April 2014

The PD2M Pipeline

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Why a PD2M Newsletter?

Shekhar Viswanath

What is PD2M?

The Pharmaceutical Discovery, Development and Manufacturing Forum (PD2M) formed in 2013 is comprised of scientists and engineers practicing in the pharmaceutical industry and in leading academic universities. The Forum was formed from Section 15b (Pharma sub-division) members who have organized Section 15b programming and the hugely popular QbD topical at AIChE National Meetings in the last few years.

Why a PD2M newsletter?

PD2M members are conducting cutting edge research in their home organizations and while AIChE National meeting has become an annual networking and knowledge-sharing venue, cost and time pressures don't allow for all PD2M members to attend every annual meeting. This necessitates the need for another communication method, the PD2M newsletter, to allow for PD2M (and AIChE) programming highlights to be shared within the membership community. Additionally, there are a significant number of consortia that members attend, and frequent regulatory guidance that are released by the FDA and other regulatory authorities which can and should be highlighted via such a newsletter. Lastly, given the rapidly changing business climate in the pharmaceutical industry, there is a growing desire to create and maintain a sustainable shared repository wherein non-proprietary process product development and manufacturing techniques and data can be shared and perfected rather than the historical go-it-alone strategies. The PD2M Newsletter can be a very useful vehicle to present updates on such common repositories and increase overall PD2M expertise. In addition, there is very good precedence to such an approach in the CAST Division of AIChE where newsletters have been issued for several years.

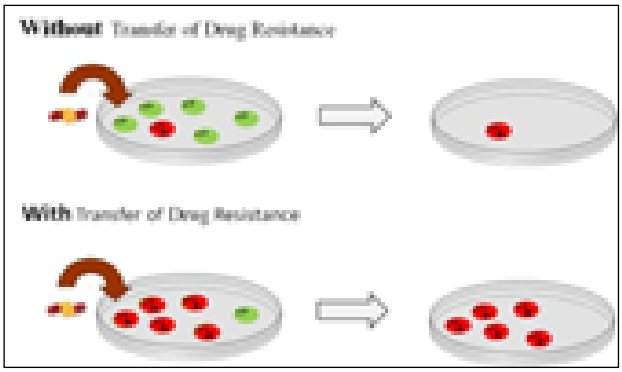
What is the Publication Frequency and Where will the Newsletter be located?

The newsletter will be published every 6 months (in March and September), and will be housed at http://www.aiche.org/community/divisions-forums/pd2m

Discovery

"Research on Transfer of Antibiotics Resistance Among Bacterial Species" - Doraiswami Ramkrishna

Diseases such as Endocarditis (inflammation of the heart's inner layer) have become life-threatening because of the resistance of infecting bacteria to a wide variety of antibiotics. The human gut hosts microorganisms that have become multi-drug resistant (MDR)



"superbugs" because of prolonged exposure to antibiotics. This is particularly true of bacteria in hospital environments. Such MDR bacteria are capable of transferring their resistance to other bacteria through a process known as conjugation. The understanding of this phenomenon is crucial to the development of new drugs that can be successfully used in the treatment of diseases such as Endocarditis. The transfer of drug resistance occurs from drug-resistant "donors" (shown in red in the adjoining figure) to non-drug-resistant "recipients" (green) while the donor and the recipient are in a state of conjugation. Conjugation is enabled through the synthesis of a protein (which acts as an aggregating substance) by the donor cell in response to a signaling molecule (pheromone) secreted by the recipient cell. Conjugation is resisted by the production of an inhibitor molecule by the donor. Depending on the relative amounts of inhibitor and pheromone, the donor would be either ready or not ready to transfer its drug resistance to the recipient.

