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Perspective

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Pharmaceutical Process Chemistry: Evolution of a Contemporary Data-Rich Laboratory Environment

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ABSTRACT: Over the past 20 years, the industrial laboratory environment has gone through a major transformation in the industrial process chemistry setting. In order to discover and develop robust and efficient syntheses and processes for a pharmaceutical portfolio with growing synthetic complexity and increased regulatory expectations, the round-bottom flask and other conventional equipment familiar to a traditional organic chemistry laboratory are being replaced. The new process chemistry laboratory fosters multidisciplinary collaborations by providing a suite of tools capable of delivering deeper process understanding through mechanistic insights and detailed kinetics translating to greater predictability at scale. This transformation is essential to the field of organic synthesis in order to promote excellence in quality, safety, speed, and cost efficiency in synthesis.

INTRODUCTION

As we reflected on the laboratories we worked in during our doctorate work in the 1990s (University of California Berkeley with Clayton H. Heathcock and University of Nottingham with Gerald Pattenden), there was a striking resemblance in the environment in which we conducted organic synthesis. The typical experimental setup included a round-bottom flask (with one to four necks), a magnetic stir plate, a magnetic stir bar, and a nitrogen gas inlet. Temperature control was achieved in one of four ways: a dry ice/acetone bath for −78 °C, an ice bath for 0 °C, room temperature, or a Variac-controlled oil bath to reach elevated temperatures. Thin-layer chromatography was used as the method of choice to follow reaction progression. Realistically, our setup was very similar to that used by students who had preceded us by 30 years and is still relevant to many organic synthetic laboratories in academia today. On the basis of this setup, there is limited scope to capture knowledge and understanding of the reaction, such as rate of formation of products, impurities, mixing, cooling, etc. For example, many reactions were typically held for 12−16 h (overnight), and as a result we had little real understanding of the reaction rate and its completion.

The biggest difference between us and our predecessors was the size of the flask. While we were able to conduct several experiments on milligram scale and initiate the total synthesis of a multistep natural product with a few grams of starting materials, this was not the case for students in the Woodward era. Two of the most important reasons for this was the introduction of high-field NMR spectroscopy, which rendered the analysis and structure elucidation of products possible with just a few milligrams of products in a nondestructive fashion, and the use of flash chromatography for purification, which was possible on very small scale and with near-quantitative product recovery.[1] Mass spectrometry has also played an increasingly important role in structural determination. In his seminal total synthesis of reserpine, Woodward utilized 3.5 kg of quinine in 2 gallons of benzene in the first step of a 15-step synthesis. Furthermore, characterization of the products was achieved through a combination of UV spectroscopy, IR spectrometry, elemental analysis, and melting point determination.[2] This is something unimaginable to a contemporary graduate student.

Additionally, product purification in the reserpine synthesis was achieved through techniques such as distillation and crystallization, which are now rarely used in academic laboratories although these methods have remained incredibly important in chemical manufacturing. Unfortunately, very few students are even exposed to, much less master, the basic principles of designing a crystallization.

While we felt prepared to join the Process Chemistry Group at Pfizer, we realized that much of our training emphasized how to approach synthetic targets and execute reactions, but our education around how to develop a chemical process suitable for manufacturing was limited and would have to result from on-the-job training. While most of the emphasis in a total synthesis is placed on the number of steps and the overall yield of the longest linear sequence, these are not always good indicators of what makes a good manufacturing process. Elements such as robustness, safety, ease of isolation, reduction of unit operations, and ultimately consistent quality are far more important in a manufacturing setting. This is what largely differentiates synthetic chemistry from process chemistry and development[3,4]

In the last 20 years, the expectations of process chemistry groups in the pharmaceutical industry have radically changed due to increasing pressures to understand the factors that

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impact quality in more detail, lower cost, and increase speed of delivery.[5] Thus, there has been an adaptation of our laboratory practices to a more data-rich environment, whereby knowledge and process understanding can be gleaned from every experiment in a more efficient manner. Detailed process understanding and quality by design (QbD) have become expectations, where changes in the chemical process are understood and predictive of the active pharmaceutical ingredient (API) quality, which is ultimately linked to drug product safety and performance in patients.[6,7] In the past, demonstration of a synthesis at increasing scale built confidence in the scalability of a chemical process and ultimately quality was demonstrated by meeting final acceptance criteria. Now, QbD demands that quality is built into a process prospectively by understanding the linkage of quality to process parameters, process design and material attributes.[8] Such process understanding demands that reaction parameters are monitored in a way that cannot be achieved in a traditional round-bottom flask setup because it does not at all mirror the manufacturing principles utilized in a plant at scale.

In this Perspective, we will discuss the role of process chemists in the pharmaceutical industry and three workflows that lead to the successful preparation of a compound at scale: route selection, process development, and technology transfer and scale-up. We will discuss the techniques and equipment that can be utilized in a laboratory setting to drive data-rich experimentation, leading to enhanced process understanding and thereby maximizing the chance of success in translating a process from lab to plant for the development of small molecules.

DISCUSSION

Route Selection. Selecting the route of synthesis of a pharmaceutical candidate is one of the most fundamental activities for a process chemist, as it sets the stage for all future development activities. In early development where speed to the clinic is key and candidate attrition is significant, the emphasis is more often placed on enabling the existing synthesis, fixing problematic steps and ensuring process robustness for manufacturing at a scale of a few kilograms in a fit-for-purpose manner.[9] The first GMP lot of API produced will often fuel toxicology studies to establish the preclinical safety of the compound, qualify process-related impurities, and lead to introduction of the candidate in phase 1 clinical studies. The expectations are very different when it comes to the identification of the proposed commercial route.[5] The timing of this activity varies from company to company but is often based on a key milestone such as establishment of the proof of concept (POC), where signs of safety and efficacy are achieved for the candidate. The considerations for the selection of the commercial synthesis are mainly driven by long-term objectives such as quality assurance around achieving a consistent purity profile for the API, cost of manufacture (which often has a direct link to Green Chemistry metrics in terms of environmental performance of the process), overall throughput, and robustness of the synthesis for future manufacturing and ultimately meeting the expectations of regulatory agencies around the world. It is very important to recognize that once a synthetic process is approved by regulatory agencies, it often cannot be modified without those same agencies agreement.

The first step in selecting the proposed commercial route is to consider as many synthetic options as possible. This can be done through an exercise such as a brainstorming session, where chemists will utilize their knowledge and experience and dig out relevant literature precedents to propose multiple possible syntheses. It is prudent to include individuals from different disciplines such as chemical engineers and biochemists, who might propose alternative synthetic strategies that may not have been suggested by chemists. One could also rely on computer-assisted synthetic design (CASD) using a retrosynthetic tool that allows for a systematic search of alternatives and may identify previously unconsidered disconnections.[8] Several potential routes will often result from this activity and it would be unrealistic to evaluate all the options. Therefore, an element of route prioritization must be applied using criteria such as expected yields, cost, scalability, number of steps, etc. Once the criteria are established each route is evaluated and ranked for prioritization. For example, as part of the selection of the commercial route for the SGLT2 inhibitor ertugliflozin, we identified over 20 possible routes from eight different potential starting materials. The potential routes were ranked and ultimately prioritized for laboratory evaluation (Figure 1).[10]

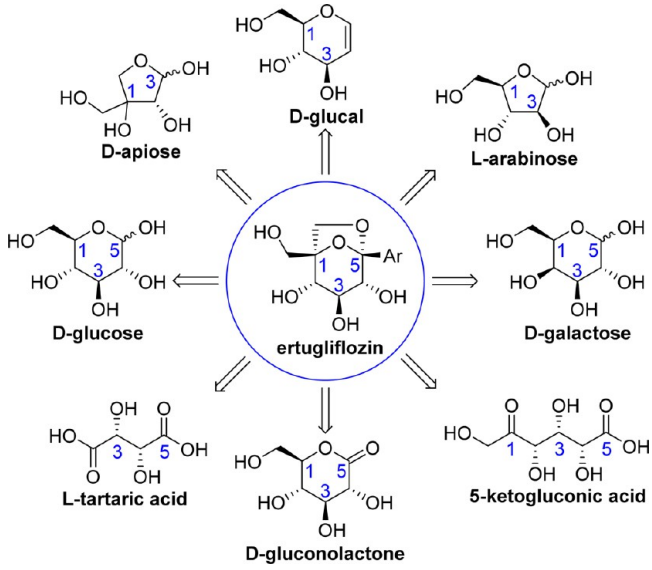

Figure 1. Potential starting materials proposed for the synthesis of ertugliflozin.

Laboratory Experimentation. As multiple potential synthetic options result from the brainstorming exercise and ranking, several routes might be evaluated in parallel. The process chemist should attempt to evaluate as quickly as possible the fundamental "kill-steps" of a proposed highly ranked route. This laboratory experimentation is often conducted at a scale similar to that at an academic setting. The objective at this point is to demonstrate technical feasibility rather than reaction optimization. Rapid reaction screening is often utilized at this stage to assess if a proposed transformation is feasible. Since quantities of materials might be a limiting factor, the ability to evaluate multiple reactions on a few grams of a single substrate and find potential hits that will require further evaluation is very important. If a decision is made that a synthetic route is not technically sound, it should be derived from conclusive evidence that a transformation cannot be achieved. Such evidence will most reliably arise from a broad assessment of conditions rather than a single experiment.

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Reaction screening can be conducted on a range of equipment.[11] High-throughput, parallel reaction screening equipment can support the assessment of hundreds of reactions with a few grams of material and is often operated by a specialist group. Such equipment has the ability to automate solids and liquids handling, cover a range of temperatures, and can be operated within a glovebox to ensure reliability of air- and moisture-sensitive chemistries. Typically, the workflow for a range of chemistries, such as amide bond formation or cross-coupling methodology, is well-defined, and reagents are "templated" into vials ahead of time to allow for rapid screening (Figure 2).

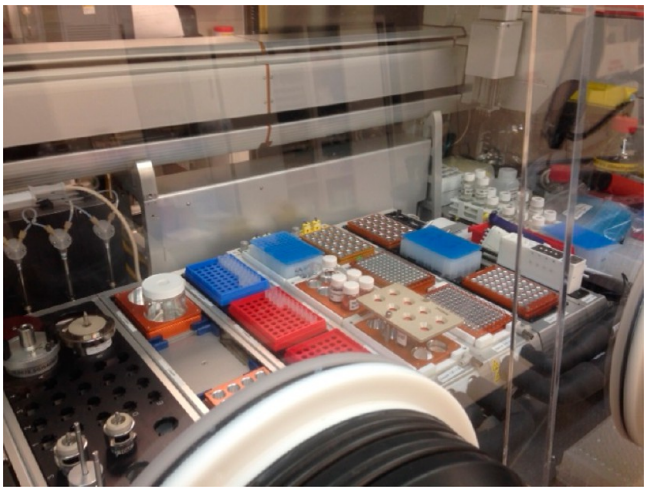

Figure 2. Representative high-throuput parallel screening platform.

