Content

October 2, 2018

PD2M Newsletter

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

Note from the Editor

Carla Luciani

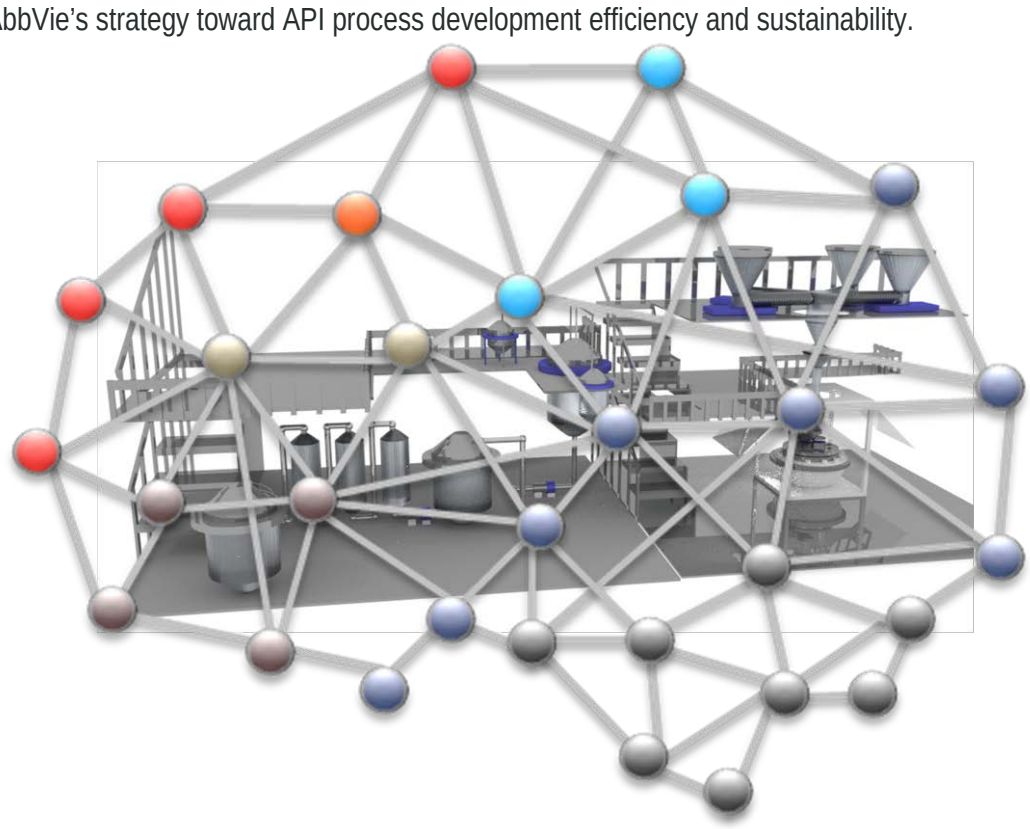
Pharmaceutical Discovery, Development and Manufacturing Forum, Newsletter Chair

Future Manufacturing Platforms Leader, Assoc. Engineer Advisor, Small Molecule Design and Development, Eli Lilly & Co.

Dear PD2M Forum members,

What do you think pharmaceutical industry will be doing 5 years from now? What about 50 years from now? Making predictions about the future is always fun. The longer the prediction horizon length, the harder is to make accurate predictions… but this issue of the Newsletter is not about accuracy… it is about **vision**! Mary am Ende (Pfizer), Meg Landis (Pfizer), and Aaron Moment (Columbia University) shared their thoughts on the future of pharma:

For the CMC section of the Newsletter, Nandkishor Nere and Moiz Diwan (Abbvie) shared AbbVie's strategy toward API process development efficiency and sustainability.



