Engineering Chemistry Innovation

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ABSTRACT: Automation of chemistry at a pharmaceutical company commonly entails bringing commercial solutions in-house, reproducing manual processes with a robot, or integrating multiple instruments to eliminate human intervention. A strategy of industrializing proven approaches, while financially justifiable, however, does not encourage innovation. On the other hand, trying to automate unproven or difficult processes may seem to be risky but can actually accelerate the adoption, modification, or rejection of novel technologies. Having chemists and engineers work together to develop automation that accelerates the development and evaluation of innovative concepts is one blueprint for delivering a competitive advantage to an organization.

KEYWORDS: Automation, engineering, innovation, integration, instrumentation.

Since the first automated DNA¹ and peptide synthesizers² were developed by Leroy Hood in the 1980s, the desire to automate chemical synthesis has captured the imagination of chemists and engineers alike. In 1995, I was given the opportunity to join the Pharmaceutical Products Division at Abbott Laboratories to form a new group to capitalize on this growing wave of automation in chemistry.

Without the benefit or burden of any previous pharmaceutical experience but with a strong engineering intuition, I founded the group with a higher mission than just saving time. It needed to deliver a competitive advantage to our drug discovery scientists by encouraging innovation.

Traditional Automation Approaches. The primary goal of automation is typically viewed as relieving the burden on humans to perform work that they do not want to or cannot do. Logic dictates that any time saved by having a robot perform an experiment is time returned to the scientist to use their brain for creative or complex activities that are difficult to automate. In fact, it is not uncommon for automation projects to be financially justified by comparing development cost (risk) to labor savings (benefit). Three common approaches to financially justify automation are (1) prioritizing opportunities that are the lowest risk, even at the expense of a reduced user base; (2) automating ubiquitous procedures to maximize the user base; or (3) completely eliminating human intervention to enable an existing workforce to multitask.

Simple Chemistry for Simple Engineering. The plethora of solid-phase synthesis systems launched in the 1990s was a reflection of the consensus opinion that it was preferable to pursue the automation of simple, solid-phase reactions over more difficult to automate, but more widely applicable, solution-phase methods. The fact that few solid-phase synthesis instruments have survived³ proves that limiting the breadth of applicability in the name of engineering simplicity is not necessarily a wise choice.

There are a number of reasons for this. First, no process is so straightforward that there is no risk to implementing an

automated instrument, so development costs are notoriously underestimated. Second, if the process is easy to automate, it is probably also easy to perform manually. Thus, the labor savings is commonly overestimated. Third, the science of chemistry is not advanced by having robots do tasks that would otherwise be done manually. Finally, innovation can potentially be decreased as chemists prioritize simple, automated workflows over more complex, manual procedures. Encouraging chemists to perform more routine chemistry is unlikely to provide any competitive advantage.

Maximize User Base by Automating Routine Operations. Similarly, developing automation for ubiquitous, routine operations such as weighing and labeling vials is also unlikely to facilitate chemistry innovation. With this approach, the hope is that the labor savings exceeds the development cost through sheer volume. Such systems are especially beneficial for groups organized around functions like high-throughput organic synthesis (HTOS) or high-throughput purification (HTP), where hundreds of samples are handled at a time, and the bench space and setup time can be amortized across many samples. Although the additional benefit of reduced potential for misidentified compounds makes this an attractive strategy, this still does little to provide a competitive advantage.

Build Integrated Systems to Eliminate Human Intervention. Building integrated systems that utilize robotic systems to eliminate all human intervention^{4,5} is another common automation strategy, but it is probably the least financially justifiable. Not only is the development cost increased, but the labor savings is reduced relative to standalone, workstation-based approaches.