Alternatively, a number of standard laboratory reaction screening blocks are commercially available for narrower screens, or a chemist may choose a low tech-vial approach. Regardless of the reaction screening equipment, a rapid and reliable analytical method such as high (or ultra)-pressure high-performance liquid chromatography (HPLC or UPLC) is incredibly valuable, especially when coupled with mass spectrometry detection of the desired product. When there are many variable parameters, such as solvent, base, catalyst, or other additives, a medium- or high-throughput reaction screen is preferable. In the development of a Sonogashira reaction with propyne, identification of the lead reaction conditions was rapidly achieved through a few screens. As indicated in Figure 3, the choice of solvent and base for the reaction was very important and would not have been trivial to predict.[12]

As knowledge of the synthetic target increases, other synthetic options might present themselves. One of the challenges for process chemists is to keep in mind the criteria set in place as part of the route ranking. Ultimately, any emerging synthetic route should be reassessed against the alternative options by using the original criteria and assumptions to ensure selection of the best path forward.

As multiple synthetic routes are evaluated, it becomes important to gain knowledge about each reaction even without carrying out a deep optimization. If a particular step is demonstrated as feasible but proceeding in a low yield, the chemist must evaluate the probability of achieving a high yield for this transformation which can be done in a number of different ways. Usually, characterization of reaction side products can lead to mechanistic insight and to modifications of the process.

Flash chromatography remains an important tool to isolate products and byproducts at this stage of development,[13] although the use of autopurification equipment, potentially mass directed, can greatly accelerate activities and save time. Other specialist separation sciences, such as reversed-phase preparative chromatography or supercritical fluid chromatography, might be employed for certain challenging substrates.

During the development of a smoothened receptor (SMO) inhibitor at Pfizer, it had been proposed that a chiral amine could be accessed diastereoselectively using a transamination reaction. Both enantiomers of the starting material were obtained using chiral chromatography. As the key transamination reaction was evaluated, it was recognized that each enantiomer led to the same final product and that epimerization through a retro-Michael mechanism occurred during the biocatalytic step, resulting in a dynamic kinetic transamination. While this result had not been anticipated, the ease of accessing each enantiomer and the power of the analytical tools available to follow the reaction allowed for a superior solution to access chirality at two stereocenters in a single step (Figure 4).[14]

Process analytical technology (PAT) can also serve an important role toward process understanding.[15,16] Early in the development cycle, PAT offers an opportunity to see what is happening in real time in a reaction and provide the opportunity to observe intermediates that would not be captured with an off-line chromatographic technique. In the synthesis of a factor Xa inhibitor, a mixed anhydride with poor stability was prepared as the activated species in an amide formation. While offline chromatography methods provided unreliable results, the use of in situ FTIR allowed for accurate assessment of the activation of the carboxylic acid and conversion of the intermediate to the desired amide (Figure 5).[17]

During process optimization, PAT can be used to further understand a reaction and monitor multiple parameters, often generating a strong kinetic and mechanistic understanding. Ultimately, PAT can be used in a commercial manufacturing operation to either avoid off-line testing or as part of a feedback-controlled process (Figure 6). The description of multiple PAT techniques will be elaborated later in this document.

The introduction to the process chemistry toolkit of auto sampling capability can allow a reaction to progress while collecting and quenching fractions at predetermined time points and utilize the dynamic range of LC for analysis. Thus, the chemist can glean an understanding of how fast the product formed, starting materials were consumed or impurities were formed, providing enhanced kinetic and mechanistic understanding. As shown in Figure 7, the autosampler can easily be included in a common reaction setup.

Defining the Proposed Regulatory Strategy. The commercial route of an API can be described in three stages; raw materials/commodities, the regulatory starting materials (RSMs) and the synthesis of the API.

The raw materials/commodities are simple synthetic building blocks produced on large scale, usually by several suppliers, for multiple chemical industries. Details about the synthetic process for the manufacturing of these compounds are sometimes not shared, and different producers might operate different technology for their production. It is usually preferable

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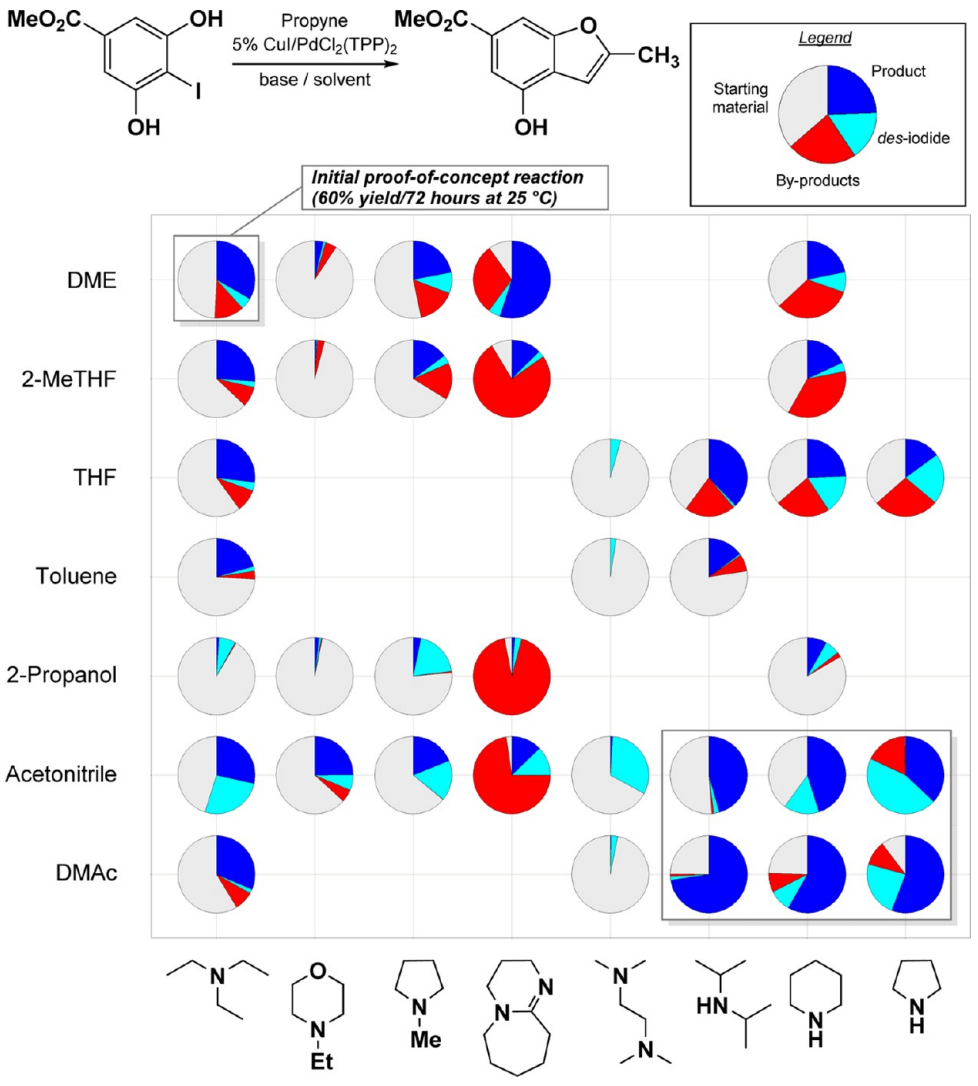

Figure 3. Screening results for a benzofuran synthesis.

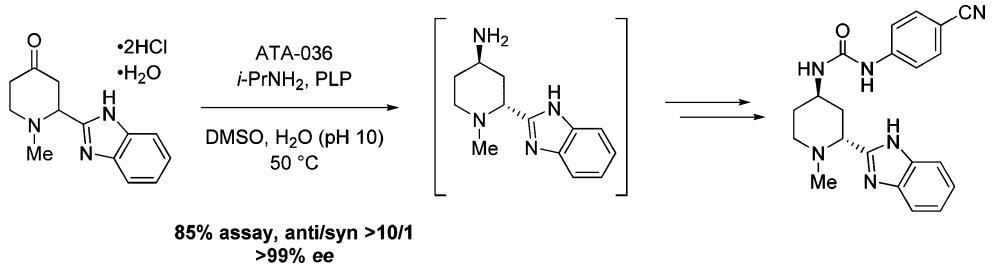

Figure 4. Dynamic–kinetic transamination reaction.

to design these materials early in the synthetic process of a pharmaceutical product.

The RSMs are synthetic intermediates that are agreed to by regulatory agencies and are often defined as the starting point for manufacturing under good manufacturing practice (GMP). The selection of a RSM should first and foremost be defined on the basis of the control strategy impacting the final quality of the API. For example, impurities in the RSM are preferably not the source of impurities in the API. The synthesis of the RSM is typically well understood, and the material tested with an appropriate analytical method. Ultimately, it is the responsibility of the pharmaceutical company to prove that a proposed RSM is aligned with the API control strategy and this selection is agreed to by regulatory agencies. Unfortunately, this is often a contentious issue. As part of the route scouting, comparing synthetic routes with the understanding of what could be an adequate quality control point and an appropriate RSM is important.

