Content

December 6, 2018

PD2M Newsletter

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

Note from the editor

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Dear PD2M Forum members,

Do you like movie quotes? I do… mostly because somebody at SMDD taught me quotes are concentrated life lessons... so concentrated that they fit in one sentence. My favorite movie of all times is *Star Wars - The Empire Strikes Back*. While training Luke Skywalker to be a Jedi, Yoda said: "*Do, or do not. There is no try*." I like this concise way of telling us that either we go all the way with something or we don't bother doing it at all.

Interestingly, I was planning this issue of the PD2M Newsletter to highlight topics that were discussed during the last AIChE annual meeting at our forum. When I returned from Pittsburgh, I realized this issue shouldn't highlight those topics that everybody is discussing… it should highlight those that just a few people are talking about. Why? Because those topics come from PD2M members who are pretty much alone doing something new. Being alone makes people go all the way ("*there is no try*")!

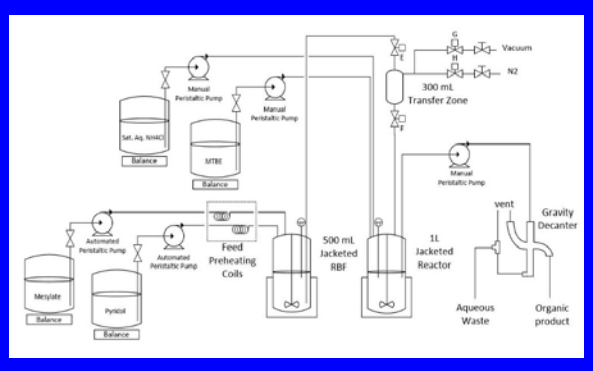
Here are a few examples of companies that are pioneering in some interesting areas:

- How is chemical engineering influencing drug discovery? Antonio Navarro, Martin Johnson, and Luke Webster at Eli Lilly discussed how continuous manufacturing impacts Drug Discovery Chemistry.

- Why is the drug substance continuous manufacturing adoption slow? We asked two of the pharmaceutical industries that have implemented fully continuous drug substance processes to share their secret. Andrew Rutter (GlaxoSmithKline) and Paul Collins (Eli Lilly) compare notes. Striking similar approaches!

- Perspectives on modeling lifecyle. For models, it looks like we always talk about inception and development… but the modeling lifecycle is more than that. Pablo Rolandi (Amgen) shares a holistic perspective.

This is the last issue of the newsletter this year… so it is time for reflections. 2018 was an amazing year for our forum. The PD2M sessions at AIChE Annual Meeting were well attended and our members had the opportunity to share technical achievements. We re-launched this newsletter to improve communication with our members. I am sure there is many other achievements that I could highlight but before closing my note, I would like to focus in one important aspect: CHANGE. PD2M Forum is changing… and new ideas will be tested. My final comment for you is: "*you can join and own this change... Do, or do not. There is no try*"



Abstract

A fully automated fill/empty system for an etherification reaction is described. The system was capable of carrying multiple operations in sequence to obtain crude dry product: charging both reactants solutions to a heated reactor, aqueous quench the reaction slurry using a transfer zone, continuous phase separation, and concentration of the organic solution containing the product.

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Automated intermittent flow approach to continuous etherification reaction

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Drug discovery typically starts with milligrams of material for primary testing, but as the compounds advance, the material needs quickly increase to tens of grams for early in vivo toxicity studies and to hundreds of grams for later toxicological studies. This scale-up is very important for a fast delivery of these quantities of material, but it often faces important challenges (safety, reproducibility, efficiency) and it is not always trivial. Continuous processes generally require orders of magnitude less scale up than batch processes. They can be scaled to production quantities with minimal optimization and minor changes in the synthetic route by simply running a reactor for extended periods of time.[1] In this article, we describe an example of a practically continuous flow process to synthesize an API precursor for pre-clinical toxicology studies. The reaction is intermittent flow and the liquid-liquid extraction is truly continuous flow. This is like an automated assembly line approach to continuous processing.[2] The additional benefit is that the discovery chemist only needs to develop a batch reaction on small scale, which is status quo. The continuous assembly line approach repeats the same reaction on that same scale a large number of times in automated fashion.[3-5] Therefore, this approach facilitates the translation from batch to “continuous” production more so than translating to homogeneous conditions in a PFR.