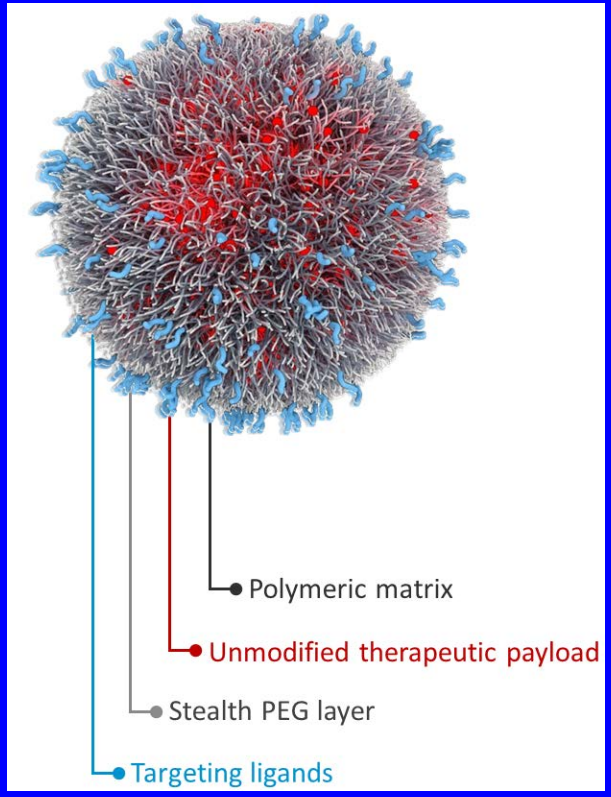
It is hard for me to imagine a future without some uglier but less violent version of *Ex Machina*. Pharma companies have significant drivers to adopt the most cutting-edge technologies in the expensive and lengthy process of drug discovery and drug development. Over the last few years, we have read/heard about artificial intelligence (A.I.) initiatives (e.g., collaborations between pharmaceutical companies and Watson for Drug Discovery, Atomwise, Exscientia, Numerate, Transcriptic, Nuritas, QuantumBlack, MIT Machine Learning for Pharmaceutical Discovery and Synthesis, just to name a few). Are there specific CMC fields that could be impacted by A.I.? Based on recent publications in the field, I am optimistic!

- Synthetic route selection (*e.g.*, Segler et al. *Nature* 2018, 555, 604–610; Klucznik et al. *Chem.* 2018, 4, 522-532; Coley et al. *Acc. Chem. Res.* 2018, 51, 1281-1289).
- A.I.-Aided process development (e.g., Zhou et al. *ACS Cent. Sci.* 2017, 3, 1337-1344)
- A.I.-Aided manufacturing (planning and scheduling, process parameter optimization, control, preventive maintenance, energy consumption) (*e.g.*, Li et al. *Front Inform. Technol. Electron. Eng* 2017, 18, 86-96).

A.I. is an interesting topic (find more about this topic in the article by Aaron Moment in page 4) and we will consider it for a future issue (let me know if you want to contribute).

However, for the next issue of the PD2M Newsletter, I have another idea. Inspired by the article of Meg and Mary, I would like to devote at least one article to highlight the ***Impact of Chemical Engineering on Drug Discovery***. Please, contact me (luciani_carla_vanesa@lilly.com) if you or a colleague would like to contribute to this important topic.

I hope you enjoy the third issue of the PD2M Newsletter!



Abstract

The future of small molecule oral drug delivery is evolving into complex drug mechanisms of action and drug delivery systems. These new drug candidates are seeking unique targets, for example protein-protein interaction disruptors and degraders. Advances in the drug delivery field are targeting drug encapsulation to protect the drug from premature degradation, as shown above by the nanoparticle.

Acknowledgements

A special thanks to BIND/Pfizer colleagues, including Maria Figueiredo and Greg Troiano.

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Lyndra device (https://www.lyndra.com/about).

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Future of Pharmaceutical Small Molecules and Drug Delivery is on Target

Meg Landis
Associate Research Fellow, Molecular Pharmaceutics Group, Drug Product Design, Pfizer

Mary am Ende
Research Fellow, Process Modeling & Engineering Technology, Drug Product Design, Pfizer
Pharmaceutical Discovery, Development and Manufacturing Chair Elect 2016-2018

The future of the pharmaceutical industry is evolving in many ways, of which this article focuses on unique biological targeting, new drug mechanisms and specialized drug delivery becoming more commonplace. The 'small molecules' are going beyond the Rule of 5 in one or more parameter. Examples include larger molecular weight, increased number of chiral centers, novel chemotypes, more heteroatoms, and extreme molecular properties, i.e. highly hydrophilic or highly lipophilic. Compounds are now substrates for carrier-mediated transporters and/or efflux pumps and display complex oral pharmacokinetics. Overall, human efficacious doses may be low, but delivery of high doses for pre-clinical studies (biology or oral toxicology evaluations) remains challenging.