The regulatory synthesis contains a number of regulatory commitments and is conducted according to GMP. This is the part of the synthesis that is highly developed and has the most process understanding. When designing the commercial route, a highly convergent synthesis that brings multiple commodities together late in the synthesis might not be attractive, as control

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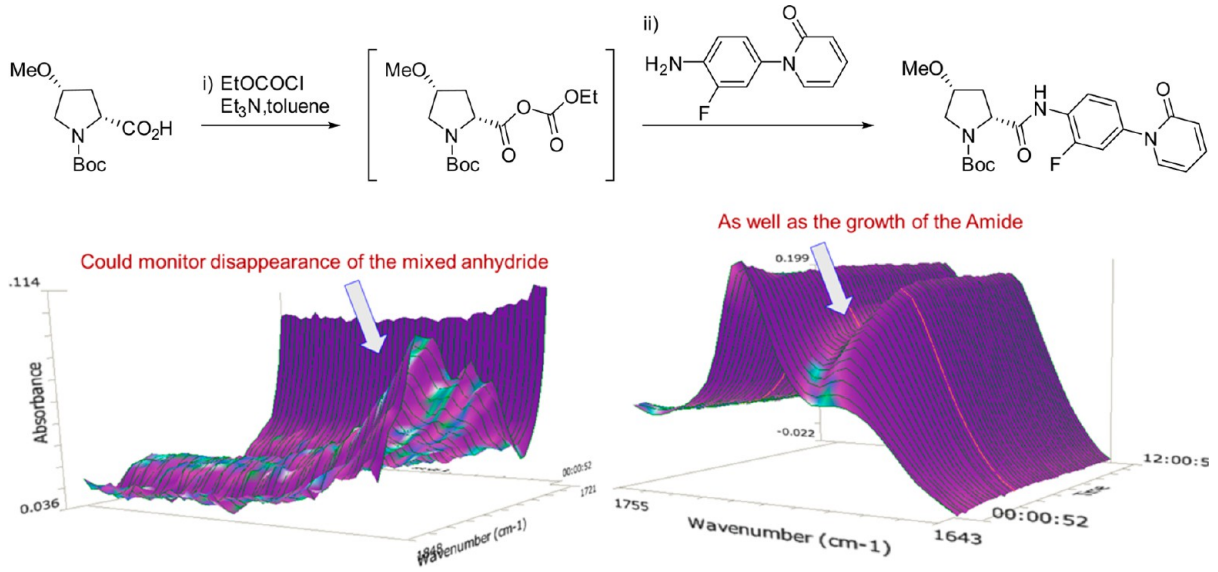

Figure 5. FTIR monitoring for an amidation.

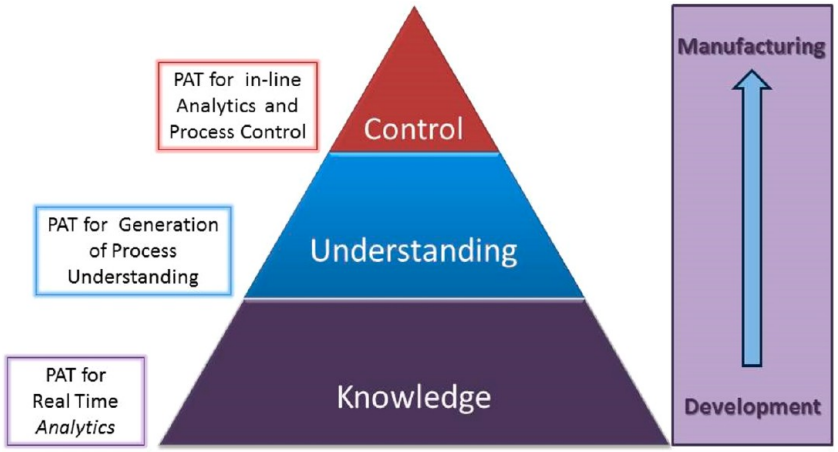

Figure 6. Potential applications of PAT.

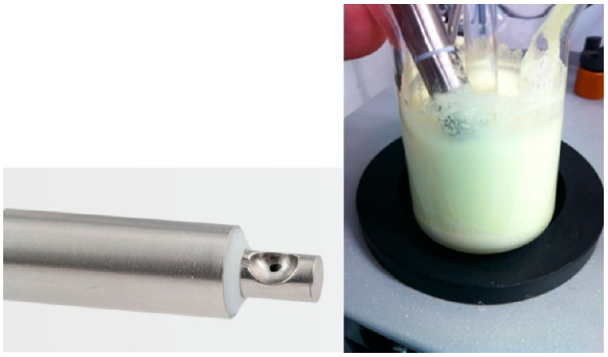

Figure 7. Autosampler that is introduced in the reaction vessel.

of the quality of the commodities might be difficult. Additionally, avoiding intermediates and reagents that are known to be potentially genotoxic late in the synthesis is important, as they will require additional measures for quality control and stricter specifications.[18] As part of the route scouting, experimental work will be conducted to ensure that the synthetic intermediates identified as part of the regulatory synthesis have good physical properties and provide opportunities for purification. This requires more detailed experimentation later in development. Nevertheless, selection of synthetic intermediates, choice of protecting groups and the order of the synthetic steps are established at this early phase. Therefore, the process chemist must judge not only if the route is viable at this point but also its potential for future process optimization. As potential synthetic steps are being evaluated, understanding where impurities are created is important, as it can lead to changing the order of the steps and avoiding a problematic side product. For example, in the synthesis of the vascular endothelial growth factor receptor (VEGR) inhibitor axitinib two strategies were considered to introduce a thioether through a Migita coupling and an alkene using a Heck reaction. While both strategies where demonstrated, introduction of the alkene early in the synthesis led to degradation products originating from olefin isomerization. Early identification of these side products provided evidence that it was preferable to introduce the olefin late in the synthesis (Figure 8).[19]

Definition of the API Final Form. Much attention in a regulatory synthesis is ultimately given to the final crystallization step, as it produces the API and therefore has a direct impact on the API chemical quality attributes, including, purity and assay, and the API physical quality attributes: solid form,

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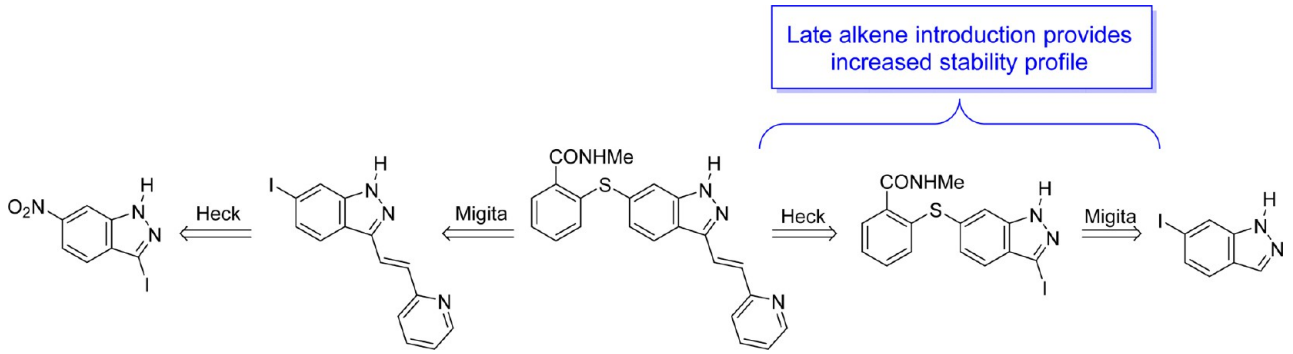

Figure 8. Synthetic strategy to axitinib.

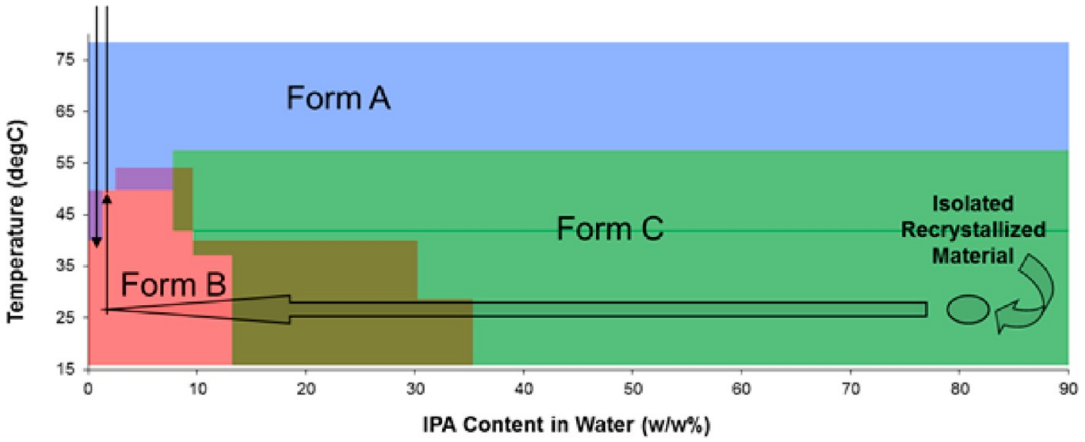

Figure 9. Phase diagram for bosutinib.

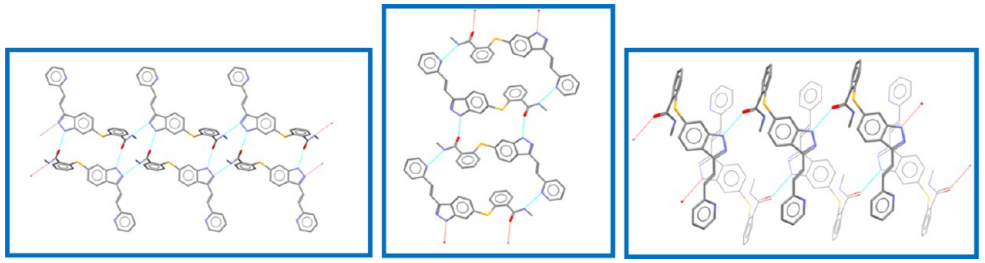

Figure 10. Crystal packing of some of the forms of axitinib.

particle size, and particle shape. While the importance of chemical quality attributes of the API in determining the ultimate quality of the corresponding drug product (DP) is relatively straightforward, the importance of the API physical quality attributes is more complex. These attributes may have a direct impact on the API or the DP stability and bioperformance. These physical quality attributes of the API may also have a significant negative impact on the manufacturability of the DP. The purpose of crystallization process design is to identify a robust process that delivers API with the desired physical and chemical quality attributes.