The step described here consists of an etherification reaction and allowed us to put together two main fragments to build the complete skeleton of the desired product. Chemically, it is a nucleophilic substitution of a mesylate derivative A of a benzylic alcohol to a pyridolate potassium salt B (Scheme).

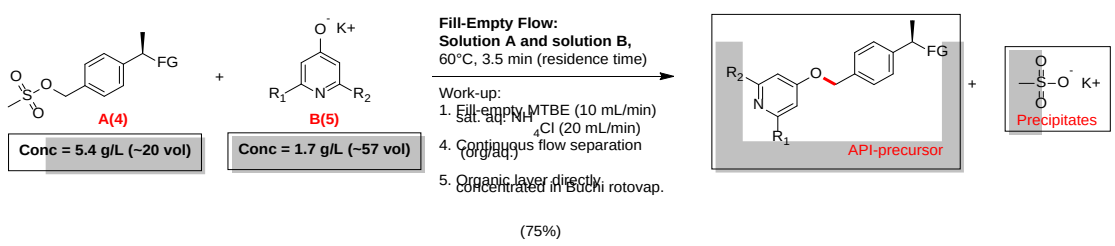

Figure 1. Automated fill/empty system.

The chemical reaction was very fast (<2 min) and formed a precipitate as a by-product; therefore, an automated fill/empty system that can handle slurries was designed (Figure 1). The advantages of this intermittent and continuous flow compared to batch, included: (i) Less scale up, (ii) Less material at risk in the reactor, (iii) Better quality assurance because of automated repeating operation, (iv) Less manual labor and material handling. A comparable batch campaign would have required dividing the starting material (476 g campaign) into 4 or 5 batches of 22L/ea. All the operations, such as reaction, quench, layer separation, and distillation would have to be done manually.

The unit operated as follows: a 500 mL jacketed reactor (Figure 1, 1) was maintained at 60 °C at all times. Materials heated quickly when they entered reactor and cooled quickly when they exited. The reactor was filled by starting material solutions A (4) and B (5) using peristaltic pumps (6) with an operating volume of 50%. The mesylate (A) was charged to the reactor first, and then the pyridol salt (B) was pumped in at a steady rate. This controlled addition of B avoided the formation of undesired by-products, such as N-alkylation derivative, and gave higher yield and selectivity. This mode of addition is feasible by the fill-empty approach described herein, but it would not be as feasible if the reaction was run in a truly continuous reactor. The residence time was set at 2 min during which a slurry formed due to precipitation of potassium mesylate. The reaction mixture (1) was transferred to a 1 L quench vessel (2) through an automated transfer zone (3) Vessel (2) was constantly fed by a saturated aqueous solution of ammonium chloride and MTBE by peristaltic pumps (6) while vigorously mixing with an overhead stirrer. The solids dissolved in the aqueous layer and the biphasic mixture from the quench vessel was continuously pumped to a gravity decanter (Figure 2). The phases were separated by

gravity and collected in collection vessels. The organic solution was transferred continuously by vacuum to the rotavapor (Figure 3) where the solvents were distilled, yielding the crude product. No feedback control loops were needed for the liquid-liquid extraction. The liquid-liquid interface level in a gravity decanter was set by the adjustable height of an aqueous overflow tee, and the liquid level in the mixer and decanter were set by dip tube level and peristaltic pumps operating at higher volumetric flow rate than the liquids.

Figure 2. Gravity decanter

Figure 3. Rotavapor

The chemical process was monitored by manually pulling an aliquot of the reaction mixture and analyzing it by Liquid Chromatography Mass Spectroscopy (LCMS). Sampling frequency was higher at the beginning and then relaxed once the process proved consistent. As shown in Figure 4, the process was very consistent over time. A total of 393 g of product were obtained by running 20 automated cycles/day.