One of the most exciting, emerging new paradigms for small molecule disease treatment is the bifunctional protein degraders or "PROTACs" (proteolysis targeted chimeras). This approach can be used across any therapeutic area where the elimination of the target protein activity is desired for therapeutic benefit. Traditionally, elimination of enzyme activity has been done by small molecule inhibitors. In the new paradigm, these enzymes are not inhibited, but marked for degradation using the naturally occurring cell processes (Proteasome), thereby achieving the same therapeutic result. The mechanism is shown in Figure 1 below. These "small" PROTAC molecules are built with three components, a molecule that binds the target protein (Figure 1, PROTAC red portion), a linker (typically small PEG lengths) and a small molecule that binds the E3 Ligase (Figure 1, PROTAC blue portion). The PROTAC binds the target protein and the E3 ligase simultaneously and the target protein is ubiquitinated and marked for degradation by the proteasome. Then the PROTAC molecule is released and can perform the same action again for another target protein.

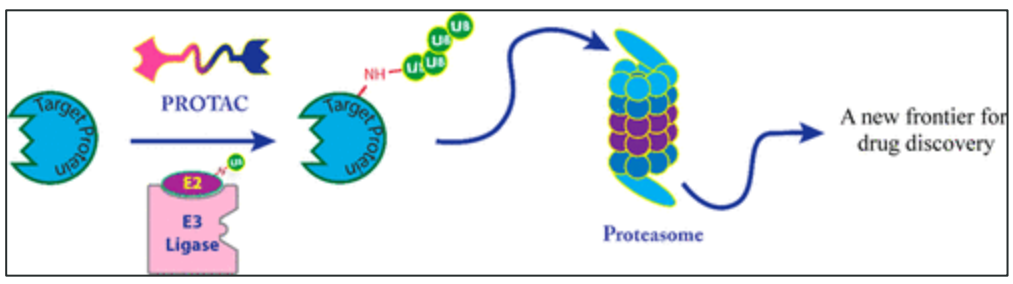


Figure 1: Representative scheme of the mechanism of action for PROTACs or bifunctional protein degraders: Used from *J. Med. Chem.*, 2018, *61* (2), pp 444–452 with permission.

The PROTAC "small" molecules are challenging from an oral delivery aspect however. They are very much outside of the typical parameters of the Rule of 5. They are larger small molecules, with molecular weight 700->1000 Da ad are generally high in Log P values (>5), have poor aqueous solubility and poor membrane permeability due to high molecular weight. They are expected to have a relatively low human therapeutic dose, however, due to recycling of PROTACs within cells.

Additionally, specialized and complex drug delivery systems long sought after are becoming a reality. The gastric retentive drug delivery approach provides several benefits, including continual gastric solubilization for weakly basic molecules, highest absorption potential in upper gastrointestinal (GI) tract, upper GI delivery to avoid gut metabolizing enzymes, lower efflux transporters, and long exposure and release profiles. However, these complex drug delivery systems often mandate specific meal requirements.

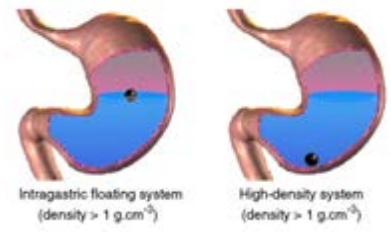


Figure 2. Gastric retentive drug delivery: floating or high density systems

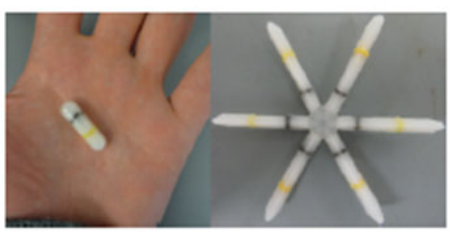
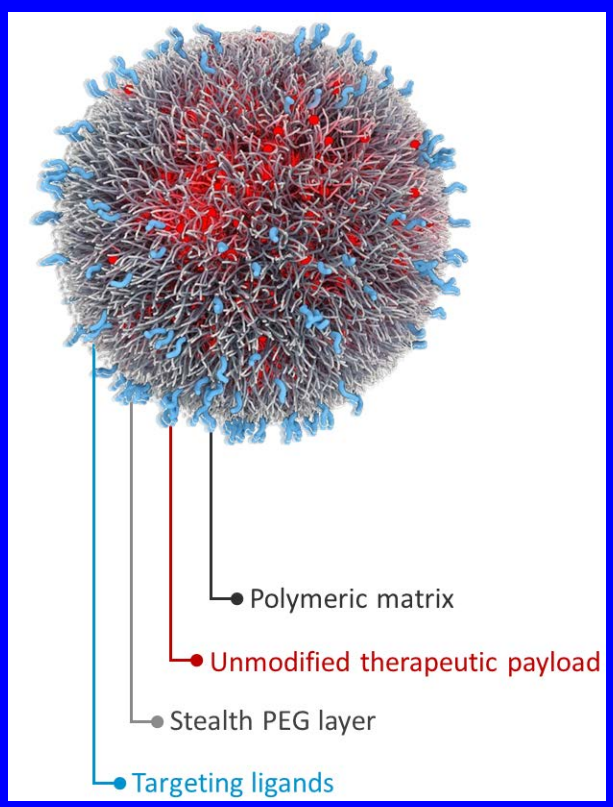