Integrated systems, especially those that combine chemistry and biology, take longer to build and debug because the development of software that can orchestrate complex

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scheduling, timing, adaptation, and error handling is exponentially more difficult than relying on a human to handle those decisions. The labor savings is limited because the narrow scope of accessible chemistry and biology restricts the automation utilization to only those situations when both the chemistry and biology are suitable. Labor savings is also limited because maintenance and repair times are increased. The reduced overall reliability of integrated systems, where the failure of one component brings the whole system to a halt, can quickly erase the benefits of unattended operation. Furthermore, while all humans make mistakes, occasionally those mistakes lead to serendipitous results that raise new avenues for exploration, so removing all human interaction in an experiment may not always be beneficial. Finally, fully integrated systems tend to be snapshots in time in a constantly evolving technology landscape and thus are difficult to adapt to continuing technological progress. This can have an inhibiting effect on an organization's goal of innovation.

The most common argument in support of integrated systems is that it has led to an enormous, high-throughput-screening industry on the biology side. But as many a chemist or biologist would be quick to point out, biology is not the same as chemistry. The relative homogeneity of biological molecules such as nucleic acids and proteins, the universality of water as the exclusive solvent, the emphasis on detection rather than synthesis, the need to run thousands or millions of experiments in parallel, or even the existence of government-driven initiatives like the Human Genome Project, have all driven the strategy for automating biology toward highly integrated systems. Conversely, at least in terms of automation friendliness, medicinal chemistry is more similar to the *in vivo* biology world, for which automation is in its infancy. If chemistry automation is to ever reach the heights of *in vitro* biology automation, we need to be willing to think beyond traditional approaches.

While these traditional approaches to automation are logical, at Abbott/AbbVie they are not our sole focus. These traditional strategies are the linchpins of the short-term part of our portfolio that builds trust in, and financially justifies, our group. In the longer term, we strive to also deliver breakthrough capabilities that do not exist anywhere else in the world.

Automation to Promote Innovation. Rather than focusing on labor savings, we paradoxically explore strategies that encourage scientists to do more work. By developing systems that lower the hurdles to access new techniques, scientists are encouraged to investigate how and where to best apply cutting-edge technology. In that way, automation delivers a competitive advantage to our scientists by fostering chemistry innovation. We see automation as a tool to encourage the exploration of new methods. By reducing the cost of experimentation, we aim to lessen the reluctance to performing riskier experiments.

At the heart of this aspect of our strategy is the makeup of our engineering group. We have had electrical and mechanical engineers at all degree levels, from associate to PhD, work in the group. Together, they possess hundreds of years of experience working in industries ranging from cell phones to aerospace. Notably, however, not a single engineer has previously worked for a pharmaceutical company. This diversity of experiences helps to promote the development of innovative solutions for our laboratories and enables us to look across the widest possible set of industries for solutions. It also

facilitates looking at automation as a tool for promoting future innovation rather than a solution in and of itself.

There are three primary approaches we have taken to foster innovation: (1) adapting novel, commercial, single-sample instruments to perform unattended, multiple sample runs; (2) utilizing automation to accelerate engineering design, build, and test cycles; and (3) developing novel technologies that maximize the utility of external innovation.

Enable More Experimentation. One often repeated theme of our engineering projects is the transformation of workstations setup for running a single sample per run into instruments capable of running multiple samples within a run. This facilitates Design of Experiments (DOE) exploration and optimization of processes and the performance of multiple experiments for libraries of compounds. We do this precisely for instruments that have not yet become commonplace in an effort to encourage our scientists to explore new technologies.

A simple example involves the adaptation of preparative supercritical fluid chromatography, or SFC, systems developed for process chemistry.⁶ These commercial systems were designed for batch purification of a single crude sample. By developing a novel, open-bed fraction collector,⁷ we enabled the purification of libraries of compounds and thereby accelerated exploration of SFC in a discovery environment.^{8,9} In the mid 2000s, we applied the same principles to counter current chromatography (CCC) to facilitate investigation of its utility in Discovery.^{10,11} Absent the ability to run large numbers of samples through these uncommon chromatographic techniques, chemists would need weeks or months to perform such evaluations, if they are done at all.

