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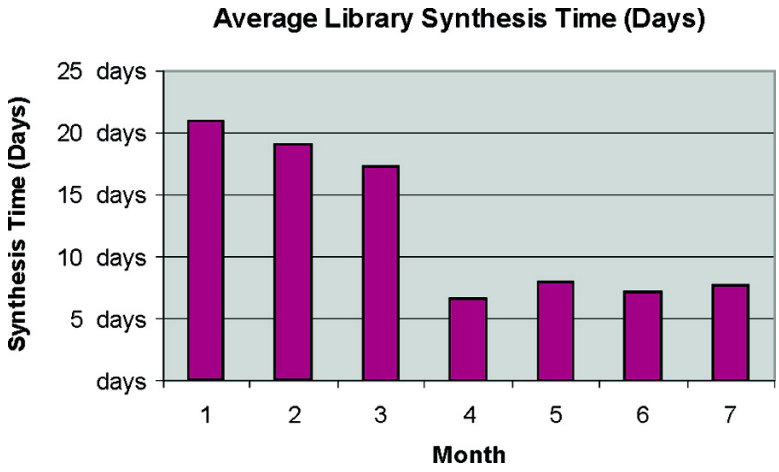

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Application of Lean Manufacturing Concepts to Drug Discovery: Rapid Analogue Library Synthesis

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The application of parallel synthesis to lead optimization programs in drug discovery has been an ongoing challenge since the first reports of library synthesis. A number of approaches to the application of parallel array synthesis to lead optimization have been attempted over the years, ranging from widespread deployment by (and support of) individual medicinal chemists to centralization as a service by an expert core team. This manuscript describes our experience with the latter approach, which was undertaken as part of a larger initiative to optimize drug discovery. In particular, we highlight how concepts taken from the manufacturing sector can be applied to drug discovery and parallel synthesis to improve the timeliness and thus the impact of arrays on drug discovery.

Introduction

Over the past several decades, the process of discovering new drugs has been transformed from a one-dimensional optimization problem (optimizing target activity in whole-animal disease models) to a multidimensional optimization problem (optimizing target and off-target activities using an array of predictive in vitro models.) At the same time new technologies, such as high-throughput screening and high-throughput chemical synthesis, have been introduced with an expectation of increased productivity. Despite these new technologies, however, the overall productivity of drug discovery has decreased over time, while productivity in other areas of the economy has increased.[1,2] Drug discovery is an inherently iterative process: design, synthesize, test, and redesign. One possible reason that new technologies have not had a broad impact on drug discovery productivity may be that they have failed to reduce the iterative cycle time, from conceptualization of a new molecule to receipt of the *key piece* of biological data, that allows design of the next generation molecule. On the basis of this hypothesis, our company has embarked on a project to leverage existing technologies across drug discovery with the goals of improving efficiency, reducing cycle times, and increasing the information content per cycle.[3] One element of this project is to increase the use and effectiveness of parallel array synthesis in lead optimization.

Over the past 10 years, parallel array synthesis of individual organic compounds has been used extensively to generate diverse structural libraries to support lead discovery efforts. The power of parallel synthesis to generate structural diversity has enabled high throughput screening of larger and more diverse pools of compounds as starting points for lead optimization efforts.[4,5] Since the synthesis of new compounds to increase the diversity of a lead discovery screening pool is not particularly time sensitive, the impact of array synthesis on lead discovery is not highly dependent upon cycle time for the synthesis of individual compound libraries. Consequently, library cycle times measured in months have proven to be acceptable for diversity generation in lead discovery.

Once a chemical lead is found, however, the focus shifts from the discovery of new chemotypes to optimization of the preferred chemotype. While lead discovery libraries are as large as 1 000−10 000 compounds, lead optimization libraries are typically in a range of 20−200 compounds. Lead optimization is an iterative process of design−synthesis−testing−redesign. Success is critically dependent upon the time required to complete each part of each productive iterative cycle. The application of parallel array synthesis to lead optimization can provide more information per cycle than individual compound synthesis (because more compounds are being tested per cycle), but if the cost is increased cycle time (resulting from increased time to synthesize a library rather than an individual compound), the overall impact of array synthesis on the progression of a drug discovery program may be limited or even negative. A number of approaches to the application of parallel array synthesis to lead optimization have been tried over the years,[6] ranging from widespread deployment by (and support of) individual medicinal chemists[7,8] to centralization as a service by an expert core team.[9,10,11] This manuscript describes our results with the core expert team approach, along with a discussion of how manufacturing concepts can be used to reduce synthesis cycle times for maximum program impact across drug discovery.