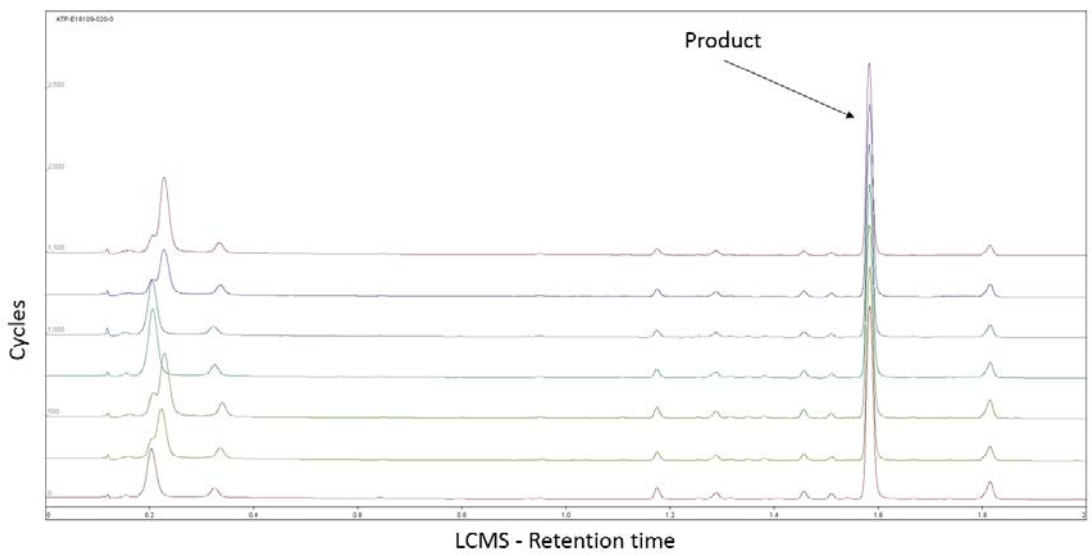

Figure 4. Stacked Representative LCMS chromatograms for different cycles.

The reactor system showed that this process can be carried out with high productivity from a small process footprint, a large number of volume turnovers each day, a seamlessly transfer of slurries formed in the reaction, and rapid heat up and cool down of solutions as they flowed in and out of the 500 mL heated reactor. The downstream operations of quench, workup, phase separation, and isolation furnished the product in a 75% yield. The product (API-precursor) was used in the final (next) step without further purification.

In summary, a continuous automated fill/empty platform developed at Eli Lilly and Company has been used to produce material for late phase discovery toxicology studies. The reliability, efficiency, and consistency of this system makes it suitable to be used in future larger scale campaigns of development. This system is versatile and can be easily modified with a different number of reaction and process separations vessels, pumps, and transfer zones to run other synthetic routes.

Abstract

Last October, I attended the 3rd International Symposium of Continuous Manufacturing of Pharmaceuticals (ISCMP 2018) organized by CMAC-MIT. It was clear then that drug product continuous manufacturing (DPCM) to produce oral solid dosage forms is here to stay, as exemplified by the growing number of approved products (e.g., Orkambi and Symdeko - Vetex; Prezista - Jannsen; Verzenio - Eli Lilly). Interestingly, the drug substance counterpart is not on the same fast track. Same conclusion can be made by comparing the numbers of talks presented recently at AIChE Annual meeting in Pittsburgh for DS and DP. While specific continuous unit operations have been used to commercially manufacture drug substances for years (hybrid processes), the adoption of fully continuous processes is much slower. In order to understand the reasons, PD2M Newsletter decided to ask the leaders of two of the companies pioneering the development of drug substance continuous manufacturing (DSCM) a few questions. What is their secret?
Striking similarities!

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Drug substance continuous manufacturing adoption – What is the secret?

Question	Paul Collins Sr Director, Small Molecule Design and Development at Eli Lilly	Andrew Rutter Sr Director, Primary Engineering Platforms at GlaxoSmithKline
		