In the synthesis domain, similar adaptations of flow chemistry systems encourage the use of these instruments, which remain unfamiliar to some medicinal chemists.¹² Ironically, despite the fact that flow chemistry is easy to automate and has been applied to an enormous menu of suitable reactions,^{13,14} including photochemistry,¹⁵ electrochemistry,¹⁶ hydrogenations,¹⁷ and sonochemistry,¹⁸ many commercial systems are still sold as single-sample-per-run instruments. For one such commercial hydrogenation flow reactor, our adaptation improved its adoption in our HTOS group.¹⁹ For a high-temperature flow chemistry system, the addition of an autosampler, a dual injection port, and a ten-port valve²⁰ enabled reaction optimization, library production, and scale-up.²¹ In both of these cases, the original synthesizers had fallen into disuse without the ability to run large numbers of samples with varying parameters.

Accelerate Engineering. A second common thread for our instrument designs is to only custom design critical elements that are not commercially available. In the previously described projects, we did not start from scratch but rather enhanced a commercially available system. This is the classic way to operate: iron out issues on a limited prototype before surrounding it with automation to increase its capacity. When such established equipment or designs are not available, however, we have found that the incorporation of automation as early as possible helps engineers to develop systems faster.

When we first decided to build an automated flow synthesizer for chemical reactions involving diazomethane, we surrounded a tube-in-tube reactor, published by Kappe,²² with a simple pipetting station. With that ability to run multiple experiments in rapid succession, we quickly found that the gas-permeable Teflon AF tubing, which served as the key component of the reactor, fouled after multiple reactions in

the presence of palladium catalyst. To overcome this, we altered the design to introduce the palladium catalyst downstream of the Teflon AF.²³

The early incorporation of automation allowed us to not only quickly unearth issues with the published design but also helped us test ways to resolve the problems and verify the reliability and robustness of our design. The early inclusion of automation in the development process also eliminated the need for any last minute modifications before the final delivery of a safe, high-throughput instrument.

Another example was our initiative to automate nuclear magnetic resonance (NMR) spectroscopy. Automated sample loaders were commercially available, but those systems merely shifted the bottleneck to sample preparation. We decided to focus on the development of an automated NMR sample preparation system capable of dissolving compound in deuterated solvents and then transferring the sample into 3 mm-diameter NMR tubes.

After considering all the common approaches to transferring solutions, we decided to construct a system around the principle of vacuum filling (Figure 1). Instead of developing

Figure 1. Automated NMR sample prep system for dissolving compounds in deuterated solvents and transferring the solution to NMR tubes. Inset shows close-up of the vacuum fill station for transferring the solution from glass vials to inverted NMR tubes.

and debugging a manual, standalone fill station first, however, we included an articulated robot arm from the beginning so we could accelerate testing of our designs and evaluate their robustness automatically. After countless iterations, the design of this critical station proved to be a novel means of transferring solutions into NMR tubes that did not require additional disposable lab supplies. Furthermore, we were able to scale up the design to enable the parallel transfer of solutions from 96-well microtiter plates.

Leverage External Innovation. A third common thread for our projects is not settling for just duplicating outside innovations. As previously described, we try to focus our creativity on those aspects of a problem that need it. When the external work is done so well that there are not any further modifications required, however, we try to look past the solutions in isolation for opportunities to combine novel technologies. In that way, we can still deliver a competitive advantage when accessing innovations that are available to anyone in the industry.

A good example is the impressive high-throughput experimentation (HTE) work pioneered at Merck for reaction scouting at the nanomolar scale.^{24,25} Their work, combined with advances in the miniaturization of in vitro biology, suggests that an innovation opportunity exists in being able to

use the nanomoles of material synthesized directly for biology assays. Furthermore, such a capability would not only benefit compounds synthesized via HTE but would also have an immediate impact on medicinal chemists throughout Discovery as the compound requirements for gathering biological data are reduced.

We decided our opportunity to secure a competitive advantage rested in the miniaturization of the preparation of 10 mM DMSO stock solutions. Fortunately, we had already developed expertise in preparing stock solutions when we implemented the Synthesis With Integrated Flow Technology system in 2011.²⁶ We only needed to add a module capable of dissolving the compound in as little as 50 μ L of DMSO to finish the system.