Drug discovery programs are typically organized into multidisciplinary teams of chemists and biologists who focus on developing new compounds to interact with a specific

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biological target. These teams generally remain together for the duration of a target specific drug discovery program which may span several years. By doing so, team members become experts in the structure−activity relationships (SAR) for a specific target, as well as for off-target activities relevant to the program. As a result, these team members are often the most knowledgeable of SAR trends and the most qualified to direct future chemical synthesis within that program. While well versed in program specific SAR, these same chemists may not necessarily be as highly qualified and experienced in the rapid execution of parallel array synthesis, particularly, if parallel synthesis is a technique used only infrequently by any individual team member. The centralized library synthesis service works to fill this gap by leaving compound design in the hands of the target-based project team while providing a core expert team to complete the actual parallel synthesis. For this approach to be successful, two broad criteria must be met: there cannot be artificially imposed limits on the structures of compounds to be synthesized, and the cycle time for library synthesis must be competitive with that for individual compounds. Our work, described herein, demonstrates that library synthesis by a core expert team can significantly reduce synthesis cycle times and thus increase the impact of array synthesis on lead optimization programs.

Lean Manufacturing Principles. When an array synthesis service is established by a core team, its operation becomes much like that of a custom manufacturing operation, such as, for example, Dell Computer.[12] In both cases, the product is custom manufactured in response to a customer order ("pull") rather than stockpiled based on future need projections ("push"), delivery time is critically linked to business success, and production depends on availability of a continuous stream of component parts (or, in our case, diverse chemical building blocks). Because of these parallels between array synthesis and custom manufacturing, it is instructive to look to the manufacturing sector for operating principles to help reduce cycle time.

The first operating principles for cycle time reduction emerged from the automobile manufacturing industry. Henry Ford commented on the inverse relationship between manufacturing cycle time and product cost as early as 1926,[13] and a set of formal principles was codified by Taiichi Ohno as the *Toyota Production System*[14] during the 1980s. In 1991, Womack and Jones named these principles *lean thinking* and popularized them in their book *The Machine That Changed the World*.[15] Indeed, these principles have now spread beyond the manufacturing sector, and an entire industry has been built to promote lean thinking, including publishing, training courses and seminars, software tools, and consulting.[16,17,18]

Lean thinking is based, in part, on eliminating waste from a process. Ohno[14] defined the *seven* wastes as *overproduction* (producing unnecessary parts or goods), *waiting* (any idle time when no value is added to the final product), *transportation* (unnecessary or repetitive moving or handling of parts or goods), *inventory* (stockpiling of raw materials, work in progress, or finished product), *motion* (movement of equipment, parts, or people that adds no value to the product), *non-value-added processing* (work carried out on the product that adds no value to the product), and *rework* (reprocessing because of poor quality control or other failure to produce the product correctly on the first try).

In addition to removing waste, a lean process will have other key attributes. Most notable is a pull system that requires customers to initiate the whole process, much like the computer order triggers the production process at Dell. A *Kanban*[19] system makes all key steps highly visible and tracks work in progress. A *workcell* arrangement places all key operations in the same location so handoff and all unnecessary transportation and motion are removed. Batch size reduction is used to convert large batch processes that often produce an enormous amount of waste to continuous-flow processes, and work teams are empowered to make immediate decisions during the manufacturing process.

Results and Discussion

Our initial goal was to test the concept of a centralized library synthesis service in support of lead optimization programs. We recognized that there could not be artificially imposed limits on the structures of compounds to be synthesized and that the cycle time for library synthesis would have to be competitive with that for individual compounds for the service to succeed. To test the concept, we set up a centralized library synthesis service team to focus initially on the execution of well-proven single-step solution-phase reactions. The group operates as a service whereby program chemists devise a library reaction scheme and provide the core molecule for elaboration. The library-synthesis team then executes library synthesis (including analysis and purification) and delivers final products into the normal workstream for biological testing. While the chemistry scope is not artificially limited, the initial focus was on simple single-step functional group manipulations (formation of amides, ureas, etc.), with the expectation that the scope of the rehearsed chemistries available to the group would grow over time.

When originally configured, the group was using shared automation equipment spread across several laboratories spanning a distance of over 200 feet. During the first 12 months of operation, the group gained key experience but did not have a significant impact on discovery programs because of long cycle times (averaging over 8 weeks per library) and limited availability of key building blocks for synthesis. Recognizing that efficiency had to improve, we reexamined our process taking into account many of the concepts of lean thinking.