In a collaborative program driven by Professors Wei-Shou Hu and Gary Dunny of the University of Minnesota, the author has been involved with modeling of the foregoing phenomenon observed in Enterococcus faecalis (1-3). The bistability behavior of the single donor cell has been modeled to secure understanding of how gene induction occurs in donor cells when exposed to externally controlled pheromone and inhibitor concentrations. Investigation of growth in a biofilm environment, using population balances (4) shows the importance of stochasticity in such systems and the possibility of the commonly used deterministic models being flawed. In continuing work, the dynamics of donors and recipients will be investigated in more realistic scenarios to examine how drug resistance is transferred to recipient cells. Such models have the potential to assist in the development of strategies for preventing the transfer of drug resistance in applications to control of diseases.

1. Chatterjee A, Johnson CM, Shu C-C, Kaznessis YN, Ramkrishna D, et al. 2011. Convergent transcription confers a bistable switch in Enterococcus faecalis conjugation. Proceedings of the National Academy of Sciences 108:9721-6

2. Chatterjee A, Cook LC, Shu C-C, Chen Y, Manias DA, et al. 2013. Antagonistic self-sensing and mate-sensing signaling controls antibiotic-resistance transfer. Proceedings of the National Academy of Sciences 110:7086-90

3. Shu C-C, Chatterjee A, Hu W-S, Ramkrishna D. 2012. Modeling of gene regulatory processes by population-mediated signaling: New applications of population balances. Chemical engineering science 70:188-99

4. Shu C-C, Chatterjee A, Hu W-S, Ramkrishna D. 2013. Role of Intracellular Stochasticity in Biofilm Growth. Insights from Population Balance Modeling. PloS one 8:e79196

Regulatory Update

John Lepore, Kevin Seibert, Tim Watson

Welcome to the first issue of the PD2M newsletter. We are very excited about this opportunity to participate in an ongoing communication serving members of PD2M. On an ongoing basis, we will be providing updates on hot topics and new releases of information relevant to those that are either involved with or interested in regulatory topics including: Quality by Design, news releases from the various global regulatory agencies, progress on new guidances, opportunities for upcoming seminars and conferences, and opportunities to engage in others with an interest in the process of receiving regulatory approval for pharmaceutical compounds.

We strongly encourage anyone with an interest in providing analysis or opinion on various regulatory topics to contact the PD2M newsletter staff with suggestions as well as submissions for inclusion into upcoming newsletters.

This month we would like to highlight some recent communications from both the EMA and FDA on topics relevant to Quality by Design.

In August, 2013, the FDA and EMA issued a lessons learnt document reflecting on the pilot program for performing parallel assessments by the two agencies. The objective of the parallel assessments were to ensure consistent implementation of the ICH guidances Q8, 9, 10, and 11 by both regions. Several questions regarding expectations of the agencies, CQAs, levels of criticality, and manufacturing descriptions were addressed in the document. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148215.pdf

In October of 2013, the FDA and EMA jointly issued a Q&A specifically on the topic of Design Space Verification. Several specific topics were highlighted including how is the design space initially developed, what is the interpretation of the design space at full scale, what is verification of the design space over the product's lifecycle, and how to address the verification of the design space in the initial submission. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500153784.pdf

In addition to this document release, one recent publication also addressed some of the same concerns with a discussion of a case study relevant to design space verification.[1]

Lastly, we'd like to highlight a recent communication on behalf of the FDA, a summary of Janet Woodcock's presentation to an FDA subcommittee in December 2013 titled, "FDA Check Up: Drug Development and Manufacturing Challenges". This testimony discussed some of the highlights of the US drug manufacturing sector, with some discussion around foreign sourcing and potential vulnerabilities. She also discussed observations relative to the QbD initiative and the standardization that is being observed in drug development. http://www.fda.gov/NewsEvents/Testimony/ucm378343.htm

[1] Watson et al., A Design Space Verification Protocol for a Small Molecule Drug Substance, J Pharm Innov (2013) 8:67–71.