Figure 3. Gastric retentive drug delivery: unfolding system



From the next generation molecules to the next generation drug delivery systems, the future of the pharmaceuticals is exciting and dynamic. PROTACs may hold the key to more safely treating new diseases, including cancer and rare diseases. New devices will also play a role in targeting drugs and making them more safe and efficient in disease treatment.

For questions related to this article, please contact margaret.s.landis@pfizer.com or mary.t.am.ende@pfizer.com.

Abstract

A high level trend in manufacturing and engineering is towards on-demand, modular, flexible, and connected elements, linked seamlessly to the underlying big data sets. The biopharmaceutical industry is not immune to this engineering evolution and some thoughts and examples are offered here.

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PD2M Newsletter

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

Envisioning the future of pharmaceutical manufacturing – modular, flexible, global, data intensive, on-demand, safe, green, and connected

Aaron Moment

Professor of Practice, Chemical Engineering

Columbia University in the City of New York

Mass production of pharmaceutical and biopharmaceuticals with high levels of attention from regulators and manufacturers on quality and compliance has been the dominant paradigm for technical, quality, and regulatory reasons. However, in recent years there has been sponsored research from government agencies as well as industrial interest in on-demand production techniques,[1] motivated by practical incentives of efficiency (e.g. reducing inventory, cycle time, capital) and also by futuristic vision. Although easy to point out the challenges of these approaches, history and also thermodynamics has taught us that change is a constant and has a forward direction, which is illustrated through the second law.

3D printing of formulations is a good example of the on-demand idea, and there are now examples of 3D printed dosage forms.[2] This has many implications for both commercial application as well as development.[3,4] This approach could reduce the API required during development cycles, as well as reduce capital requirements required for formulation.

Cell based therapies are here and by design are personalized and on-demand; chemical engineering approaches (i.e. automation, process monitoring, control, and focus on logistics and operations) are called for to transition this into a commercial space.[5] For consistency and quality, regional manufacturing centers are receiving attention as a way to take cell based therapies out of a hospital environment and into a manufacturing one.

Moving on to modularity and flexibility. These two attributes are important in engineering design because they allow systems to cope with change as well as the global nature of the industry. Eli Lilly's new building is deliberately modular to allow for the inevitable future changes in equipment and research directions.[6] Another contemporary example are single use bioreactors and related equipment[7] which are inherently more flexible to build and design than hard piped plants. One can imagine using this technology to develop a process and then move it to another location using a copy exactly philosophy.

Big data and computation is an ever evolving part of process development and using analytics to predict n+1 given n = 10,000 or more previous pieces of data is a present reality.[8,9] Moreover, adapting the predictions based on additional data is an interesting math problem that may be described loosely as AI, machine learning, algorithms, and data science. Incorporating these tools into development has clearly happened and will continue. Because of this trend, having some type of coherent data strategy becomes important in development and manufacturing.

In manufacturing, big data becomes more "potent" due to the regulatory and also technical aspects. The sophistication and ease of dash-boarding and data visualization continues to increase and in cases like biologics where the process is the product that means the process data may be considered to be the product, too; and hence a lot of effort will continue to be spent on the data science there. For product release and review, on-demand reporting of official analytical data from a database, where all instruments have a standardized file structure is an ideal situation and may be enabled through collaborations such as Allotrope.[10]

Last but not least, process safety and green chemistry continue to be baked into process development as related attributes, and this is an area where both chemists and chemical engineers shine. A shorter more hazardous route may be less tractable at scale relative to a slightly more "steppy" benign one. The earlier these considerations can be taken into account the better, but experience has shown that even for an existing commercial process, companies have taken the initiative to introduce a safer, greener version. Safer processes are generally more portable, which is aligned with flexibility and modularity, and it is encouraging to see collaboration across companies and open sharing via Pistoia Alliance Chemical Safety Library.[11]

Thanks for reading and for or questions and comments (I welcome feedback of all sorts) related to this article, please contact ajm2293@columbia.edu.