The first initial step in the development of an API crystallization process is selection of the API solid form, which can be a free form, a hydrate or solvate, a cocrystal, a salt, or potentially a mix of these solid form types.[20] More often than not, the driving force for the selection of an API solid form is based on DP bioperformance.[21] Once a solid form has been selected, the second part of the evaluation is polymorphism, which leads to the identification of the solid form of choice. A compound can exist in multiple crystal forms, and these different forms may exhibit different solubility, stability, bioavailability, and other physiochemical properties. As many API molecules have low solubility in water, the API solid form and polymorph can play an important role in the rate-limiting process of drug dissolution in the gut, thereby influencing how much drug is absorbed into the body.[22] The lowest energy, most stable polymorph is preferred as it minimizes the risk of a form change during processing or storage. A number of experimental methods can be used to complete the polymorph screening,[23,24] and new computational techniques have been developed to complement these experimental methods.[25,26] These screening studies can be used to identify the most stable polymorph as well as to map out the solid form landscape, including any possible solvates or hydrates that may form as part of the API crystallization process. In the case of bosutinib, several known polymorphs were identified and could be produced in aqueous isopropanol. Generating the phase diagram provided an understanding of which polymorph

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would be obtained at a given temperature and water/isopropanol mixture and guided the design of a process. This is depicted in Figure 9 where form C was an isopropanol dihydrate, form B was a hexahydrate, and form A was monohydrate (Figure 9).[27]

Selection of the solid form has an impact the design on the commercial route as preparation of a salt or a polymorph conversion may provide an additional synthetic step to further enhance the purity of the API. It is the general expectation that the API is a single solid form and polymorph. When the selected API solid form is polymorphic, the API crystallization conditions may be limited to ensure that the desired polymorph is produced. In the case of axitinib, over 20 different forms were identified, and the proposed commercial form is prepared under a specific set of conditions. Figure 10 shows representation of the crystal packing of some of the forms isolated.[28,29]

When performing a crystallization, it is important to have a controlled, preferably seeded, crystallization to avoid slow-filtering solutions of small crystals that may not purge impurities. An essential part of process design is ensuring that a balanced equation is considered to understand how side products, such as gases, can be managed safely and effectively.

Finally, experimental instrumentation to understand crystallizations have become increasingly important over the years. Tools such as focused beam reflectance measurement (FBRM) and particle vision and measurement (PVM) provide a real time picture of when crystallization occurs and the properties of the crystals generated. Figure 11 shows the PVM obtained during the course of a crystallization.

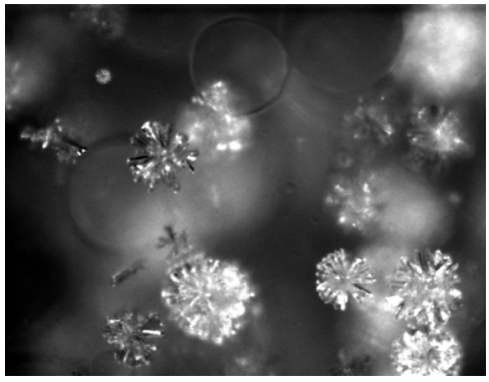

Figure 11. PVM of a crystallization.

■ PROCESS OPTIMIZATION

Attributes of a Good Process. Once the commercial route has been nominated, the process for each step must be developed with much more rigor than in early development. This entails effective process design and understanding to yield safe, robust and efficient operations on a manufacturing scale and ensure that the desired quality is obtained in a reproducible, controlled, and predictive manner. The typical parody of a process chemist was captured by Sir John Cornforth, when he stated that "The ideal chemical process is that which a one-armed operator can perform by pouring reactions into a bath tub and collecting pure product from the drain hole."[30] While the modern process chemist can manage a vast array of complexity in a commercial manufacturing process, there is certainly elegance and exquisite science in designing a safe, robust, efficient, and well-controlled process.

From a design perspective, a number of key criteria must be met. First and foremost, a process must be safe, with minimal use of hazardous materials. It should also minimize highly exothermic reactions and potential side reactions. A process should be robust and not operated near an edge of failure. Processes should be designed to have good stability over extended periods with several potential holding points. Each intermediate should be stable across all hold points, ideally crystalline, and have define procedures to ensure appropriate quality consistently. Processes should ideally be simple, employing minimal pieces of equipment, requiring as few unit operations as possible and avoiding large volume swings. Processes should be able to accommodate a readily achievable range of impurity profiles in the starting materials and employ typical quality reagents and solvents that can be readily disposed of or recycled. As a general rule, heterogeneous reactions can be hard to scale-up as they introduce scale dependent mass-transfer parameters, whereas homogeneous reactions can avoid such pitfalls unless they have really fast kinetics leading to potential micromixing concerns. Often the reaction is the easy part, and the workup and isolation is where the challenge begins. Common challenges can be the need for multiple washes, creating large volumes of waste, thick slurries that are difficult to manipulate, sensitive pH adjustments, inefficient separations and extractions, lengthy solvent replacements, and removal of solvent to very low volumes (i.e., stripping to dryness). Another important consideration is how the vessel can be cleaned following completion of the process. Telescoping in a common solvent is a useful trick for minimizing manipulations. For example, in the synthesis of the hepatitis C drug candidate filibuvir, the product of a Sonigashira reaction was acetylated and taken forward through a hydrogenation, where the desired alkane was isolated as the tosylate salt. From a throughput perspective, this is a far more effective way to proceed, as the time spent on workups and isolations is minimized (Figure 12).[31]

Quality by Design and Data-Rich Experimentation. The primary consideration for process development is safety. This includes process safety, environmental safety, and the safety of the patient who will take the drug. Patient safety is predicated on the quality of the API, which is the primary focus of API development. The quality by design, or enhanced, approach to process development is founded on a scientific and risk-based approach to establish the linkage of API quality attributes (such as impurities or solid form characteristics) to process parameters (such as temperature and stoichiometry) and material attributes (such as starting material or intermediate quality specifications). An understanding of the functional relationships between quality attributes and process parameters/material attributes allows for a meaningful control strategy to be developed in a prospective manner.

In order to develop process understanding in an efficient manner, each experiment must be conducted in such a way that process parameters can be effectively monitored and controlled, with the ability to vary multiple parameters in an automated fashion. The typical laboratory setup involving a round-bottom flask, offers sparse control and few opportunities for monitoring process parameters. Control of temperature is limited to the temperature of the cooling or heating bath, control of mixing is limited to the speed of a magnetic stir bar and other potentially important parameters, such as heat and mass transfer are

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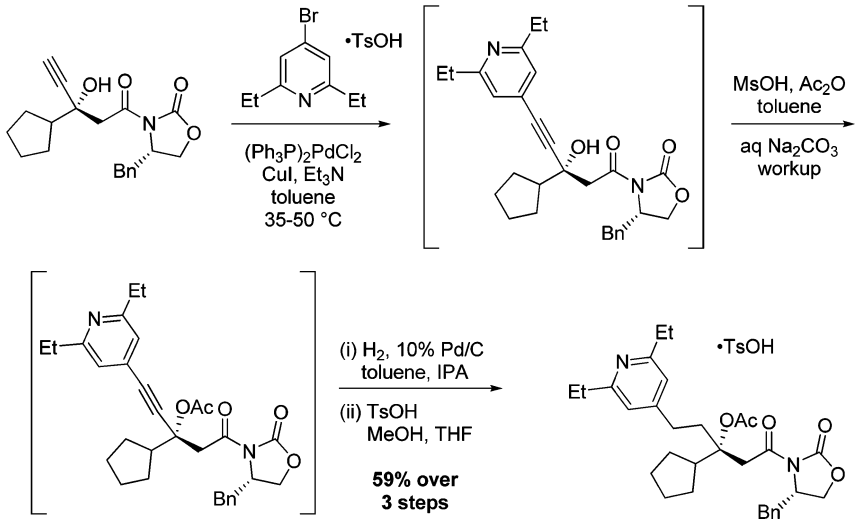

Figure 12. Telescoped Sonogashira–acylation–hydrogenation salt formation sequence.

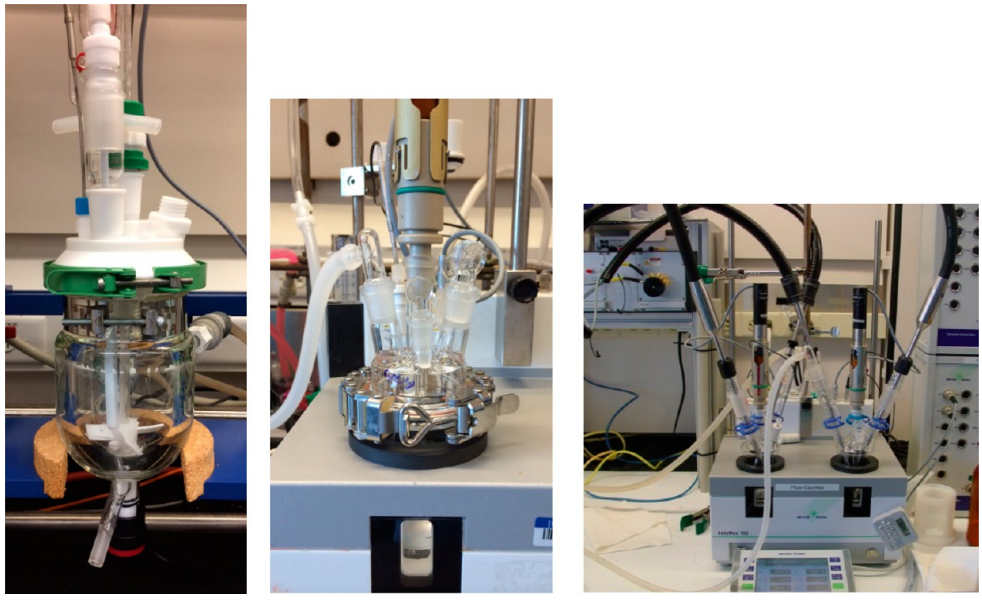

Figure 13. Jacketed reactor vessel and automated parallel reactor systems.

challenging to consider. Similarly, it is very hard to monitor reaction progress other than by discrete observations of the temperature or by taking a sample to conduct an analytical test, such as TLC or NMR. Experiments are typically conducted by modifying one factor at a time and operations are very manual in nature. The data that can be gleaned from such a system is sparse and does not necessarily translate well to increased scale.

In contrast, the modern process chemistry laboratory, referred to as Lab of the Future within our company, offers a data-rich platform. Round-bottom flasks have been replaced with automated laboratory reactors (Figures 13 and 14). A typical setup involves a glass vessel of similar configuration to a typical manufacturing scale vessel. The automated laboratory reactor is equipped with the option of overhead stirring, a baffle, and may have a bottom runoff valve. Temperature, mixing conditions, pH and dosing can be exquisitely controlled and monitored in real time. Many systems are equipped with reaction calorimetry capability. The reactors can be fully integrated with PAT, such as infrared or particle size measurement techniques, with autosampling capability and

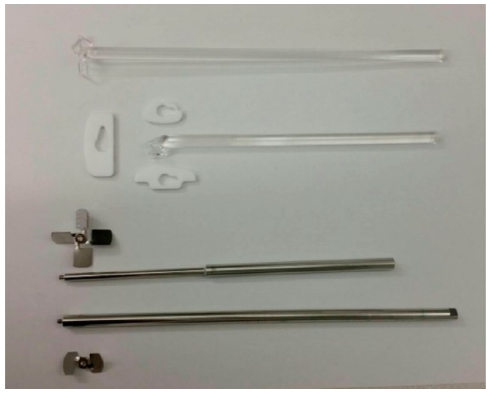

Figure 14. Overhead stirrers used to evaluate mixing effects and replicate impellers in a plant.

with other analytical techniques. The setup allows for excellent control, monitoring and the study of multiple parameters in an automated or semiautomated manner. Parameters that are

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J. Org. Chem. 2015, 80, 2943–2958

likely to be scale dependent, such as mixing and heat and mass transfer can be studied, monitored and modeled, leading to greater confidence in scale-up. The systems can be interrogated to access, manipulate and interpret time-stamped data. This mode of data-rich experimentation is a powerful tool when harnessed by synthetic chemists, engineers and analytical chemists, and is the platform of choice to rapidly develop and understand an effective process.