Green Chemistry

David Leahy

The pharmaceutical industry has long recognized green chemistry as an excellent vehicle to advance its sustainability goals in an environmentally, socially and economically responsible fashion. In a collaborative spirit, a number of pharma companies partnered with the American Chemical Society Green Chemistry Institute (ACS GCI) to form the ACS GCI Pharmaceutical Roundtable. Established in 2005, it currently has fifteen member companies representing a diverse cross section of the global pharmaceutical industry, focusing on four strategic priorities:

* Inform and influence the research agenda
* Develop tools for innovation
* Provide education resources
* Enable global collaboration

By far, solvents are the largest contributors to pharmaceutical process related waste and emissions. An ACS GCI Pharmaceutical Roundtable benchmarking study revealed that organic solvent and water account for ~90% of the total mass of material used in typical pharmaceutical manufacturing processes.

Hence, one of the largest environmental impacts that can be made early on in a drug's development lifecycle is selection of as green a solvent system as possible from the outset of development. In an effort to provide tools to drive green decisions during development, members of the ACS GCI Pharmaceutical Roundtable have recently published the first collaboratively developed solvent selection guide. This guide groups solvents into chemical classes and ranks their hazards with respect to safety, health, and the environment.

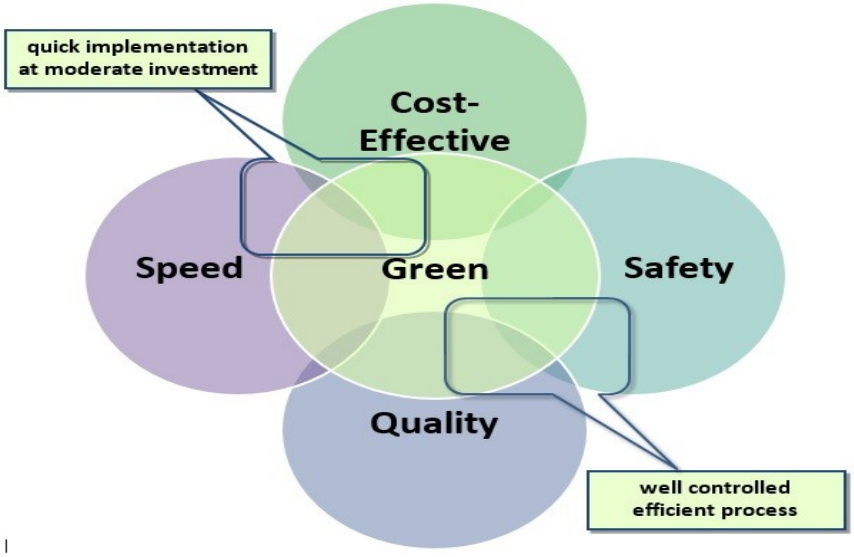


Figure 1: Overlapping drivers to implement continuous processing.

The same benchmarking study concluded that the mean process mass intensity (PMI) of the processes in the study was 120 kg/kg, meaning 120 kg of raw materials were used to manufacture 1 kg of API. In order to provide scientists with an easy tool to assess the PMI of a process, with the ultimate goal of improvement, the Roundtable also developed a PMI calculator. This Excel spreadsheet with embedded calculations requires only basic and readily available information to calculate PMI for linear sequences. Both of these powerful tools are universally available to the public free of charge at www.acs.org/gcipharmaroundtable.

The ACS GCI Pharmaceutical Roundtable has identified continuous processing as a top priority. In order to help promote and facilitate its widespread adoption throughout the pharmaceutical industry, the Roundtable critically evaluated the business drivers for implementation of continuous processes among its member companies. The four most frequent drivers identified are safe handling of unstable materials, speed of implementation, savings in investment and "right the first time" performance. Each of these drivers has considerable synergies with green chemistry and sustainability (see Figure 1).

For more information, or to collaborate with, or join the ACS GCI Pharmaceutical Roundtable, please contact Julie Manley at j_manley@acs.org

Continuous Processing

Martin Johnson

The purpose of this newsletter is to highlight recent publications and technology advances for continuous processing in the pharmaceutical industry. Please suggest topics and make contributions for future newsletters.

