Making medicinal chemistry more effective—application of Lean Sigma to improve processes, speed and quality

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The pharmaceutical industry, particularly the small molecule domain, faces unprecedented challenges of escalating costs, high attrition as well as increasing competitive pressure from other companies and from new treatment modes such as biological products. In other industries, process improvement approaches, such as Lean Sigma, have delivered benefits in speed, quality and cost of delivery. Examining the medicinal chemistry contributions to the iterative improvement process of design-make-test-analyse from a Lean Sigma perspective revealed that major improvements could be made. Thus, the cycle times of synthesis, as well as compound analysis and purification, were reduced dramatically. Improvements focused on team, rather than individual, performance. These new ways of working have consequences for staff engagement, goals, rewards and motivation, which are also discussed.

Introduction

The challenges that face the pharmaceutical industry have been clearly articulated by industrialists and business analysts. Despite increasing investments in R&D (research and development), the number of new drugs reaching the market has been declining during recent years [1]. There are now positive signs of increasing volume in early development, but there is still a clear need for the pharmaceutical industry to improve, if only for the simple reason of being able to fund the progress of these growing pipelines.

Many companies have embarked on major improvement programs, which have included internal re-organization, greater externalization to embrace the biotech culture and capture innovation, and the movement of investments to lower cost countries. The challenges our industry faces are not, however, unique. Indeed, the need to simultaneously improve the speed of delivery and the quality of the product, while reducing the cost of operations, is ubiquitous in any commercially competitive arena. As a result, we, as well as others [2–7], have attempted to apply the structured process improvement methodology 'Lean Sigma', which has its origins in manufacturing, to the medicinal chemistry contributions to the drug discovery process (Box 1).

Lean Sigma draws on a structured approach to process improvement [7]. It does so by putting the customer's view at the heart of the definition of what is quality and of value and by delivering that consistently and quickly with the minimum of waste. Lean Sigma frequently focuses on establishing and optimizing processes for activities that are repetitive in nature, as well as on driving out

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BOX 1

Methods such as Lean, Six Sigma, and Lean Six Sigma have their origin in manufacturing, where they are deployed to increase process efficiency. Recently these methods have been put to use to increase efficiency also in pharmaceutical R&D [7]. Definitions of the three methods are given below, together with our interpretation of what Lean Sigma means in the context of drug discovery.

Lean (www.lean.org): Lean Enterprise—A business system for organizing and managing product development, operations, suppliers, and customer relations. Business and other organizations use lean principles, practices, and tools to create precise customer value-goods and services with higher quality and fewer defects—with less human effort, less space, less capital, and less time than the traditional system of mass production.

Six Sigma (www.isixsigma.com): Six Sigma is a methodology that provides businesses with the tools to improve the capability of their business processes. This increase in performance and decrease in process variation leads to defect reduction and vast improvement in profits, employee morale, and quality of product.

Lean Six Sigma (www.sixsigmainstitute.com): Lean Six Sigma provides an integrated and balanced combination of the speed and variation reduction power of both Lean and Six Sigma to achieve business management process full optimization.

Lean Sigma: Application of Lean Sigma in Pharmaceutical R&D focuses on identification of common processes, which are then optimized so as to reduce non-value adding steps, that is, removing waste. In a drug discovery context Lean Sigma also focuses on reduction of variation and defects in these processes, but not to the extent of reducing these parameters to a Six Sigma level. Because Lean Sigma provides a structured and data driven way for improvements, it is well suited for the highly scientific environment of R&D, and usually leads to high engagement of co-workers.

waste from these processes. Such simple principles are generic and can be applied to the inventive discovery process [4,6,7,8]. It should also be emphasized that Lean Sigma relies on involvement of the staff working in the process that is being subjected to an improvement initiative in order to deliver most benefits. Since Lean Sigma provides a structured framework for improvements, it is well suited for use in the highly scientific environment of R&D and usually leads to a high level of engagement of the co-workers.