Three factors complicated the design of this component of the Source NMR Assay Plate Prep (SNAPP) system. First, we chose to recover compound from the NMR tube rather than necessitating a unique aliquot of material from the chemists. Second, because we chose to use Biotage V10 instruments to rapidly remove the deuterated solvent (DMSO in many cases), the quantified material could be anywhere on the internal surfaces of a 4 mL glass vial. Finally, because the amount of material in the NMR tube can vary from micrograms to milligrams, the amount of solvent required to make the stock solution varied from tens of microliters to milliliters.

Our final design for the resolution module resembled a cement mixer with a replaceable glass vial as its drum (Figure 2). It incorporated a heated, vial-rolling stage capable of

Figure 2. Custom resolution module of SNAPP system for quantitative dissolution of as little as 500 nanomoles of compound in 50 μ L of DMSO.

pivoting at any arbitrary angle from vertical to below horizontal depending upon the amount of DMSO held. For the most challenging samples that only required tens of microliters of DMSO, we slowly rock the rotating vial around a nominally horizontal position to “roll” the droplet across all the internal surfaces. A final heating of the upper portion of the vial to approximately 10 °C hotter than the bottom half of the vial sufficiently reduces the viscosity and surface tension of the DMSO caught in the upper shoulders of the vial to cause it to be pulled down to the cooler solution at the bottom of the vial. The system is capable of quantitatively dissolving as little as 500 nanomoles of compound in 50 μ L of DMSO and now facilitates the testing of sub-milligram amounts of material through primary in vitro biology assays for potency determination and a multitude of quantitative, in vitro

absorption, distribution, metabolism, and excretion (ADME) assays for dose estimation.^{27,28} Further reduction in the quantitative preparation of DMSO stock solutions should be possible by shifting the entire process to smaller vials.

Automating Other Sciences. One of the additional benefits of equipping the AbbVie engineering group with the talent, skill, and opportunities to pursue automation in an innovative fashion is the opportunity to provide a competitive advantage outside of chemistry. Examples of our past work include automated protein crystal handling for X-ray crystallography,²⁹ automated protein concentration,³⁰ parallel oocyte electrophysiology testing,³¹ and automated evaluation of cardiovascular toxicity.³² We also recently presented custom developed systems for automated drug conjugation and purification,³³ research cell line generation,³⁴ and miniaturized, biologics physiochemical property screening.³⁵

Current Chemistry Automation Challenges. Challenges that we are currently tackling include the development of an automated photoredox reaction optimization instrument and the further enhancement of HTE technologies to deliver sufficient accuracy and precision to not only screen but also optimize chemical transformations at the nanoscale.

For photoredox reactions, we want to develop a platform similar to our other projects for encouraging the exploration of unfamiliar chemistry. Unlike the examples described previously, however, we cannot simply surround a commercial photoredox reactor instrument with our standard components. This is because the reaction vessels^{36,37} in those commercial systems are much deeper than the penetration depth of the light, so optimized conditions do not translate well to different reactor designs such as flow³⁸ or continuous stirred tank reactors.³⁹

To attempt to enable the broadest variety of chemical reactions in an HTE system, we are pursuing technologies capable of accurately dispensing submilligram amounts of solids and mixing heterogeneous mixtures in microliters of solvent while maintaining high temperatures and an inert environment. The ability to control accurately the ratios of reagents, we believe, would extend the utility of HTE to reaction optimization. Furthermore, the ability to synthesize nanomoles of material would enable the collection of primary bioassay and ADME data using SNAPP.

Conclusion. An unconventional approach to developing automation that supplements projects aimed at delivering labor savings with those that encourage innovation has been described. By utilizing automation to lower the barriers to accessing new technologies, we facilitate the evaluation of unfamiliar techniques and thus accelerate their adoption, modification, or rejection. Incorporating automation at the earliest stages of developing a novel instrument accelerates the inevitable, iterative design, build, and test cycles. At the same time, constantly striving to not just duplicate but leverage external innovations in creative ways keeps teams of skilled chemists and engineers at their peak performance. By encouraging innovation, such diverse teams can deliver a competitive advantage to scientists across drug discovery.

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