The first step in a lean process transformation, called *value stream analysis*, is to identify those parts of the process that truly add value. Value stream analysis of our parallel array synthesis process quickly identified both the main value stream and non-value-added (wasteful) steps. The most common non-value-added parts of our process were the many waiting steps. For example, the process of actually selecting building block reagents for the library adds value, but waiting for those building blocks to physically be delivered to the lab adds no value. Waiting also occurs within several of the batchwise steps where the first sample in a sequential batch must wait for the last sample in the batch to complete the

step before the entire batch can move on to the next step. Much of this waiting is a direct outcome of large batch (or library) size, because less waiting occurs with smaller batches. Other non-value-added steps in our process included repeated, and sometimes unnecessary, dry down and format changes, repeated chemical analysis, and any steps that were repeated because of error or instrument failure.

The next step in a lean transformation is to eliminate as many non-value-added steps as possible. We began by eliminating waste from the reagent selection and acquisition processes. These are often the most inefficient steps in a library synthesis, especially when minimal constraints are imposed on the universe of potential building-block reagents. For an array to have maximum impact on a discovery program, there can be no artificial constraints on the structures of its members, and thus no artificial constraints on the chemical building blocks that will make up the array. At the same time, to avoid waste (of time), all necessary reagents must be readily available when needed. Maintaining a large internal building-block inventory has been proposed as the solution to this problem,[11] but it is neither practical nor cost-effective. Lean manufacturing has turned to just-in-time delivery, whereby components are ordered, manufactured, and delivered only in response to the "pull" of end-user customer orders. This is possible in the manufacturing sector because the number of potential component parts is always finite and usually not large. In contrast, the universe of potential chemical building blocks is infinite. Just-in-time synthesis of any possible building block is clearly not practical, and no such system currently exists. In the absence of very rapid custom building-block synthesis, we have devised a solution which provides very rapid access to a relatively small set of commonly used building blocks while still allowing acquisition of less readily available reagents when mandated by the specific structure−activity drivers.

The attempt to acquire a reagent which is not actually available on reasonable terms (e.g., out of stock, discontinued, or too expensive) constitutes pure waste. Accordingly, our efforts in this area have focused on a two-tiered model: on the front end, providing chemists with data-rich and data-accurate reagent selection tools and, on the back end, working internally and with vendors to create reagent collections which can be acquired rapidly and which have a high degree of availability. First, we have assembled a relatively small reagent collection (∼2000 reagents) for which, because we maintain complete control, we can guarantee immediate availability. For access to a wider array of reagents, we have worked with our primary vendor to gain real-time access to actual inventory information, and this inventory information is populated into our own databases. Now, when selecting reagents, chemists do so with real-time knowledge of which reagents are actually available for immediate shipment. When time is our most critical factor, we order only from the universe of immediately available reagents; on the other hand, we have the flexibility to order specific reagents when the target structure is more important than delivery time. Further, a number of reagent vendors are now offering custom packaging and weighing of building-block reagents, and we have successfully incorporated this feature into our synthesis work flow. As a result of these innovations, we can now order preweighed reagents in automation-ready custom packages with the certainty that they are in vendor inventory and will be delivered within 24−48 h. This minimizes the most common waiting steps in library synthesis and allows us to move quickly in response to library synthesis requests.

Other unnecessary steps in our process have been reduced or eliminated by creating an integrated team empowered to make immediate decisions. For example, we had previously dried down all synthesis samples before handing them off for purification. Now, the integrated team makes an immediate and informed decision about the need for dry down: often the volume and nature of the synthesis solvent are such that dry down is not needed. Similarly, prepurification analysis and purification were previously two distinct steps performed by different groups in different labs. Now, with increased use of modern chromatography equipment, prepurification analysis and purification are often done in a single unattended step. Removal of these unnecessary steps from our process can reduce the cycle time by many days.

Our original process also included waste associated with waiting for shared instruments to become available and with the transportation and motion involved in moving samples. To address this obvious waste, we identified specific instruments that could be dedicated to these tasks and relocated them into a single laboratory where they are aligned roughly along the lines of our process flow. Lean thinking recommends that every individual involved in a production process should be able to determine the status of the entire production line at a glance without leaving the production area or resorting to cumbersome computer systems.[17] In our lab, we implemented a simple white board system for tracking libraries through the process and providing up to date scheduling and planning information to all team members.