The pharmaceutical industry has long been dominated by batch processing. Why might a manufacturing site choose to run a reaction, separations unit operation, or complete synthetic route continuous rather than batch?

First, a manufacturing site might choose to run a reaction continuous if this achieves: (1) better yield and selectivity for fast reactions in series with unstable intermediates, or for reactions that benefit from all-at-once stoichiometric addition of multiple reagents, (2) better safety for reactions that are highly exothermic, use hazardous reagents with diazo, azo, azide, hydrazo, nitro, or peroxide functional groups, hazardous gas reagents at high pressures, neat, or if there are safety advantages of no headspace (3) wider operating windows for reactions at extreme temperatures less than -20 °C or superheated far above solvent boiling point and extreme pressures. Examples of all of these can be found in recent review papers by Volker Hessel (Hessel et al 2013) and Neal Anderson (Anderson 2012).

Second, a manufacturing site might choose to run an entire multistep process including drug substance and drug product fully continuous to enable on-demand drug production, reduce inventories, and drastically decrease plant footprint. It also affords the opportunity to integrate drug substance and drug product which enables adding excipients or glidants (e.g. SiO2) upstream of drying which can improve the formulation process. A recent Novartis/MIT paper reports a fully continuous end to end manufacturing train of a pharmaceutical, from advanced starting materials to formulated drug product (Mascia et al 2013). One of the important roles of chemical engineers is automation and control of fully continuous processes, for example see the Novartis/MIT paper and references therein by the Barton group.

Third, a manufacturing site might choose to run a separations unit operation continuous if it achieves: (1) higher yield, for example if multistage countercurrent results in less product going to waste stream, or by using centrifugal extraction or short path distillation if the product is unstable to workup conditions, (2) less waste or more efficient processing, for example continuous multistage distillation or extraction, or fixed bed adsorption, (3) steady state control and consistency, for example continuous crystallization and drying, (4) throughput advantages and debottlenecking. There are not as many literature examples of continuous separations compared to continuous reaction, but several are highlighted in the Novartis/MIT paper including extraction, crystallization, filtration, and drying. The number of continuous crystallization examples in the literature is rapidly increasing for pharmaceutical compounds. For example see the Novartis/MIT paper and references therein for the design and development advancements of the Myerson group.

One common misconception is that continuous reactions must have very fast kinetics. The Anderson review highlights several published examples of flow chemistries with mean residence times greater than 1 hour. In addition, the solvent-free aminolysis reaction developed by the Jamison and Jensen groups and documented in the Novartis/MIT paper had 4 hour mean residence time in the flow tube. Furthermore, in order to enable a high percentage of pharmaceutically relevant reactions to run continuous, engineering technologies must be developed for solids in flow. One recent example of feeding solids to a continuous reactor is a continuous Grignard alkylation, scaled up to a Lundbeck pharmaceutical manufacturing facility in Denmark (Pedersen 2013). Also, see the Novartis/MIT paper and its references for the development by the Jensen and Jamison groups of continuous Boc deprotection reaction with solids precipitates.

This newsletter update focuses on continuous operations on the drug substance side. Continuous drug product will be the focus of a future newsletter highlights.

- Anderson, N. G. Org. Process Res. Dev. 2012, 16, 852.
- Hessel, V.; Kralisch,D.; Kockmann,N.; Noel, T.; Wang, Q. ChemSusChem 2013, 6, 746-789.
- Mascia, S.; Heider, P. L.; Zhang, H.; Lakerveld, R.; Benyahia, B.; Barton, P. I.; Braatz, R. D.; Cooney, C.L.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F.; Myerson, A. S.; Trout, B.L., Angew. Chem. Int. Ed. 2013, DOI: 10.1002/anie.201305429.
- Pedersen, M.J.; Holm, T.L.; Rahbek, J.P.; Skovby, T.; Mealy, M.J.; Dam-Johansen, K.; Kiil, S.; Org. Process Res. Dev., 2013, 17 (9), pp 1142–1148.