Purification and Impurity Control. During our Ph.D. studies, the purity of our compounds was generally determined by NMR and TLC and was somewhat qualitative in nature, while elemental analysis was considered the quantitative assessment. In the pharmaceutical industry, we soon realized the need for more rigorous and quantitative quality control for impurities, including process-related impurities, metals, and solvents. Guidelines for impurity control are set by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an organization that brings together the views of regulators and industry across the United States, Europe, and Japan. For example, process related impurities over 0.1% should generally be identified and must be qualified in appropriate toxicology studies if found over 0.15% in the final API (assuming less than a 2 g dose).[32] Impurities shown to be genotoxic must be controlled to even stricter levels, defined as the threshold for toxicological concern (TTC), often at parts per million levels.[33] An array of highly sensitive analytical methods are available to track process related impurities, metals and solvents down to extremely low levels. Such techniques include UPLC, gas chromatography, inductively coupled plasma mass spectrometry, and supercritical fluid chromatography. With this in mind, much of the focus on process design is centered on effective impurity control and strong collaboration with analytical chemists to demonstrate such control.

Understanding Solubility to Aid Design. In order to develop an effective process and to aid design, one of the first considerations is the understanding of the solubility of starting materials, products, reagents, and process-related impurities. Understanding solubility can aid design for a number of reasons. Two common reasons are to simplify workup and isolation of a product and to ensure homogeneity of solution in order to minimize scale sensitivity.

The isolation of intermediates and APIs is often achieved through crystallization of the desired product. This is almost always preferred over traditional column chromatography, as it is much more efficient and uses far less solvent. One of the most efficient techniques is the development of a direct drop process whereby the reaction product is insoluble in the reaction solvent and crystallizes out upon formation. Assuming potential process-related impurities such as starting materials, reagents, and byproducts are soluble in the reaction solvent, the reaction workup can simply entail a filtration and drying operation to isolate the desired product. This can save a huge amount of time and costly manipulations when compared to a typical aqueous workup that may involve the need to quench, wash, dry, solvent swap, crystallize, filter, and dry. Solubility screening of the starting materials, product, and relevant reagents and intermediates can be utilized to identify the preferred solvent. For example, in the development of the synthesis of sildenafil, it was found that a key amidation could be achieved using an acyl imidazole. While the starting amine and carboxylic acid were soluble in ethyl acetate, the product of the reaction was not. Since the imidazole generated in the reaction is also soluble in ethyl acetate, the desired product could be isolated in high yield and purity following a direct drop filtration of the reaction mixture (Figure 15).[34]

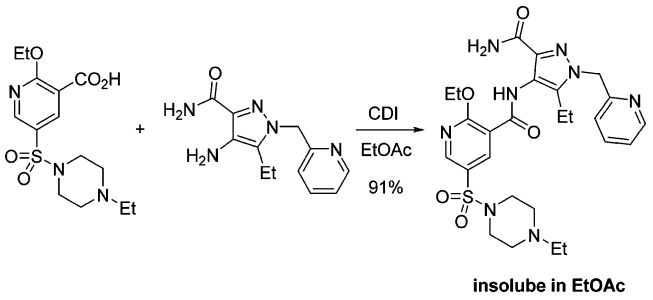

Figure 15. Direct drop process for the preparation of a PDE5 inhibitor.

Alternatively, solubility screening can help identify a solvent where the desired product is soluble but unwanted byproducts or process related impurities are insoluble and can be purged through filtration.

Understanding solubility to ensure reaction homogeneity is also a common practice since homogeneous reactions are much less prone to scale dependency than heterogeneous reactions. In the synthesis of axitinib, the step 4 Heck reaction was conducted in NMP to ensure homogeneity of the solution and eliminate scale dependent variables (Figure 16).[19]

Understanding the solubility profile of a compound can be very informative in the design of a crystallization. Using measured solubility data, design of a crystallization process is primarily focused on controlling the level of supersaturation. In general, crystallization processes are designed to maintain consistent and low levels of supersaturation throughout the process, as higher levels of supersaturation can lead to inconsistent API chemical and physical quality.[35] While multiple methods may be used to increase the level of supersaturation, such as antisolvent addition and solvent evaporation, cooling is the preferred method for generating supersaturation due to the ease of control and the consistency of the operation upon scale-up. The use of seeding to initiate a crystallization process is also preferred, as spontaneous nucleation is a random process and can also lead to inconsistent crystallization processes.[36,37]

In the design of a crystallization for crizotinib, the solubility of the compound was measured at different ratios of acetonitrile/water and at different temperatures. In order to achieved a controlled crystallization, nucleation was achieved at 40 °C in 30% aqueous acetonitrile, followed by addition of water to a 70% aqueous acetonitrile mixture and cooling to 5 °C, where the product has low solubility. This protocol avoided precipitation of impurities maximizing recovery of the product (Figure 17).[38]

In practical terms, solubility screening is greatly enhanced by automated technologies. A typical workflow might involve use of a solids-dosing robot to weigh out multiple samples of the solid to be assessed which are then transferred to an automated parallel reactor. A range of solvents can be added to each sample, potentially with an automated liquid handling unit, and the mixtures can be heated to different temperatures to dissolve the solid to varying degrees. Many units are capable of transferring a sample to a UPLC vial at temperature through a

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J. Org. Chem. 2015, 80, 2943−2958

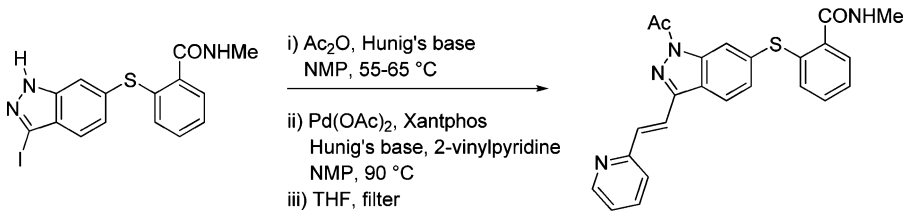

Figure 16. Nonscale dependent processing in steps 3 and 4 of axitinib.

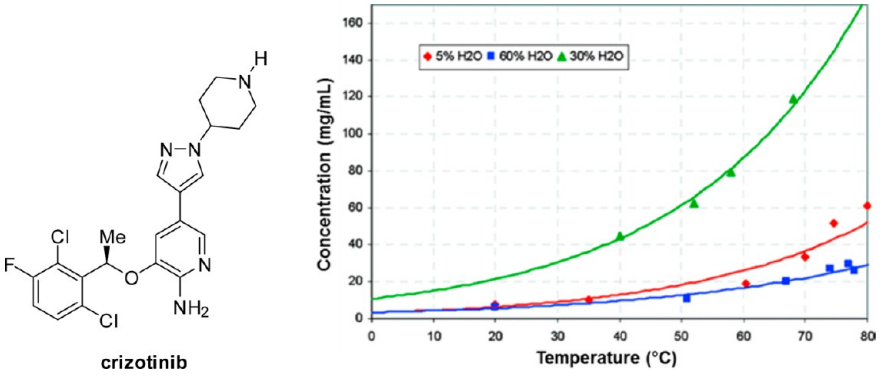

Figure 17. Solubility measurement of crizotinib in MeCN/H_2O.

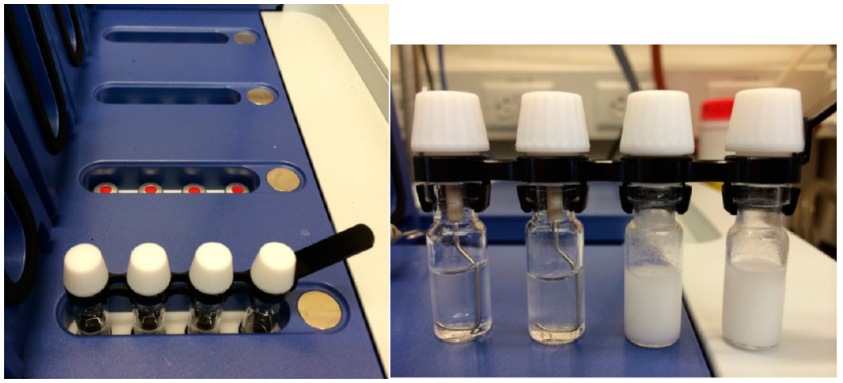

Figure 18. Equipment with 16 individual reactors with temperature control, mechanical stirring, and turbidity measurement for developing a crystallization.

heated needle. This allows for a quantitative solubility to be determined at a particular temperature based on UPLC data and calibration with a predetermined solubility curve. Other approaches include using turbidity to define the point of dissolution and crystallization as a function of temperature and concentration (Figure 18). Another tool gaining popularity is the use of computational solubility predictions.[39]

Reaction Kinetics. A typical Ph.D. thesis will likely contain many overnight reactions where often a final TLC, HPLC, or NMR is the sole in-process control that determines reaction completion. The process chemist has access to many tools to glean a strong understanding of the reaction kinetics, leading to mechanistic insight and allowing the chemist or chemical engineer to better design the process and ensure control. The optimal stoichiometry, temperature, concentration, or time of reaction can be quickly determined on the basis of readily accessible data to optimize yield and quality. For example, the realization that a product forms quickly and then begins to degrade to a side product will greatly impact the way a process is controlled vs the knowledge that a product is stable to prolonged exposure to reaction conditions. Additionally, a kinetic model can be created with commercially available software based on the data collected, and simulation can assist in identification of the optimal reaction conditions.[40]

In recent years, a growing set of tools has allowed chemists, analysts, and chemical engineers to collaborate and acquire greater kinetic understanding, from simple analysis to detailed modeling and understanding. PAT such as IR, Raman, UV, quantitative NMR,[41] and flow NMR provide real time data to define the kinetic profile. Many automated jacketed laboratory reactors are capable of providing calorimetry data to help define the reaction kinetics. More recently, the use of autosampling capability allows LC data to be collected for unattended reactions. For example, a Migita coupling between an aryl bromide and a sulfide proved problematic due to the formation of an impurity (Figure 19). The reaction was monitored by Raman and IR simultaneously, and a kinetic model was built to understand the reaction mechanism. This in turn allowed the process to be designed such that the level of the impurity was effectively controlled.[15,42]

Process Modeling. During the development of synthetic processes, there are many factors that can complicate scale-up.