An important component of Lean thinking is the leveling of a production sequence, which in turn is closely related to batch size (this is referred to as *Heijunka*). In traditional manufacturing settings, components are manufactured in large batch sizes to maximize machine utilization. This leads to waste (manufacturing more than is needed, resulting in excess inventory) and waiting (because all samples in a batch have to wait for the last sample in the batch before moving on to the next step.) These same concepts apply in drug discovery. The library synthesis team receives requests for synthesis of libraries varying from about twenty members to as many as several hundred members. We previously synthesized these libraries as complete libraries, one library at a time, in the order that requests were received. Thus, we might find ourselves making a library of twenty compounds and then, following that, making another library of several hundred compounds. Because the library-processing time for a given step, purification by preparative HPLC for example, varies by the number of compounds in the library, it was impossible to establish a repetitive schedule, resulting in haphazard instrument use. Furthermore, larger libraries tended to have longer turnaround times than would be expected from simple linear math, when compared with small

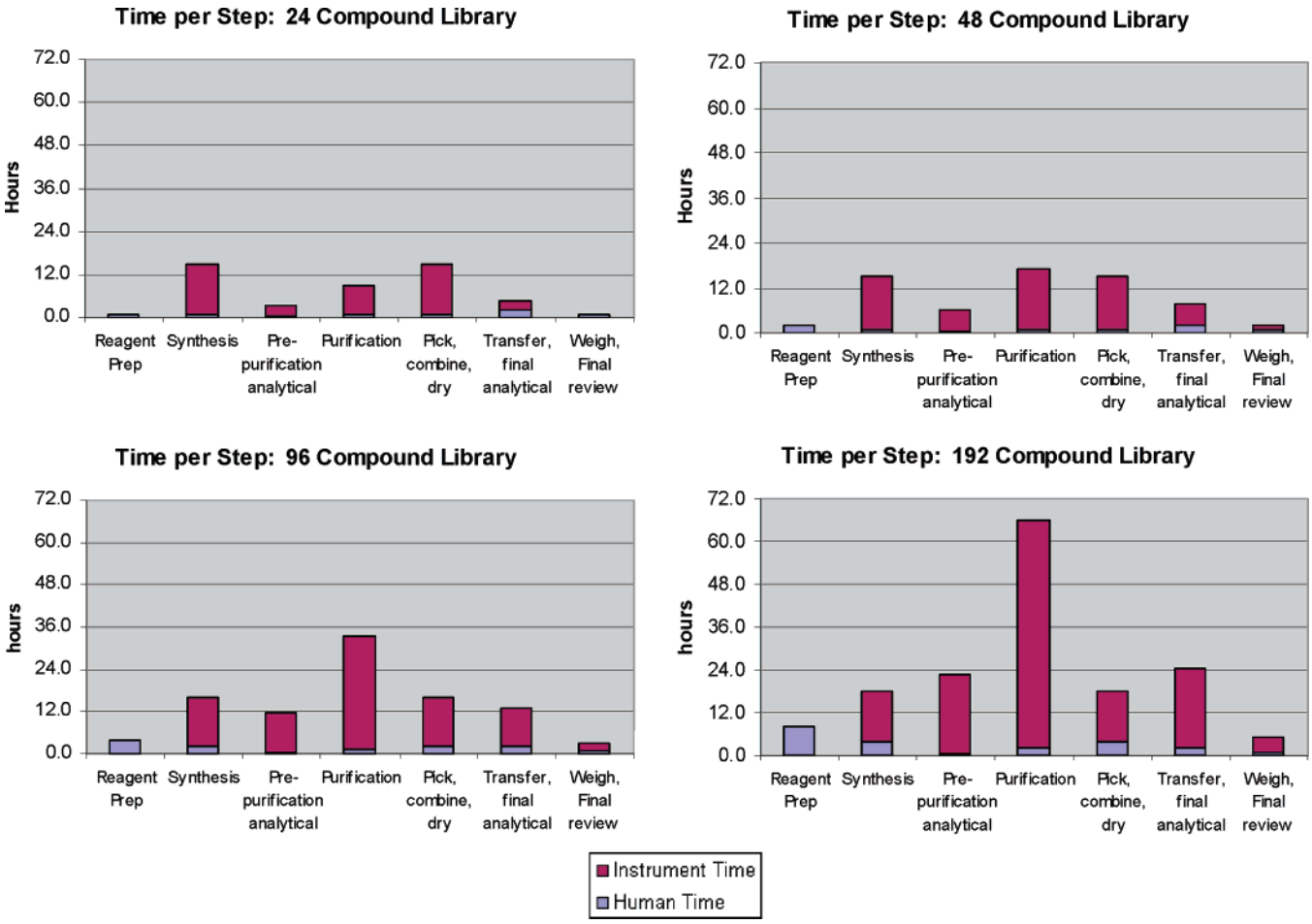

Figure 1. Processing time per step vs library size.