At the outset of our work, we examined the lead optimization process at a high level. It became clear to us that the lead optimization phase fell into two separate subphases, the first being the iterative process of improving lead compounds through the design-make-test-analyse (DMTA) cycle (Figure 1). Then, once a quality compound has been identified and successfully progressed through initial testing *in vitro* and *in vivo*, a more comprehensive assessment of developability risks takes place. It was found that the phase in which DMTA was operational was the longer of the two subphases of lead optimization (LO), and hence offered a great opportunity for improvement. Even more significantly, the DMTA cycle became the focus of our attention because its iterative nature offered cross-project benefits that could be reaped over and over again. As a result, we began to focus on how we could make the contribution of medicinal chemistry to the DMTA cycle more effective in terms of speed and quality.

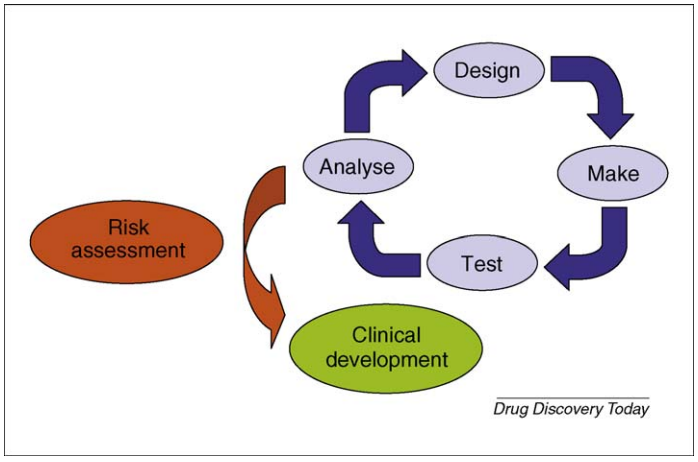


FIGURE 1

Lead optimization can be described as consisting of two separate subphases, the first one being the iterative process of improving lead compounds through the design-make-test-analyse (DMTA) cycle. Once a quality compound has been identified in this iterative phase, it is assessed in more advanced models to identify any risks before proceeding to clinical development.

The DMTA cycle

Testing

Improvements in high throughput screening (HTS) technologies and reductions in cost per test have been well delivered across the pharmaceutical industry. Although this revolution began in centralized environments, primarily conducting biology testing to find new hits, many of the technological developments have subsequently been decentralized to mainstream biology labs and have been further extended into non-efficacy testing environments such as drug metabolism and pharmacokinetics (DMPK) and physical chemistry. As a result, the speed and capacity of testing have generally increased over the past decade or more. These increases in capacity have also allowed a wider spectrum of tests to be conducted in parallel. When used wisely, that is, when compounds are screened in parallel, in tests selected on the basis of the issues faced by the project, this allows for a more effective lead optimization than if screening is done sequentially [8,9].

Analysis of data

Perhaps also driven by the HTS revolution, many companies have expanded their computational chemistry capabilities in recent years to be able better to handle the large volume of data that was becoming available. This increase in specialist computational chemistry support has improved our ability to analyze data in new and more insightful ways [10]. An additional and important impact has been seen from the emergence of powerful, but relatively simple and user-friendly, applications for data analysis, which have become available to the non-specialist. These tools have made it possible for the wider community of medicinal chemists to explore more complex data in visually simple ways, resulting in improved interpretation. Taken together, the increased test capacity in combination with improved data analysis provides drug discovery teams with an excellent platform of data and information, which should result in increased efficiency and effectiveness in the DMTA cycle.