Abstract

This articles details the genesis to establish AbbVie's engineering centers of excellence to enhance the efficiency of API process development. It also delves into the strategy, operating model and the due business impact made in a shorter time span.

Figure A. Driver to establish COEs.

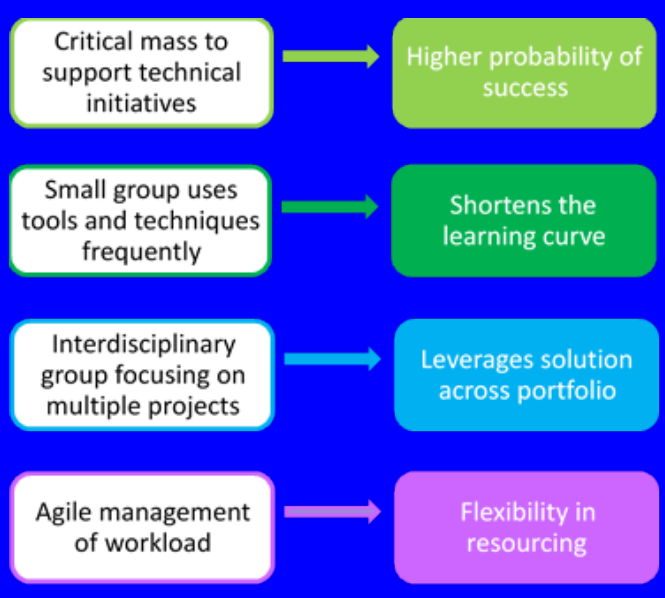

Figure B. Key benefits of CoEs

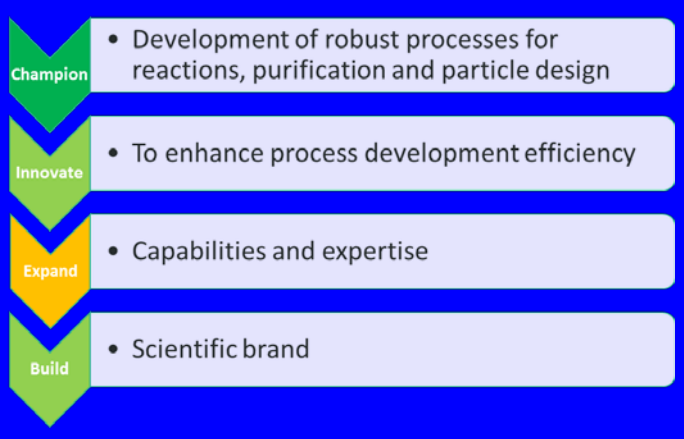

Figure C. Mission of CoEs in AbbVie

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AbbVie's Strategy Toward Efficient and Sustainable API Process Development through Centers of Excellence

Nandkishor K. Nere
Head, Center of Excellence for Isolation and Separation Technologies (CoExIST) and Cross-functional Modeling Forum (CMF)
Process Research and Development, AbbVie Inc.
e-mail: nandkishor.k.nere@abbvie.com.

Moiz Diwan
Head, Center of Excellence for Reaction Engineering (CRE)
Process Research and Development, AbbVie Inc.
e-mail: moiz.diwan@abbvie.com

Traditionally chemical engineers have contributed to various aspects of API process development from early stage to commercialization. Due to limited engineering resources in conjunction with large demand for their input, engineers have been stretched thin across multiple physico-chemical transformations involved in API manufacture. Operating models of chemical engineering groups in pharmaceutical industry have evolved to a 'unit operation/process' based laboratory. This focused operating model has been found to be more efficient than a general engineering model where one chemical engineer is engaged in developing multiple unit operations and/or processes. In our assessment, the general engineering model falls short in consistent application of the best practices, tools and technologies. Moreover, the focused operating model provides career growth opportunities by developing in-depth scientific expertise. To cater to these needs, AbbVie has institutionalized two key engineering Centers of Excellence (CoEs) within the Process Research and Development organization. This article will provide a snippet of the motivation for the CoEs and the impact made by this efficient operating model at AbbVie within a short span of time.