Modeling and Simulation

"Putting the Fun in Fundamental" - Joe Hannon

A sideways look at some recent papers in chemical engineering of interest to the PD2M community, from the DynoChem team at Scale-up Systems. In this edition, we focus on process modeling and continuous processing.

Many of us have heard that 'if you're not part of the solution, you're part of the precipitate"; some have even bought the t-shirt[1]. We were reminded of this while reading the recent flow chemistry review[2] by Klaus Jensen and colleagues, which tells us that 'if you can stand the heat, get out of the flask'.

This is a useful review and if you are working to persuade your chemist colleagues to take a look at continuous reactions, the list of chemistries that benefited in Table 2 of the paper may provide useful material for you. Table 3 lists examples where enhanced heat transfer benefitted several chemistries and Figure 10 provides a decision tree that may be helpful for you. The modeling component includes references to classical treatments of continuous reactors as well as evaluation of fluid mixing times in tubes and tanks.

We never shirk from quoting Shakespeare when the opportunity presents itself. It was a pleasure then to come across a similarly focused essay[3] named 'The Flow's the Thing, Or Is it?' in the same journal from the previous year, by Donna Blackmond and several co-workers then based in the UK. This review confines itself to homogeneous reactions and again contains interesting chemical examples and a flow chart for decision support based on classical models of reactor systems.

Research and development in Ireland plays a growing role in this field and we have some seen some fine at-scale implementations of continuous reactions in API synthesis recently, including one by Lilly at Kinsale and presented at AIChE 2013[4]. The SSPC cluster[5] will continue research in this area that connects academics working in both chemistry and chemical engineering with companies looking to free up their long batch based supply chains and find better ways to make smaller quantities of products more locally and flexibly. Andrew Rutter of GSK gave a fine talk on this topic at a recent conference organized by SSPC[6] and much of his presentation content may be found on the web here.

That meeting also featured great talks from Steve Ley's group[7] in Cambridge, where multi-disciplinary collaboration leads to multi-step synthesis of complex organic chemicals at continuous production scales relevant to today's new chemical entities. We particularly liked the innovative use of cameras and open source tools like Python to increase automation. A nice review of this work was published recently[8] in the Belistein Journal.

We are in the modeling business and of course modeling plays a significant role in design for continuous processing. Modeling helps batch data to be used to design continuous processes and vice versa when appropriate. Modeling allows us to explore regions and change parameters that are difficult to access experimentally. The most powerful combination is model-based process development, using experiments and modeling hand-in-hand.

In a recent article connecting many of the above concepts[9], Mike Doherty, Chris Burcham and Thomas Vetter calculated the regions of attainable particle size in continuous and batch crystallizers.

They calculated the conditions leading to a given particle size, subject to constraints on yield and inputs such as temperature and anti-solvent amounts, producing for three different systems with known solubility and kinetics, contour maps guiding towards the set of conditions in which a given size could be achieved. This powerful application of modeling yielded results that would be impossible to generate using experiments alone and is timely and impactful given the current high level of industrial, regulatory and academic interest in continuous processing.

Hyperlinks:

[1] http://www.neatoshop.com/product/if-youre-not-part-of-the-solution

[2] http://onlinelibrary.wiley.com/doi/10.1002/anie.201004637/abstract

[3] http://onlinelibrary.wiley.com/doi/10.1002/anie.200906095/abstract

[4] http://www3.aiche.org/proceedings/content/Annual-2013/extended-abstracts/P337362.pdf

[5] http://www.ul.ie/sspc/

[6] http://www.ul.ie/sspc/content/1st-sspc-continuous-processing-workshop-factory-future