libraries, partly, because of unexpected delays related to the processing of large sets and also because of the difficulty of scheduling larger blocks of sequential time for steps that require human activity. Finally, we found that downstream of our laboratory, larger libraries often became a "work in progress" waiting to be tested in biology labs because of the throughput limitations of the testing regimen. The solution to all of these problems was batch-size reduction to enable load leveling.

To determine the optimal batch size, we first analyzed our process to identify steps whose processing time is dependent upon batch size. From this, we identified the following distinct processing steps:

1. Reagent Preparation
2. Synthesis
3. Prepurification analytical
4. Purification
5. Pick fractions, combine, and dry down
6. Transfer to final tared containers; final analytical
7. Weigh and final review

Next, we looked at those steps to estimate the largest batch that could be processed through each of those steps in a single unattended overnight run (16 h), assuming moderate HPLC gradient times for all analysis and purification steps (Figure 1). An examination of the figure shows that all steps require less than 16 h total time for a libraries of 24 or 48 compounds. For a 96 compound library, the purification time exceeds our 16 h target (1.5 h human time for preparation and 32 h of instrument time). When the library size grows to 192 compounds, both the analysis and purification steps exceed our 16 h target. On the basis of these considerations, we settled upon a maximum batch size of 48 compounds per synthesis batch. Requests for synthesis of larger libraries are broken down into smaller batches of 48 or less compounds. By working with libraries of 48 compounds or less, we are now able to fully use unattended overnight machine time (for example HPLC or LCMS analytical equipment) while completely processing a single batch on a machine during that overnight time. This allows the entire batch to be moved on to the next step by the operators during the following day.

In fact, the actual human time required for each step during the day is generally only a few hours. Thus, it is possible to start a new library synthesis every day and to maintain a steady state of six libraries in progress at any one time (reagent prep and synthesis are often combined into a single day), with one library being at each step of the process. With a team of six scientists, the team has delivered an average of one library, of up to 48 compounds, every working day over a period of many months. This pace still leaves time for other activities including client interaction, reagent selection and management, chemistry rehearsal, and technology development.

By using optimized batch sizes and breaking our process down into discrete daily steps, we now produce something that is beginning to approach a continuous flow of new

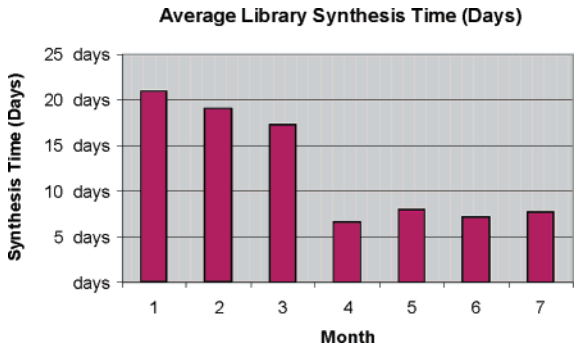

Figure 2. Library cycle time reduction through batch-size control (batch-size control was introduced after month 3).

compounds. Since we are working with several discovery programs at once, we can deliver a continuous flow of libraries to many programs without saturating the biological testing capacity of any single program. For example, if we are working at capacity and starting a new library every day, we can deliver one library per week to each of five different discovery programs or one library every other week to up to 10 programs. In a typical month, we now work with a range of about 8−12 programs with some receiving only one library and others receiving up to four libraries per month. This continuous flow of compounds into program biology is more consistent with their testing patterns and avoids a build up of work in progress in biology labs.

Library Synthesis Results. By applying the principles outlined above, we have reduced our library synthesis cycle time from over eight weeks to well under two weeks from the day we begin actual synthesis. The removal of some of the important waste steps gradually reduced our cycle times to four weeks. The most dramatic cycle time reduction came via process leveling through batch size reduction; as shown in Figure 2, there was an immediate pronounced synthesis cycle time reduction after month 3 when we began to limit batch size to no more than 48 compounds. After the initial synthesis request from a program, the first library can usually be delivered in less than two weeks; subsequent libraries are delivered at regular intervals with the synthesis time for each individual library averaging 6−7 days from the initiation of synthesis to submission of final compounds. This was done without making significant changes to our actual synthesis infrastructure: synthesis is done using the MiniBlock or MiniBlock-XT Plus synthesizer,[20] and analysis and purification are done using the customized Shimadzu Discovery-VP chromatography package[21,22,23] or, more recently, commercial systems from Waters and Dionex. Other manipulations are done as previously described for larger lead discovery libraries.[24]