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J. Org. Chem. 2015, 80, 2943−2958

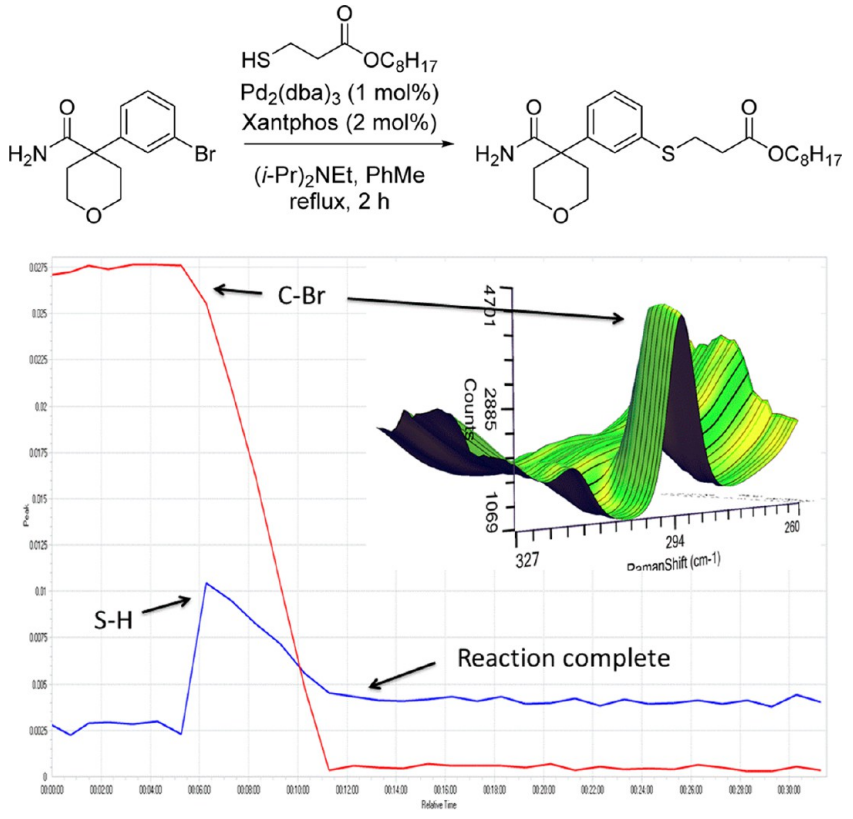

Figure 19. Raman trace of a Migita coupling.

In addition to understanding chemical reaction kinetics, the physical rates of heat transfer, mass transfer and mixing need to be understood and can be scale- and equipment-dependent. Thermodynamic equilibria need to be studied and understood, and physical property changes can be challenging to monitor and control. Since it is costly and inefficient to experiment and risk failure on scale, process modeling offers an opportunity to better predict the interactions of chemical and physical rates as a function of operating conditions, scale and equipment configuration. A number of tools are available to generate first-principle mechanistic modeling to predict and understand scale and equipment dependency and allow the chemical engineer to set appropriate parameters, such as the reactor type, baffling configuration, stirring rate, or tip speed to allow for effective mixing. In the example depicted in Figure 20, computational fluid dynamic (CFD) was used to predict the gas distribution in a hydrogenation at different positions of a reactor and to evaluate the effect of mixing and guided reactor selection for the reaction.

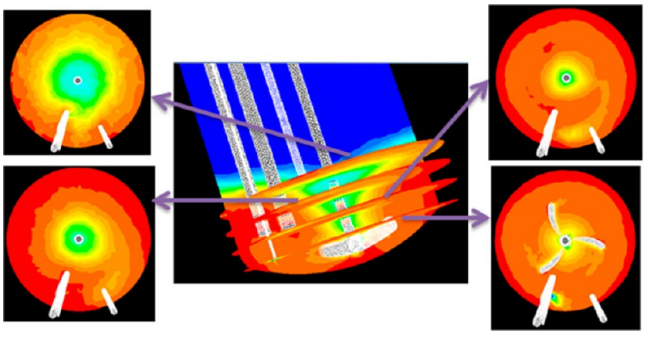

Figure 20. Utilization of multiphase CFD to understand gas distribution in a reactor.

Batch and Flow. Despite advances in prediction through process modeling, there are limitations to what can be achieved on scale with regard to physical reaction rates. For example, as a reactor increases in size, the surface area-to-volume ratio decreases and hence constrains the efficiency of heat transfer. In some instances, the limitations of scale can be overcome by switching from a batch reactor, such as a typical round-bottom flask or automated jacketed reactor, to continuous processing (flow chemistry). Continuous processing configurations, such as a continuous stirred tank reactor sequence or plug flow reactor can be advantageous in many regards, such as capital cost, speed of development, ease of scale-up, and a smaller equipment footprint. Significant advances in the academic and industrial settings now allow for rapid screening of both batch and flow processing to demonstrate the best mode for attaining quality and control. This is true for both a typical homogeneous reaction and heterogeneous reactions such as hydrogenation. The results from the screening experiments can be rapidly utilized for scale-up in a manufacturing setting (Figure 21).[43]

Continuous processing is well suited for PAT applications that offer real time analytics and, in some cases, can be incorporated as part of a feedback control loop but require strong analytical support in development.[44] An advantage of continuous processing is the fact that reproducibility is guaranteed once a stable steady state is achieved, which can be especially attractive for operations such as continuous crystallization, to provide API of consistent quality. Selection of the parameters of how to achieve the preferred reaction conditions occurs as a result of a strong collaboration between chemists and engineers. Continuous processing requires evaluation of factors such as identification of the appropriate

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J. Org. Chem. 2015, 80, 2943−2958

Figure 21. Laboratory-based screening tool for flow chemistry evaluation.

residence time, which can be modified by changing pressure or length of a reaction tube. One advantage often highlighted in favor of flow chemistry is that a flow reactor offers a large heat transfer area per unit volume. Therefore, highly energetic chemistry that would be dangerous to process in a batch configuration with limited cooling potential might be safely operated in a continuous processing mode. For example, continuous processing methodology was utilized to minimize accumulation of the highly energetic and potentially explosive diazonium salt and hydrazine intermediates for the safe scale-up of N-aryl pyrazoles (Figure 22).[45]

Design of Experiments. The study of process parameters that impact physical and chemical rates and, ultimately, quality can be greatly accelerated by the use of statistical design of experiments (DOE) or experimental design. This statistical and experimental technique is essential to understand the multifactorial interaction of parameters and their relationship with a specific quality attribute and to allow an appropriate range to be determined. Univariate experiments, whereby one parameter or factor is modified at a time (OFAT), are very useful in developing a process, but it is extremely resource intensive to understand the impact of a broad range of parameters on a quality outcome, such as the level of a specific impurity, using this methodology. Based on the large number of parameters and complexity of interactions, the experimental design approach allows the study of a large range of parameters simultaneously. Statistical software is utilized to design a set of experiments whereby a set number of combinations are studied in addition to a number of center points that help define experimental variability. The experiments are often executed on automated jacketed laboratory reactors with exquisite control. A recipe is typically created for each experiment wherein temperature set points are programmed and liquid additions are conducted using syringe pumps to give precise control of addition rates and mimic operations in a plant (Figure 23). While the designed experiments in a DOE approach are frequently executed with automated setups, it should be emphasized that the statistical power of this approach is equally valid with any laboratory equipment.

The output is a statistical model that represents the interaction of parameters on a quality outcome, often displayed as a contour plot (multifactorial design). This can be used to determine the acceptable operating range for a parameter, often described as a "design space", that will lead to acceptable product quality. In Figure 24, the contour plots outline the level of a synthetic intermediate present in the reaction as a function of catalyst loading, time, and temperature. In order to drive the reaction to completion, parameters were optimized such that the intermediate would be near 0%. These contour plots can be used to outline the appropriate design space to ensure

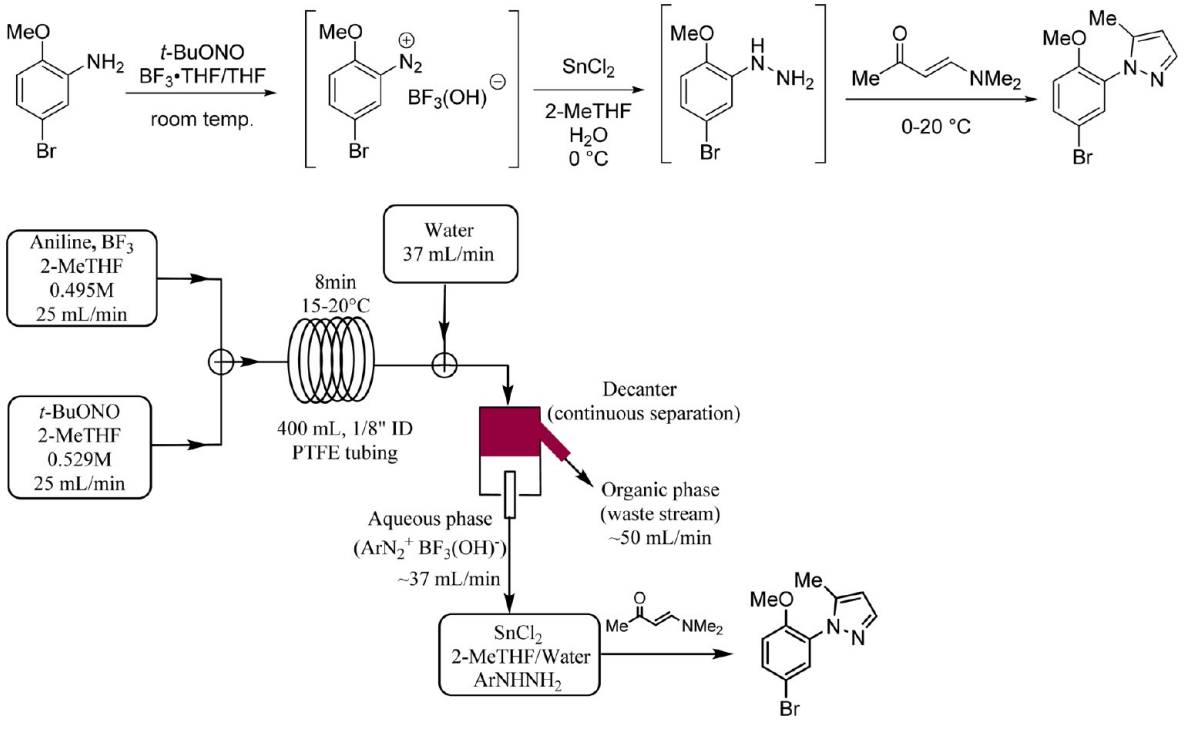

Figure 22. Implementation of a three-step process including a diazotization in flow.