Motivation for COEs & Mission

Growing number of compounds in the pipeline coupled with the need for accelerated product development warrant efficient and non-iterative development approaches. With some therapeutic areas that require shorter clinical studies, there is limited opportunity to generate in-depth process understanding through multiple API development batches at large scale. This challenge is compounded by increased regulatory expectations regarding enhanced process understanding for the assurance of product quality.

Development of robust commercial processes requires cross-functional expertise. For example, robust reaction process design needs input from

- Chemists in terms of reaction mechanism and impurity identification.
- Chemical engineers for reaction kinetics and scale-up considerations.
- Both chemical engineers and chemists for innovative solutions to enable traditionally-challenging synthetic routes by using specialized reactor designs such as flow reactors.

Similarly, design of robust crystallization, filtration and drying processes is benefitted by:

- Solid state chemists in terms of the understanding of crystal form landscape and materials characterization.
- Chemical engineers through the understanding of crystallization/drying kinetics and scale-up.
- Solid state chemists and chemical engineers to innovate and develop enabling technologies.

Development of reaction, purification and particle design solutions also requires appropriate online and offline data generation and analysis via process analytical technology (PAT) and/or other analytical methods. With these considerations in mind, we have established two CoEs: one CoE for chemical reaction engineering (CRE) to cater the needs pertinent to reaction process development, and another CoE for Isolation and Separation Technologies (CoExIST) to serve objectives related to purification and particle design. While CRE has SMEs from chemistry, engineering and PAT, the CoExIST has SMEs from engineering, solid state chemistry and PAT.

The membership of these CoEs is meant to be on a rotational basis to train scientists and engineers so that when the SMEs return to their original group, they can apply their expertise to a wide range of API projects including early stage ones. Key drivers for CoEs in AbbVie include advancing more candidate molecules into clinical development with high quality robust processes, and developing and retaining key talent. Figure A. summarizes the key drivers while Figure B. illustrates key benefits of CoEs.

Figure C. depicts the mission statement for these CoEs through four underlying objectives of championing process design, process development and optimization through innovative approaches, enabling technologies, and continuous expansion of capabilities and skill sets while building a strong scientific brand for developing, attracting and retaining key talent.

Core deliverables and operating model

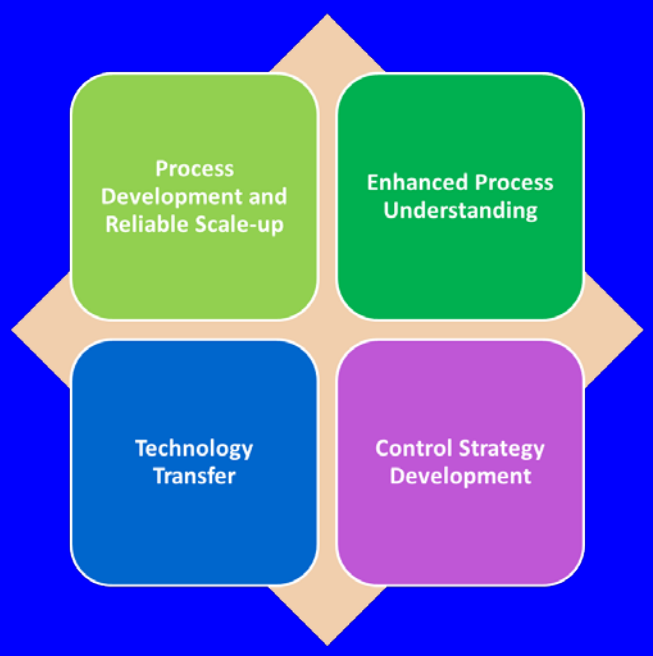
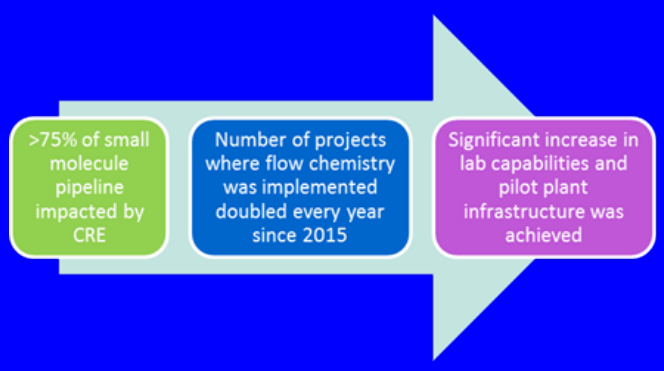