Keeping in mind that our original goal was to test the concept of a centralized library synthesis service in support of lead optimization programs, we believe that we have now shown that such a service can deliver high-impact libraries to discovery programs in a timely fashion. For example, in a recent 12-month period, a team of 6 scientists delivered over 190 libraries (4688 compounds) with an average turnaround time of 9 days, an average success rate (number of compounds successfully synthesized out of total number of attempts) of around 80%, and an average purity of 98%.[25] These libraries were made in support of 20 different discovery programs at various phases and included about a dozen different chemical reaction types. More importantly, by integratation of rapid parallel synthesis with rapid biological evaluation against both primary and selectivity targets, several of these libraries led to unexpected structure−activity relationships that turned their respective discovery programs in new directions. Recent trends are toward increased synthesis productivity as the group gains experience and continues to improve its process.

Over the course of a year, the most common reaction request received by the library-synthesis team was amide formation (60% of requests), followed by related ureas, sulfonamides, and carbamates (16%, 7%, and 6% respectively). Alkylation and displacement reactions were the next most frequently requested, followed by the formation of more unusual functional groups. Interestingly, carbon−carbon bond-forming reactions (Suzuki, etc.) were not requested in large numbers, even though they are available in our repertoire. A recent trend, though, is toward requests for increasingly complex chemistry as discovery groups become more experienced with use of the centralized library synthesis concept.

Our drug discovery organization is located at three geographically distinct sites: two close to one another and the third somewhat distant. The original centralized library synthesis team was located at one of the two proximal sites. Statistics from the first year of operation show that the vast majority (>90%) of synthesis requests were generated from one of the two proximal sites and not from the more distant site. This suggests that proximity is important to facilitate discussions about potential library opportunities, as well as for technical information exchange during library synthesis. On the basis of those observations, we are now moving from a “centralized” library-synthesis model to a “federated” model, in which there will be a library synthesis team located at each major site.

Conclusions

The successful application of array synthesis to lead optimization programs requires that the compounds synthesized be of the same quality (in terms of both design and purity) as compounds supplied by traditional methods and that they be delivered to programs in the same time frame as compounds synthesized traditionally. With the iterative design−synthesize−test cycle of drug discovery, it stands to reason that, if the cycle time is the same for a library of new compounds as it is for a single new compound, then the information-rich nature of the library (versus a single compound) should empower the library approach to deliver more *productive* cycles of learning than the individual compound approach. This concept has been difficult to test in the past because of compromises in terms of compound design and cycle time associated with library synthesis. In an attempt to reduce the cycle time difference between library synthesis and individual compound synthesis, we created a centralized library-synthesis team to focus on refining the library-synthesis process. This, in turn, allowed us to use well-proven manufacturing principles as a framework for optimizing the synthesis process.

The lean thinking manufacturing principles allowed us to identify simple process improvements that reduced our synthesis cycle time from eight weeks to under two weeks. Implementation of lean principals in our lab involved the following transformational steps:

1. Value stream analysis

2. Elimination of non-value-added steps

3. Empowerment of team members to make rapid decisions

4. Implementation of a white board system for internal communications

5. Process load leveling through batch-size reduction and normalization.

By applying rapid iterative library synthesis, we have shown that array synthesis can compete with individual compound synthesis in driving program SAR. Importantly, we have also shown that the centralized expert-team approach can satisfy the long-held aspiration of empowering large medicinal chemistry departments with parallel synthesis capability without the cost and overhead of a large support and training group.

The reduction of the cycle time for actual synthesis has now shifted the bottleneck to other parts of the process. For example, the first time we work with a new program or group there is a tendency for the reagent selection process to become prolonged and iterative as the group learns the process. When we work in an iterative fashion with a single group, on the other hand, reagent selection is generally rapid but reagent-management logistics can become time-consuming. We are currently developing new tools to address this part of the problem and will report our results when they become available. In addition, we have engaged in optimization of sample distribution and biological testing cycle times. Application of this approach to distribution and testing, as well as to specific drug discovery programs, will be reported in the context of those programs at the appropriate time.

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(25) These results are in line with results recently reported from other groups that have also moved to the centralized library service paradigm, for example, see ref 5.

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