When did your company start developing drug substance fully continuous processes? What was the business driver?	We started looking at continuous reactions and separations in 2006. Fully continuous, multi-step CM as a concept in lab hoods was probably 2010. The business driver was capital avoidance for smaller volume products that didn't fit well in existing large batch infrastructure.	We started in 2003, the original driver was capital cost avoidance.
Why do you think DSCM adoption is much slower than DPCM?	See Andrew's answer to the right! I would agree with what he said and perhaps expand the "harder" comment by saying that there are a lot of unit operations running in connected fashion for a 3-4 step synthetic sequence.	For three reasons: it is harder (particularly multistep), there are fewer benefits for R&D (most play out in commercialization of production), and often we are competing against underutilized batch assets.
Did your company produce GMP material using DSCM?	Yes, and for multiple projects	Yes.
What are the major barriers you encounter in the process of adopting DSCM (technical, personnel, internal, external)?	Again, I agree with Andrew's statement to the right. In addition, "regulatory fear" plays a large role here. Being out in front means you will answer the most questions from regulatory authorities.	The inertia that batch technology has. To overcome this takes investment that takes a while to payback.
How did your company overcome those barriers?	It's funny how much Lilly has mirrored GSK's experience. Strong management sponsorship was critical. We also tried multiple "business case" angles in discussing across the company. Every company will be different on this point. Process safety spoke loudly for us in many of our proof of concepts with manufacturing.	Strong Senior Management sponsorship, persistence, coupled with a fantastic team passionate about the technology.
What are the major changes needed to enable faster adoption of DSCM?	External involvement is critical. Nobody convinces us to change more than someone else – other companies' success encourages more to try. If you tend to be internally oriented and insulated at your company, you'll need to be involved in the CM external community.	More good examples of successful implementation. Better integration of modelling and experimentation. Experience. Opportunities to support acceleration of NCE supply.

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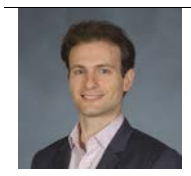
A field perspective of the industrial modeling process



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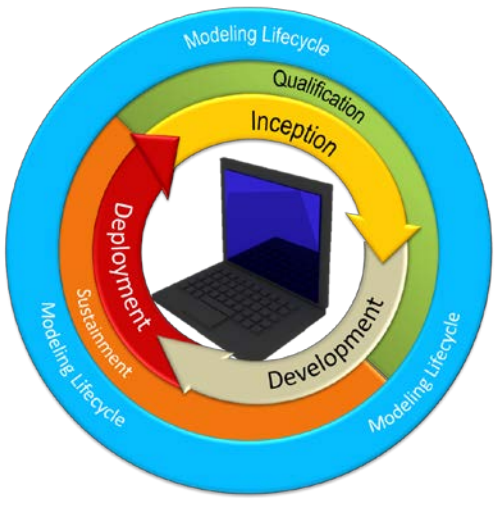

Abstract

First-principles models are created to support decision making processes. Managing a diversified modeling portfolio highlights the need for a holistic framework that enables a better characterization and communication of the modeling lifecycle.

In this article, Pablo Rolandi shares Amgen's approach to face this challenge.

Twenty years ago, Foss, Lohmann and Marquardt (Foss et al, 1998) published their seminal field study of the industrial modeling process, which laid out the first framework that I used to conceptualize the modeling process. Over the last three years, managing a diversified modeling portfolio at Amgen has highlighted the need for a holistic framework that would enable a better characterization and communication of the modeling lifecycle. In this article, I would like to share this perspective with you.

In an industrial setting, first-principles models are created to support decision making processes that yield technical outcomes or business outcomes with positive impact for the organization. The success factors that determine how effectively this is accomplished fall into four broad categories: strategy, organization, culture and technology. At Amgen, these factors combine in such a way that there is a preference for building reusable, enterprise-level modeling assets over creating disposable, one-off models. This strategy generates the need for maturity assessment and portfolio governance processes underpinned by a modeling lifecycle framework. The framework consists of five phases: inception, development, deployment, qualification and sustainment. Each of these five phases contains four key activities. It is understood that not every phase or activity is required for every modeling asset, although models with the greatest maturity normally do exhibit this characteristic.

The lifecycle process starts with the inception stage, which is more important than one might think. Peter Drucker said "there is nothing so useless as doing efficiently that which should not be done at all", and this step is designed to avoid onboarding modeling projects with a high opportunity cost or an unclear business value proposition. Inception ensures strategic alignment, adequate resourcing and clear assessment of the effort/risk/impact profile of any given proposal. Understanding the modeling data requirements is one of the key activities during inception. A success factor at this stage is clear sponsorship from all involved functions as well as allocated resources to the project team. Not having end user representatives (subject matter experts) early in the project team is a major warning sign that the solution will struggle to gain grassroot adoption.