Figure D. Areas of impact of CoEs



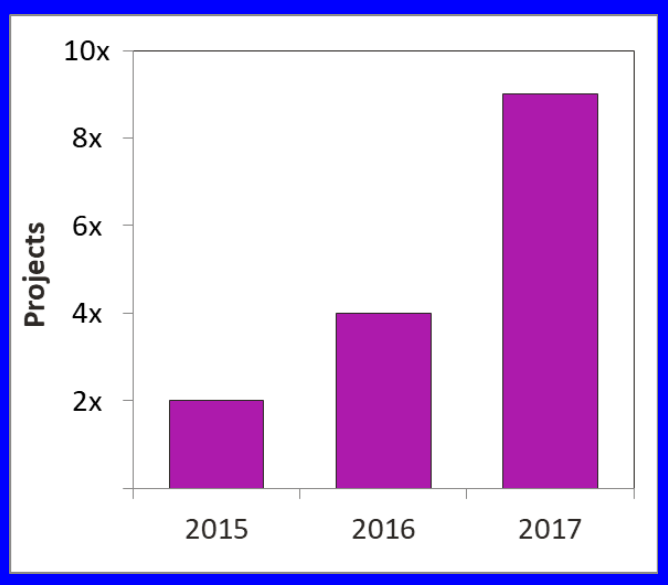


Figure E. Increasing pipeline project impact by CoEs.

Acknowledgements

This study was sponsored by AbbVie Inc. AbbVie contributed to the design, research, financial support and interpretation of data, writing, reviewing, and approving the presentation. Nandkishor K. Nere and Moiz Diwan are employees of AbbVie Inc. Authors would like to thank Shailendra Bordawekar for his vision to establish these CoEs and the critical review of this article. We also thank Samrat Mukherjee for the detailed review of the article. Authors are indebted to Ahmad Sheikh, Seble Wagaw, Wayne Pritts and Shuhong Zhang for their candid support to make these centers of excellence truly cross-functional and productive. A ton of thanks to our team members: Moussa Boukerche, Jie Chen, Steven Doherty, Travis Dunn, John Gartner, Matthew Graaf, Bradley Greiner, Kaid Harper, Manish Kelkar, Eric Moschetta, Darshan Patel, Daniel Pohlman, Pankaj Shah, Kushal Sinha, Michael Tudesco, and Anuj Verma for their instrumental contributions to our CoEs.

AbbVie's CoEs serve the core API project needs while allowing for enabling technology development. This obviously sets a stage for sustainable impact. At the heart of their mission is project ownership which requires them to deliver process solutions for reaction and purification and/or particle design problems. Prioritization of center resources is critical to ensure focus on resolving critical project needs in timely manner. While more hands-on involvement is warranted in high impact areas, the CoEs provide consultation and a platform for brainstorming to come up with a fit-for-purpose solution in collaboration with other scientists and engineers. For example, CoExIST is accountable for developing and delivering commercial processes for crystallization, filtration and drying processes with enhanced process understanding for all small molecule APIs. It is also responsible for collaborating with the technical operations group to support scale-up and troubleshooting of early stage processes. Figure D. shows core impact areas of our CoEs. The center's expectations and core deliverables are defined as follows:

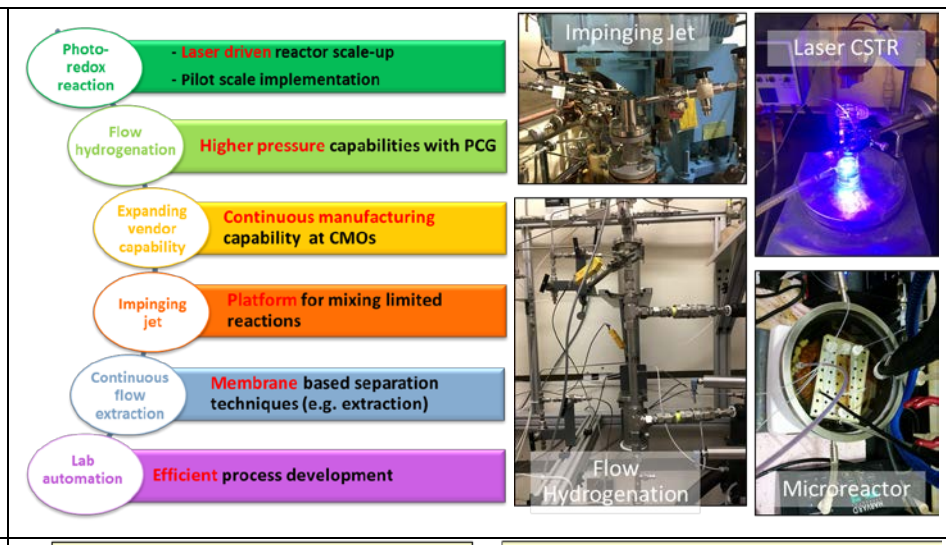
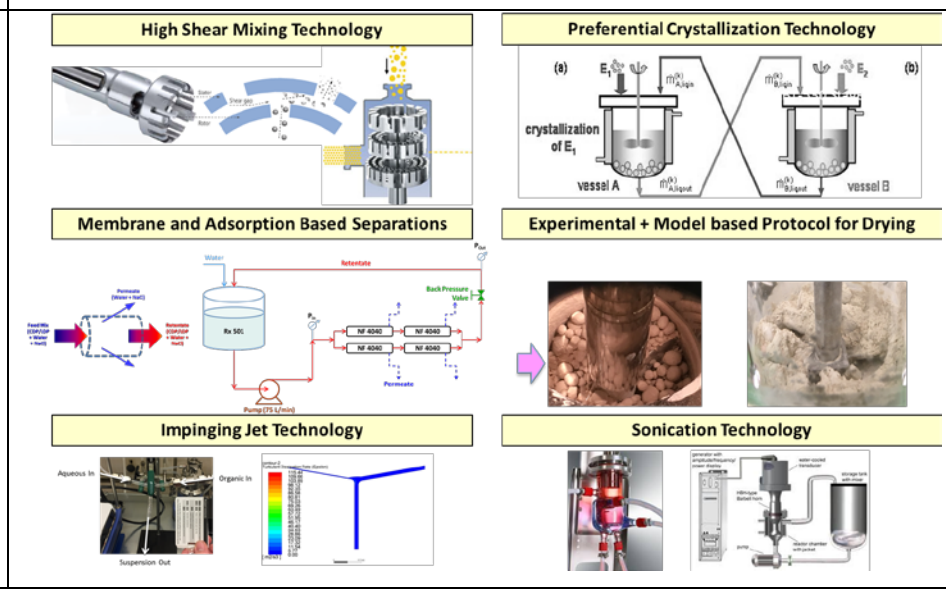
- Develop and demonstrate processes at scale. Support the scale-up and tech transfer of processes to appropriate clinical and commercial manufacturing sites in collaboration with technical operations group.
- Provide appropriate support to define commercial control strategy and author process characterization document in collaboration with API project teams.
- While serving the core project needs, proactively develop efficient workflows, guidance protocols and enabling technologies to further the efficiency of process development. Anticipate future needs and invest appropriately to be ready for future opportunities.
- Publish and present novel applications and case studies internally and externally to promote best practices and build a strong scientific brand for AbbVie.

CoE team members act as extended resources of API project teams and work in close collaboration with all the relevant functions. Members of CoExIST play an important role at the interface of API and drug product in defining the control strategy for drug substance physical properties.

The members of CoEs are required to rotate across CoEs and project teams to gain depth in scientific areas and breadth in project experience, which is essential for well-rounded career development.

Figure E. demonstrates a significant increase in the number of projects that were tangibly impacted by CoEs. More than 75% of the small molecule pipeline was positively impacted by the CoEs since their inception. Table 1 lists some of the enabling technologies demonstrated for commercial process development.

Table 1. Enabling technologies demonstrated for commercial process development by our CoEs

CRE	
CoExIST	

Summary

While the CoEs have made a significant business impact not only in terms of delivering API project solutions in a timely and efficient manner, but also in terms of talent development, there are still opportunities for continuous improvement. We welcome comments and suggestions from colleagues across the biopharmaceutical community on this topic. Further discussion and debate through precompetitive collaborations would help in refining the modus operandi of CoEs to leverage their potential to the fullest extent and take them the next level for sustainable impact.

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