Design of new compounds

The rise of robotic and combinatorial chemistry around 1990, with the demand for more and more compounds for corporate screening libraries, inevitably steered medicinal chemists toward chemistries that were robust and reliable across a range of substrates. At that time, ease of synthesis became more important than before. Most medicinal chemists now acknowledge the importance of compound properties that influence ADME (absorption, distribution, metabolism and excretion) and toxicity and the consequences of failure to control them [11,12]. When analyzing the DMTA cycle, it is helpful to consider that many ideas can be created at relatively high speed and low cost at the design stage, but that the capacity of synthetic chemistry to convert all those ideas into testable compounds is limiting. Furthermore, almost all the properties of the compound that we as medicinal chemists are interested in optimizing (such as affinity, solubility, permeability, clearance, safety, and so on) are directly related to the structure and are, therefore, fixed at the point of conception. From a process optimization perspective, it is logical to try to put more emphasis on improving the quality of compound design, while it is still cheap to explore the many options, but then to select only the very best, highest quality ideas to progress into the more resource-intensive activities of synthesis and testing. This should lead to fewer compounds having to be made to achieve progress within a drug discovery project, and potentially fewer DMTA cycles being required to do so [8]. Additional benefits should be reaped as compounds that have predictable problems are deselected during the design process, thereby freeing up further capacity in synthetic chemistry and testing. Therefore, in order to improve the quality of design, we have introduced Design Teams in which representatives from medicinal, synthetic, computational and physical chemistry, and DMPK can all contribute to the design process. Furthermore, we have introduced guidelines for some parameters that can be computed or predicted with reasonable reliability before synthesis commences, such as lipophilicity, molecular weight, and structural alerts for reactivity and reactive metabolite generation.

Make—synthesis of compounds

There have been many initiatives to try to improve the efficiency of synthetic chemistry and its contribution to drug discovery projects in recent years. These have included attempts to increase individual productivity, training to increase knowledge in synthetic and medicinal chemistry, as well as reduction of synthetic complexity and route length. Retrospectively, it is somewhat surprizing that the time spent on synthesis has rarely been considered as a dimension for improvement, perhaps with one notable exception [2]. There seems to be an implicit acceptance that research is unpredictable, and the time taken to complete novel chemistry is unpredictable and difficult to alter. To our knowledge, for the first time in our organization, we decided to turn our attention to the speed of synthesis in order to try to make the DMTA cycle turn faster.

The analysis of 'make' using Lean Sigma as a method

Within 'make', that is, synthesis of novel compounds for biological evaluation, the main steps are; (i) deciding on the route for synthesis of the target compound, (ii) ordering and assembly of reagents and starting materials, (iii) carrying out the synthetic sequence, and (iv) final purification and analysis of the product. This 'synthesis process' was further analyzed using a data driven Lean Sigma approach, which revealed a number of opportunities for improvements.

When examining how chemists decided on how to make compounds, that is, how they selected the route and the procedures for the individual steps, it became evident that different chemists approached the task in different ways. Chemistry team meetings, however, often focused on repeated failures that were reported retrospectively, rather than having an emphasis on evaluation of route planning in a prospective manner to anticipate and avoid problems. From a process point of view, this was an important finding because the decision about how to approach the synthesis of a novel molecule is one of the most important in 'make', since a good decision secures rapid success, while a bad decision incurs unnecessary, unsuccessful work.

Data were then gathered for the steps subsequent to route selection, that is, ordering and delivery of reagents/starting materials, and carrying out the synthesis. A large variation in lead time was found for ordering and delivery of starting materials and reagents. The internal process to place orders took several days (median three days), while the external delivery process from the vendor took around a week (median six days). As one would expect, depending on which chemical was ordered and which supplier was involved, the lead time for delivery from the provider varied between hours and months. Only patchy data were available on the lead time for the synthesis part of 'make', that is, from the point in time when synthesis of a target compound was started to when it was available for screening. We therefore had to acquire these data, retrospectively and in real time. Typically, this showed that the lead time for synthesis was long, with a median of three to four weeks (Figure 2a). Furthermore, the variation in the synthesis lead time was large, with significant numbers of compounds taking up to three months to reach completion. In support of the data gathered, a voice of the customer (VOC) survey also suggested that provision of new compounds could be slow and variable. This survey also revealed that waiting for re-synthesis of compounds, which had been consumed in the initial parts of the screening cascade, sometimes led to significant delays in projects. Finally, analysis of deviation reports completed by chemists indicated room for improvement in the infrastructure put in place to support chemists in wide range of areas.