[7] http://www.leygroup.ch.cam.ac.uk/

[8] http://www.beilstein-journals.org/bjoc/single/articleFullText.htm?publicId=1860-5397-9-118

[9] http://www.sciencedirect.com/science/article/pii/S0009250913007379

Manufacturing

"The Value Proposition of PAT in Pharmaceutical Manufacturing"

Daniel Hallow

Process Analytical Technology (PAT) is widely used in many chemical industries to provide real-time analysis of chemical processes to increase efficiency, reduce quality risks, and improve safety. Despite broad adoption of PAT across chemical, petrochemical, and food manufacturing, the pharmaceutical sector has been considered a slow adopter of PAT. In 2004, the FDA released its PAT guidance to provide a framework for implementing PAT and to encourage innovative development of PAT in the pharmaceutical industry[1]. While adoption in research and development has seen growth over the last decade, there are still relatively few examples of PAT applications in commercial manufacturing of pharmaceuticals[2]. This trend can be rationalized analyzing the costs and benefits of PAT implementation in manufacturing[3,4].

One important value proposition for the use of PAT in manufacturing is knowledge gathering and process verification. Increased process understanding can enable continuous improvement (e.g., identifying cycle time, yield, or reagent/solvent usage improvements) or enable verification of robust process performance when changing equipment scale or configuration. However, paradoxically, it has been argued that the increased use of PAT in earlier stages of development (i.e., at the lab and pilot scale) to enable the Quality by Design (QbD) has reduced the value proposition of its use at the commercial scale. By the time the process has reached the commercial manufacturing , a high level of process understanding and robust process design has been achieve, and, therefore, may diminish the benefits of PAT in manufacturing. In terms of cost, the high initial infrastructure outlays for implementing PAT on the commercial scale poses a significant hurdle. It is important to note that PAT is a large class of tools (e.g, Near-IR, Mid-IR, Mass Spectrometry, Raman, FBRM) and each may have different equipment and support needs. These costs are further magnified due to factors and trends unique to the pharmaceutical industry. Pharmaceutical plants are increasingly multipurpose facilities, producing several small volume products produced on an infrequent basis. Pharmaceutical manufacturing facilities will need to create a flexible infrastructure to accommodate the various PAT instruments or experience significant down time for the PAT infrastructure, if it is not applicable to the process.

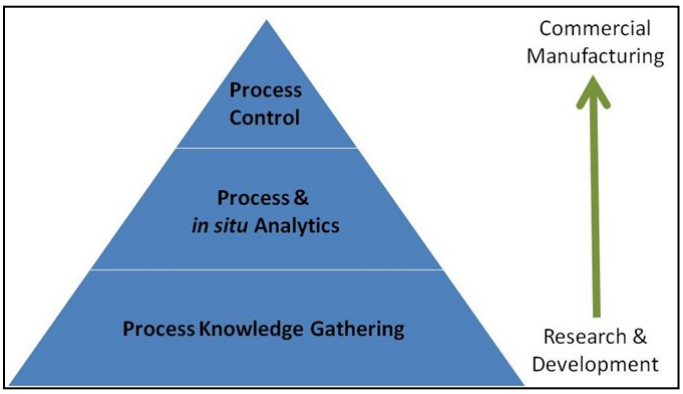


Figure 1: PAT usage across pharmaceutical development (adapted from Reid,*et al.* [2])

Another value proposition of PAT is for real-time control. Real-time control may offer significant additional value by ensuring quality (e.g., for a continuous process where the quality of the output is monitored in real time), safety (e.g., a Grignard reaction where PAT has often been used to ensure no buildup of hazardous intermediates[5]), or product performance (e.g., use of PAT to control crystallization process performance[6]). In addition, the use of PAT may offer significant benefits, such as shorter analytical times, and in some instances a superior analytical technique to traditional methods. Unfortunately, the use of PAT for in-process control also leads to significantly higher costs compared to PAT for knowledge gathering due to the need to comply with regulatory standards for hardware calibration, chemometric model validation, life-cycle model maintenance, and CFR 21 Part 11 compliant software.