Following inception, the development stage takes places as a largely unstructured undertaking, with four coarse-grained activities: model formulation and model identification are the first two of those, and hands-on modeling specialists excel at these two core modeling tasks. Then, the application of the model within the scope of the project charter is paired with an assessment of the model's predictive ability. This determines whether the modeling cycle needs to be iterated, or an exit is possible. A well-established literature body, a dependable analytical and experimental team, or a strong collaboration with academics and vendors are typical success factors. Shifting priorities during development can be a reason for lack of progress and early discontinuation of the modeling effort. Multi-year model development efforts can suffer from significant setbacks resulting from a discontinuity of internal knowledge as team members change responsibilities.

The deployment stage provides access to the model beyond its first application and creates a pathway for adoption of the model by end users. Deployment is a necessary (but not sufficient) condition for democratization of modeling and acceleration of digital transformation roadmaps. Deployment is effectively a product development step, that entails four activities: user requirements gathering, product development with an end-user focus, product documentation, including user guides and training materials, and product release, including product testing (manual and automated) and any necessary end-user engagement tasks. The "appification" of the modeling asset into a modeling app is one common deployment path. The product can also be released (i.e., deployed) as a modeling library or a modeling solution. The release step transfers the modeling asset to the enterprise digital store. It is easy to underestimate the effort associated with the deployment stage, which demands that the decision to promote a promising model the category of modeling asset is made conscientiously. At present, the lack of unified, universal model deployment platforms is a factor that increases the total cost of ownership of this stage. However, there are established commercial deployment environments and fast-evolving open source deployment frameworks that can simplify and expedite this undertaking. It is worth noting that deployment does not equal adoption, as described in the sustainment phase.

The qualification stage is initiated to meet the needs for model documentation and model qualification. The former entails documents describing the technical characteristics of a model (i.e., technical documentation), and the latter is a document assessing the gains and risks that result from applying the model to specific business problems. This last document features a model fidelity assessment, model credibility assessment and model qualification evaluation following internal guidelines and industry best practices, some of which are heavily influenced by systems engineering validation and verification methodologies [3]. The qualification stage is completed with business process documentation (e.g., guidelines, manuals and SOPs) and computer systems validation if required. Overall, qualification adds value to the lifecycle to the extent that it either enables a credible model to be used routinely in the business or stops a poorly vetted model from informing a decision that could create unnecessary business or patient risk. Fortunately, there is a growing body of literature describing the methods around model credibility [2], although more progress is needed in this area.

The sustainment stage gets started as soon as a modeling asset goes into routine utilization by subject-matter experts and model application engineers. This is where the investment made in the four previous stages (inception, development, deployment and qualification) begins to yield systematic returns (exploitation) beyond the initial application (exploration) by supporting directly programs in the discovery/development pipelines and/or the manufacturing network. Routine execution takes place in the form of computer-aided process and product design, with simulation, optimization and statistical inference being the three main categories of numerical studies carried out by end users. Approaches where the model is assumed to be have little parametric or structural uncertainty can give way to more advanced and inherently probabilistic (likely Bayesian) analyses. Sustainment goes beyond routine utilization and encompasses the activities of supporting/maintaining, advocating and embedding the modeling asset in the business.

The five stages above do not take place in a sequential way, as it is typical of waterfall methodology development approaches. In practice, agile development methodologies let multiple phases co-exist and produce valuable feedback and feedforward information loops for more efficient, effective and reliable execution. However, the modeling portfolio is monitored periodically through the constructs of the modeling lifecycle with the goal of having an optimal allocation of resources to maximize the value from the portfolio of modeling projects and assets.

This lifecycle framework enables us to be best equipped to embrace the successes and failures around the modeling assets we create (including those pragmatic and valuable one-off models). Let's continue the incredibly rewarding journey of making first-principles modeling a transformative force for our industry.

I would like to thank Will Johnson, Ahsan Munir, Fabrice Schlegel and Xiaoxiang Zhu for their contributions to the lifecycle framework presented in this article, and Cenk Undey for his sponsorship.

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