When we set out to make medicinal chemistry more effective, steps were already under way to improve the existing processes for analysis and purification. The Lean Sigma analysis of ''make'' provided further support for these ongoing improvements. This analysis also suggested additional improvements, for instance, ones affecting use and maintenance of walk-up instruments for analysis and purification, as well as for how to make the dedicated plate-purification service more attractive to chemists.

Through process improvement lenses, the above descriptions suggested there was considerable opportunity for improvement within 'make'. We saw opportunities to reduce the classic lean waste of re-work by increasing the quantity of compound made and by improving route selection to increase 'right first time' or success rate. In addition, there was a clear opportunity to reduce the variation and magnitude of lead time in synthesis, as well as in analysis and purification.

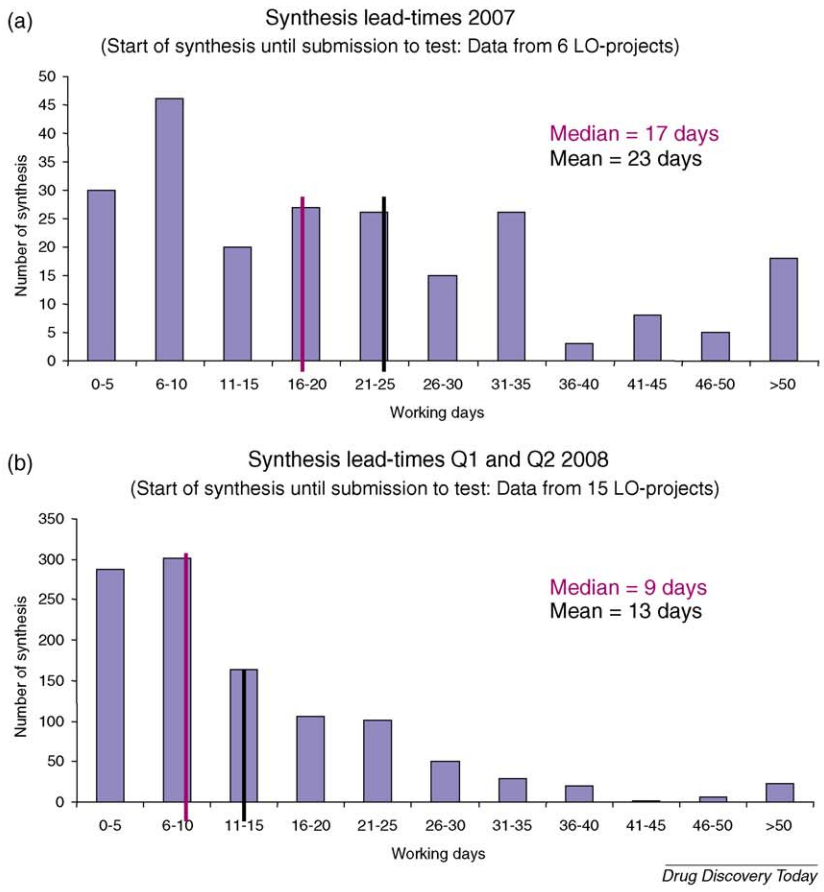


FIGURE 2

(a) Historical synthesis lead times, recorded before performing a Lean Sigma analysis, often reached up to 35 working days or more. **(b)** After implementing improvements that controlled the work in progress of chemists and increased team work the synthesis lead times were reduced significantly. Thus, most synthetic targets were completed in less than 15 working days, and very few required more than 30 days. Lead times refer to synthesis of individual target compounds, not to sets of compounds designed to answer a hypothesis.