In summary, the value proposition of PAT in pharmaceutical manufacturing often involves tradeoffs between the benefits and costs that have to be assessed on a case-by-case basis from a strategic and operational perspective. Ensuring a return on investment is often a key driver for manufacturing in the implementation of any new technology. As the PAT hardware and software technology advances, the regulatory landscape evolves, and expertise increases in the field, these benefits and costs will shift in a direction that is more favorable for PAT on scale. A periodic review of the value proposition is therefore prudent.

[1] www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf

[2] Process Analytical Technology (PAT) in pharmaceutical development, Reid, George L.; Ward, Howard W., II; Palm, Andrew S.; Muteki, Koji, American Pharmaceutical Review (2012), 15(4), 115453/1-115453/12.

[3] http://www.pharmamanufacturing.com/assets/wp_downloads/pdf/tunnell_pat_insider_wp.pdf

[4] PAT/NIR Roundtable, *American Pharmaceutical Review* - Volume 13, Issue 7

[5] Safety Improvement of a Grignard Reaction Using On-Line NIR Monitoring, Jacques Wiss, Markus Länzlinger, and Markus Wermuth, Org. Process Res. Dev., 2005, 9 (3), pp 365–371

[6] Process Analytical Technology: An Investment in Process Knowledge, Frank Sistare, Laurie St. Pierre Berry, and Carlos A. Mojica, Org. Process Res. Dev., 2005, 9 (3), pp 332–336

IQ Consortium Update

Ilse Peterson

The International Consortium for Innovation and Quality in Pharmaceutical Development is a not-for-profit organization of pharmaceutical and biotechnology companies with the mission of advancing science-based and scientifically-driven standards and regulations for pharmaceutical and biotechnology products worldwide.

Recent Publications and Surveys

IQ has thirty Working Groups formed and supported by its Leadership Groups that advance IQ's mission through information sharing, joint research and publication. Recently, IQ has published papers on strategies and approaches to investigation of therapeutic protein drug-drug interaction, prediction of Cytochrome P450-mediated drug interaction, and green chemistry programs. Other Working Groups such as "Best Practices in Contract Manufacturing" and "Impact of Excipient Variation on Drug Product Performance" have completed and shared comprehensive surveys within IQ member companies.

Workshops & Regulatory Engagement

IQ was invited by FDA to be the only industry partner for a May 2013 Symposium on development of microphysiological systems for use as regulatory tools. Several IQ Leadership Groups also had constructive exchanges with FDA in 2013. In June, the Clinical Pharmacology and Drug Metabolism Leadership Groups met with FDA's Office of Clinical Pharmacology to discuss model-based drug development. In July, the 3Rs Leadership Group held a workshop with FDA and CAAT (Center for Alternatives to Animal Testing) focusing on ways to enhance 3Rs in toxicology studies. IQ also sponsored two workshops, one on GMPs in Early Development and the other one on 3Rs Best Practice Sharing in February 2014.

External Collaborations

IQ has recently established strategic partnerships with the National Center for Advancing Translational Science (NCATS), International Pharmaceutical Excipients Council (IPEC), the European Pediatric Formulation Initiative (EuPFI) and Pharmaceutical Research and Manufacturers of America (PhRMA).

New Initiatives

Establishment of a database framework for the Consortium, which will provide an unparalleled infrastructure for current and future data sharing initiatives, is currently underway. Other initiatives include the aforementioned collaborations with NCATS and IPEC. IQ participants are also actively exploring several other topics and may bring them forward as additional "next-level" initiatives.

Connecting with IQ

IQ's website is an up-to-date source for information about IQ news and events. IQ also has a LinkedIn group, which is open to Consortium participants. You can contact the Consortium at info@iqconsortium.org.

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Pharmaceutical Discovery, Development, and Manufacturing Forum (PD2M)