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J. Org. Chem. 2015, 80, 2943−2958

Figure 23. Experimental setup for DOE experimentation.

acceptable quality of the final API, in addition to acceptable yield.[46]

TECHNOLOGY TRANSFER AND SCALE-UP

Despite the large number of tools available to study and understand a process, the first scale-up in a kilo lab, pilot plant, or manufacturing setting is challenging as it typically represents a significant step-up in scale. The aim of a process chemist is to appropriately manage risk throughout development with a staged approach to process development and understanding. As the program advances though developmentover several years, a number of additional steps are required to manage risk. First and foremost, the physical safety of the process must be demonstrated. The project team must build confidence that unit operations can be effectively executed on scale with acceptable outcome and control. This section looks to outline some of the tools available to aid the management of risk during technical transfer.

Process Safety. A primary concern when scaling any process is to ensure that it can be managed without harm to the operating staff, the local community, the environment, the building, and the equipment. As such, every process goes through a safety assessment. On a laboratory scale, this will entail research into the reagent hazards and compatibilities, generation of a balanced equation to assess products and byproducts, and an assessment of any specific high-energy functional groups. As scale increases, differential scanning calorimetry (DSC), thermal screening unit (TSu) and reaction calorimetry testing will be undertaken to understand the potential for exotherm, runaway reaction, and off-gassing. As required, additional tests can be conducted in specialized process safety laboratories to ensure the safety of a process and trigger redesign where necessary. In the formation of an acyl azide by reaction of an acid chloride with sodium azide (Figure 25), the acyl azide was thermally unstable and so was kept as a toluene solution. Since the following Curtius rearrangement required elevated temperature, it was determined that the safest way to conduct the reaction was by adding the toluene solution of the acyl azide at 105 °C in the presence of benzyl alcohol to ensure rapid rearrangement and trapping of the isocyanate, avoiding any accumulation of the azide above its decomposition temperature. While it might be counterintuitive to perform the rearrangement at a higher temperature, it was the safest procedure, as it minimized and controlled the effective concentration of the acyl azide in the reaction.[47]

Predictive Tools and Process Fit. As a process is scaled up, the equipment configuration will change. To manage risk it is essential that a process-fit exercise is conducted. Typically, the process is broken down into unit operations, using

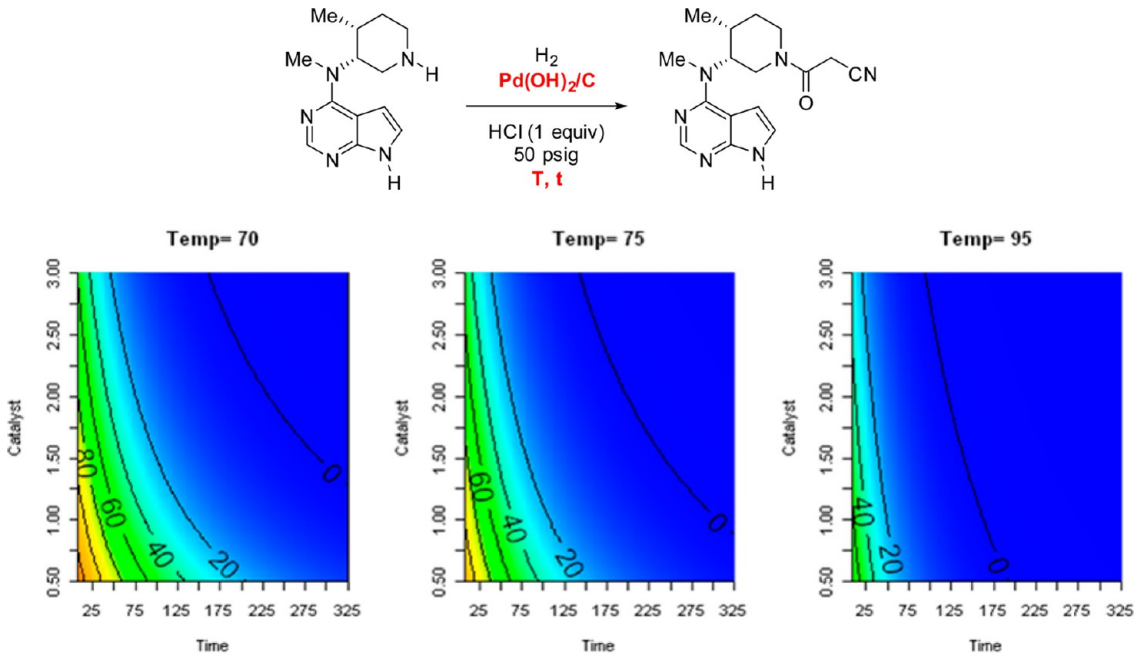

Figure 24. Utilization of DOE for process optimization.

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J. Org. Chem. 2015, 80, 2943−2958

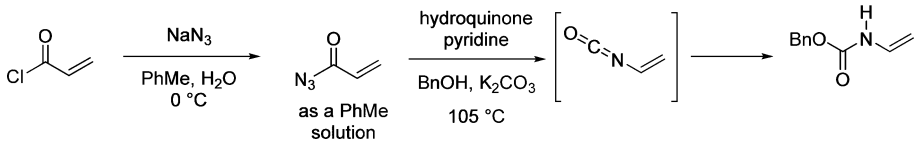

Figure 25. Process safety evaluation of a Curtius rearrangement.

specialized software, and the process is assessed versus the configuration of the scale-up facility. For example, if a reagent is added from a syringe on lab scale, it will likely require a header tank on the main reactor. If a process is filtered on a Buchner funnel in the laboratory, it may be isolated on an agitated filter dryer in the scale-up facility. The filter dryer must be within range of the reactor vessel and the slurry of product in solvent must be sufficiently mobile to pass through potentially hundreds of feet of connector line without settling and clogging. Many risks are encountered and the process-fit exercise aims to uncover those risks and either reconfigure the process or the equipment. Traditionally, this has been a somewhat subjective assessment, however the development of predictive tools has helped to better quantify risk. For example, during the filtration exercise aforementioned, the rate of filtration could be accurately predicted based on small scale measurements and translation to the plant equipment. For the first use of an agitated filter dryer, there is the risk of attrition or agglomeration of primary particles that could also be assessed with an appropriate predictive tool ahead of execution. Several predictive tools are available that greatly reduce the risk of scale-up in operations such as crystallization, filtration, solubility, extraction, mixing, distillation, isolation and drying. A recently published example outlines a predictive tool for use of an agitated filter dryer to dry a compound in methanol. The tool illustrates a high-risk area for the formation of agglomerates, allowing the drying parameters to be carefully managed on scale to avoid such an issue.[48] Likewise, the ability to predict the performance of a distillation at scale can be difficult in a laboratory setting. However, based on the properties of the solvents considered, phase diagrams can be generated and predict where an azeotrope resides and how the solvent composition will change in the course of a distillation (Figure 26).[49]

Data Management. As process chemists generate more and more data, the platforms for data capture, interpretation, visualization, storage, and retrieval become increasingly important. One of the most important tools is the use of an electronic laboratory notebook. When using a paper notebook, the system is somewhat limited as to what data can be included, and knowledge sharing is severely restricted by the lack of searchability. The electronic notebook allows experiments to be cloned and rapidly reproduced and modified and is an essential part of a data management architecture to link data-rich experimental methodologies. As our informatics approaches evolve, it is becoming increasingly easier to capture knowledge and track it through our workflow, including translation from lab to plant. There are many different tools for processing data to generate knowledge and understanding, for example, software packages to build kinetic models, computational fluid dynamic models, surface area plots to illustrate a design space, or Spotfire plots to represent different chemical reaction yields and selectivities.

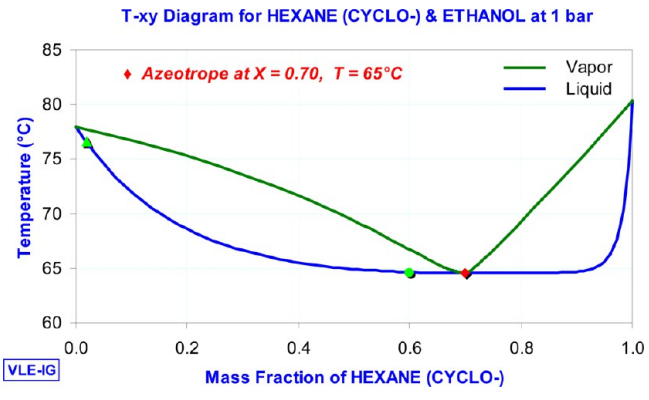

Figure 26. Predicted phase diagram used to model a distillation.

CONCLUSION

The modern industrial process chemistry laboratory now demands a suite of tools capable of delivering highly efficient processes and exceptional quality control based on greater process understanding and predictability at scale. This has led to a rapid transformation of the laboratory environment and replacement of the round-bottom flask and other conventional equipment familiar to a traditional organic chemist. The new environment is incredibly data-rich and involves collaboration across multiple disciplines. As the lab environment continues to evolve, our workforce must continue to develop an array of skills. New recruits, expected to be experts in their field of study, quickly learn about data-rich experimental methods and their application to process understanding and predictability at scale. Tremendous opportunity exists for growth in computational design, informatics and programing, as critical skills. As we continue to evolve, continued collaboration is required across government, industry, and academia to disseminate current data-rich methodology and to foster future innovation in chemical and enabling technologies. We must also work together to continue to develop a highly skilled workforce capable of meeting future challenges.

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Notes

The authors declare no competing financial interest.

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Nick Thomson graduated from the University of Edinburgh, Scotland, with a BSc (Hons) in Environmental Chemistry. He joined the group of Prof. Gerald Pattenden at the University of Nottingham, England, where he received his Ph.D. in 1997. He started his industrial career at Pfizer in Sandwich, England. He now works in Groton, CT, as a Director in Chemical R&D, with oversight for the Pfizer Lab of the Future initiative and Technology API group.

