk on the latest development of the freezing process modeling and simulation.

Through the development of the group, I have come to fully appreciate that the key role of PSE to speed-up the development of advanced and novel pharmaceutical processes and technologies. PSE acts as the “enabler” of agile and comprehensive exploration of the decision space in pharmaceutical process design and operation. Further PSE research is therefore encouraged towards realizing more systematic decision-making in the pharmaceutical industry by providing a wide range of useful models/tools/methods for both established and emerging technologies.

Taking this opportunity, I would like to announce the following special issue in Processes (MDPI). We welcome wide range of articles on decision-making in pharma processes regarding products, lifecycle phases, scales, model types, and design objectives.

- Special Issue: Decision-support Tools for Pharmaceutical Processes (website)
- Editors: Hirokazu Sugiyama, Sara Badr (The University of Tokyo), Thomas De Beer, Ingmar Nopens (Ghent University)
- Deadline: April 30, 2020

Recent publications

[1] K. Matsunami, et al., A large-scale experimental comparison of batch and continuous technologies in pharmaceutical tablet manufacturing using ethenzamide, Int. J. Pharm., 559, 210–219 (2019) Open Access (website)

[2] K. Matsunami, et al., Decision support method for the choice between batch and continuous technologies in solid drug product manufacturing, Ind. Eng. Chem. Res., 57, 9798–9809 (2018) Open Access (website)

[3] H. Shirahata, et al., Multiobjective decision-support tools for the choice between single-use and multi-use technologies in sterile filling of biopharmaceuticals, Comput. Chem. Eng., 122, 114–128 (2019) (website)

[4] H. Shirahata, et al., Alternative generation and multiobjective evaluation using a design framework: case study on sterile filling processes of biopharmaceuticals, Comput. Chem. Eng., 123, 286–299 (2019) (website)

[5] H. Shirahata, et al., Online decision-support tool "TECHoice" for the equipment technology choice in sterile filling processes of biopharmaceuticals, Processes, 7, 448 (2019) Open Access (website)

[6] G. Casola, et al., Uncertainty-conscious methodology for process performance assessment in biopharmaceutical drug product manufacturing, AIChE Journal, 64, 1272–1284 (2018) (website)

[7] G. Casola, et al., Data mining algorithm for pre-processing biopharmaceutical drug product manufacturing records, Comput. Chem. Eng., 124, 253–269 (2019) (website)

[8] K. Yabuta, et al., Design-oriented regression models for H2O2 decontamination processes in sterile drug product manufacturing considering rapidity and sterility, Int. J. Pharm., 548, 466–473 (2018) (website)

[9] H. Sugiyama, et al., A distribution-based approach for determining lot sizes in the filling of human-induced pluripotent stem cells, Regen. Ther., in press, Open Access (website)

[10] Y. Hayashi, et al., Slow Freezing Process Design for Human Induced Pluripotent Stem Cells by Modeling Intracontainer Variation, Comput. Chem. Eng., in press (website).