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■ REFERENCES

(1) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665−681.
(2) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1−57.
(3) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green Stuart, P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002−3027.
(4) Caron, S., Ed. *Practical Synthetic Organic Chemistry: Reactions, Principles, and Techniques*; John Wiley & Sons, Inc.: Hoboken, NJ, 2011.
(5) Abdel-Magid, A. F., Caron, S., Eds. *Fundamentals of Early Clinical Drug Development: From Synthesis Design to Formulation*; Wiley-Interscience: Hoboken, NJ, 2006.
(6) International Conference on Harmonization. International Conference on Harmonization Guideline Q8(R2); Pharmaceutical Development, FDA 2009.
(7) am Ende, D.; Bronk, K. S.; Mustakis, J.; O'Connor, G.; Santa Maria, C. L.; Nosal, R.; Watson, T. J. N. *J. Pharm. Innovation* **2007**, *2*, 71−87.
(8) Law, J.; Zsoldos, Z.; Simon, A.; Reid, D.; Liu, Y.; Khew, S. Y.; Johnson, A. P.; Major, S.; Wade, R. A.; Ando, H. Y. *J. Chem. Inf. Model.* **2009**, *49*, 593−602.
(9) Thomson, N. M.; De Koning, P. D.; Gillmore, A. T.; Tao, Y. *RSC Drug Discovery Ser.* **2011**, *9*, 66−89.
(10) Bowles, P.; Brenek, S. J.; Caron, S.; Do, N. M.; Drexler, M. T.; Duan, S.; Dube, P.; Hansen, E. C.; Jones, B. P.; Jones, K. N.; Ljubicic, T. A.; Makowski, T. W.; Mustakis, J.; Nelson, J. D.; Olivier, M.; Peng, Z.; Perfect, H. H.; Place, D. W.; Ragan, J. A.; Salisbury, J. J.; Stanchina, C. L.; Vanderplas, B. C.; Webster, M. E.; Weekly, R. M. *Org. Process Res. Dev.* **2014**, *18*, 66−81.
(11) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. *Chem. Rev.* **2006**, *106*, 2794−2810.
(12) Berliner, M. A.; Cordi, E. M.; Dunetz, J. R.; Price, K. E. *Org. Process Res. Dev.* **2010**, *14*, 180−187.
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(14) Peng, Z.; Wong, J. W.; Hansen, E. C.; Puchlopek-Dermenci, A. L. A.; Clarke, H. J. *Org. Lett.* **2014**, *16*, 860−863.
(15) Reid, G. L.; Ward, H. W., II; Palm, A. S.; Muteki, K. *Am. Pharm. Rev.* **2012**, *15*, 1−12.
(16) Chanda, A.; Daly, A. M.; Foley, D. A.; LaPack, M. A.; Mukherjee, S.; Orr, J. D.; Reid, G. L.; Thompson, D. R.; Ward, H. W. *Org. Process Res. Dev.* **2015**, *19*, 63−83.
(17) Caron, S. Process Research and Development of a Factor Xa Inhibitor, *Stereochemistry Gordon Research Conference*, Newport, RI, Jul 29, 2008.
(18) Dobo, K. L.; Greene, N.; Cyr, M. O.; Caron, S.; Ku, W. W. *Regul. Toxicol. Pharmacol.* **2006**, *44*, 282−293.
(19) Chekal, B. P.; Guinness, S. M.; Lillie, B. M.; McLaughlin, R. W.; Palmer, C. W.; Post, R. J.; Sieser, J. E.; Singer, R. A.; Sluggett, G. W.; Vaidyanathan, R.; Withbroe, G. J. *Org. Process Res. Dev.* **2014**, *18*, 266−274.
(20) Aitipamula, S.; Banerjee, R.; Bansal, A. K.; Biradha, K.; Cheney, M. L.; Choudhury, A. R.; Desiraju, G. R.; Dikundwar, A. G.; Dubey, R.; Duggirala, N.; Ghogale, P. P.; Ghosh, S.; Goswami, P. K.; Goud, N. R.; Jetti, R. R. K. R.; Karpinski, P.; Kaushik, P.; Kumar, D.; Kumar, V.; Moulton, B.; Mukherjee, A.; Mukherjee, G.; Myerson, A. S.; Puri, V.; Ramanan, A.; Rajamannar, T.; Reddy, C. M.; Rodriguez-Hornedo, N.; Rogers, R. D.; Row, T. N. G.; Sanphui, P.; Shan, N.; Shete, G.; Singh, A.; Sun, C. C.; Swift, J. A.; Thaimattam, R.; Thakur, T. S.; Kumar Thaper, R.; Thomas, S. P.; Tothadi, S.; Vangala, V. R.; Variankaval, N.; Vishweshwar, P.; Weyna, D. R.; Zaworotko, M. J. *Cryst. Growth Des.* **2012**, *12*, 2147−2152.
(21) Newman, A. *Org. Process Res. Dev.* **2013**, *17*, 457−471.
(22) Variankaval, N.; Cote, A. S.; Doherty, M. F. *AIChE J.* **2008**, *54*, 1682−1688.
(23) Miller, J. M.; Collman, B. M.; Greene, L. R.; Grant, D. J. W.; Blackburn, A. C. *Pharm. Dev. Technol.* **2005**, *10*, 291−297.
(24) Aaltonen, J.; Alleso, M.; Mirza, S.; Koradia, V.; Gordon, K. C.; Rantanen, J. *Eur. J. Pharm. Biopharm.* **2009**, *71*, 23−37.
(25) Abramov, Y. A. *Org. Process Res. Dev.* **2013**, *17*, 472−485.

DOI: 10.1021/jo502879m
J. Org. Chem. 2015, 80, 2943−2958

(26) Abramov, Y. A.; Loschen, C.; Klamt, A. *J. Pharm. Sci.* **2012**, *101*, 3687−3697.
(27) Tesconi, M. S.; Feigelson, G.; Strong, H.; Wen, H. WO, 2007005462, 38pp.
(28) Chekal, B. P.; Campeta, A. M.; Abramov, Y. A.; Feeder, N.; Glynn, P. P.; McLaughlin, R. W.; Meenan, P. A.; Singer, R. A. *Org. Process Res. Dev.* **2009**, *13*, 1327−1337.
(29) Campeta, A. M.; Chekal, B. P.; Abramov, Y. A.; Meenan, P. A.; Henson, M. J.; Shi, B.; Singer, R. A.; Horspool, K. R. *J. Pharm. Sci.* **2010**, *99*, 3874−3886.
(30) Cornforth, J. *Chem. Br.* **1975**, *11*, 432.
(31) Peng, Z.; Ragan, J. A.; Colon-Cruz, R.; Conway, B. G.; Cordi, E. M.; Leeman, K.; Letendre, L. J.; Ping, L.-J.; Sieser, J. E.; Singer, R. A.; Sluggett, G. W.; Strohmeyer, H.; Vanderplas, B. C.; Blunt, J.; Mawby, N.; Meldrum, K.; Taylor, S. *Org. Process Res. Dev.* **2014**, *18*, 36−44.
(32) International Conference on Harmonization. International Conference on Harmonization Guideline Q3A (R2), Impurities in New Drug Substances. FDA, Rockville, 2008.
(33) International Conference on Harmonization. International Conference on Harmonization Guideline M7; Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, FDA, Rockville, 2008.
(34) Dale, D. J.; Draper, J.; Dunn, P. J.; Hughes, M. L.; Hussain, F.; Levett, P. C.; Ward, G. B.; Wood, A. S. *Org. Process Res. Dev.* **2002**, *6*, 767−772.
(35) Mullin, J. W.; Nyvlt, J. *Chem. Eng. Sci.* **1971**, *26*, 369−377.
(36) Beckmann, W. *Org. Process Res. Dev.* **2000**, *4*, 372−383.
(37) Choong, K. L.; Smith, R. *Chem. Eng. Sci.* **2004**, *59*, 313−327.
(38) de Koning, P. D.; McAndrew, D.; Moore, R.; Moses, I. B.; Boyles, D. C.; Kissick, K.; Stanchina, C. L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P. R. *Org. Process Res. Dev.* **2011**, *15*, 1018−1026.
(39) Loschen, C.; Klamt, A. *Ind. Eng. Chem. Res.* **2012**, *51*, 14303−14308.
(40) Bright, R.; Dale, D. J.; Dunn, P. J.; Hussain, F.; Kang, Y.; Mason, C.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2004**, *8*, 1054−1058.
(41) Do, N. M.; Olivier, M. A.; Salisbury, J. J.; Wager, C. B. *Anal. Chem.* **2011**, *83*, 8766−8771.
(42) Cai, W.; Chekal, B.; Damon, D.; LaFrance, D.; Leeman, K.; Mojica, C.; Palm, A.; St. Pierre, M.; Sieser, J.; Sutherland, K.; Vaidyanathan, R.; Van Alsten, J.; Vanderplas, B.; Wager, C.; Weisenburger, G.; Withbroe, G.; Yu, S. In *Transition Metal-Catalyzed Couplings in Process Chemistry*; Magano, J., Dunetz, J. R., Eds.; Wiley−VCH; Weinheim, 2013; pp 253−266.
(43) Cyr, P.; Deng, S. T.; Hawkins, J. M.; Price, K. E. *Org. Lett.* **2013**, *15*, 4342−4345.
(44) Xiang, Y.; Lucas, J.; Van Alsten, J.; Li, B.; Preston, B.; Lovdahl, M.; Hayward, C. M. *Am. Pharm. Rev.* **2012**, *15*, 56−61.
(45) Li, B.; Widlicka, D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J. C.; O'Neil, B. T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y.; Young, J. *Org. Process Res. Dev.* **2012**, *16*, 2031−2035.
(46) Dugger, R. W. A QbD Approach to the Process Development of Tofacitinib Citrate, *27th International Organic Process Research and Development Conference*, Clearwater, FL, Mar 11, 2013.
(47) Am Ende, D. J.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Process Res. Dev.* **1998**, *2*, 382−392.
(48) am Ende, D.; Birch, M.; Brenek, S. J.; Maloney, M. T. *Org. Process Res. Dev.* **2013**, *17*, 1345−1358.
(49) Cordi, E. M. *Batch Distillation Predictive Tools for Pharmaceutical Process Development*; Aspen Webinar, Houston, TX, 2009.

DOI: 10.1021/jo502879m
J. Org. Chem. 2015, 80, 2943−2958