Improving the synthesis process

The opportunity to reduce unnecessary remakes of screening compounds, revealed in the VOC survey, presented us with the quick win of increasing the quantity of compound made. It was therefore agreed that in LO the target should be to make sufficient material in the first batch to cover the needs of primary *in vitro* screens (potency, selectivity, physical chemical properties, and an *in vitro* DMPK panel), an *in vivo* rat PK (pharmacokinetics) study, as well as material to go into the corporate HTS collection. For most project in the LO phase this means that 30–35 mg of material should be made.

From analysis of business processes it is well known that there is an inverse relationship between the quantity of work in progress (WIP) and the time taken to complete the work [http://www.factoryphysics.com/Principle/LittlesLaw.htm]. This relationship should also apply to synthesis, indicating that it should be possible to reduce the synthesis lead time by limiting the work in progress of chemists and chemistry teams. Traditionally, chemists have worked alongside each other, each working on multiple target compounds independently from the other members in the team. Unless managed very carefully by the team leader, this model results in a large, and relatively invisible, amount of work in progress across a team of chemists. In order to reduce the lead time for each target, it was decided to introduce more cooperative team working, combined with actively restricting the work in progress. The key driver to achieve and sustain these two goals was the introduction of a visual planning system that enables control of work in progress and also facilitates work sharing across the team (Figure 3). Such a visual planning system also allows the team to keep track of ideas, arrival of starting materials, ongoing synthesis and compounds being purified. It also makes problems more readily recognizable when they do occur.

We have reflected on why chemistry teams have always been organized in such an individual-based way. We believe that a major factor lies in the education and training of chemists at universities, in particular at the doctoral and postdoctoral level, which is always focused on delivery of separate pieces of work by the students. This habit has then been maintained in the pharmaceutical industry even though team working, with chemists supporting each other in the delivery of compounds, would be beneficial and reduce synthesis lead times.

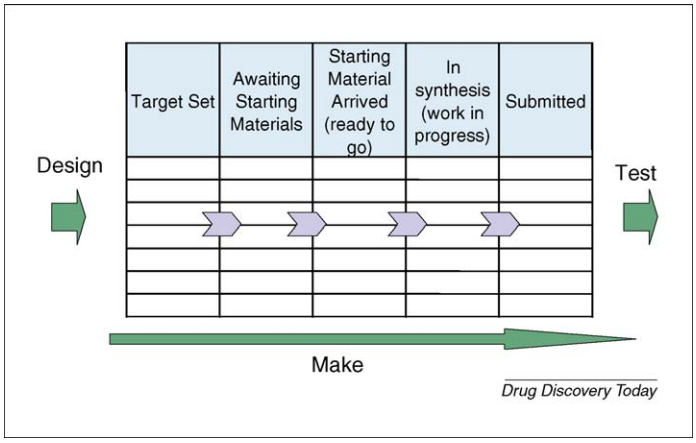


FIGURE 3

Outline of a visual planning board that allows chemistry teams to visualize and track the status and flow of compounds through the synthesis process. Some teams prefer to use ordinary whiteboards, while other teams have moved to an electronic version.

In addition to introducing visual planning of the work in chemistry teams, two other drivers of change for chemistry team meetings were found. First, team members reported that the retrospective information-sharing meetings served little value to them as attendees and presenters. In addition, there was little opportunity for team members to give and receive advance input into upcoming chemistry, which would maximize the probability of putting on the right reactions first time. We saw the opportunity to tackle these two problems with a single solution: forward looking chemistry meetings (FLCM) at which proposed synthetic routes were discussed, improved and agreed by the team in advance of ordering starting materials. This approach also had the additional benefit of gaining commitment to the route from all of the team, thereby enabling any member of the team to conduct the lab work at a later date.

Whiteboards for visual planning and reduction of the work in progress were introduced. These, together with forward looking chemistry meetings, led to significant reductions in lead time for synthesis (Figure 2b). The median lead time from starting the synthesis of a target compound to when it was available for screening in compound management, was reduced from 17 to 9 working days. In addition, the variation in the synthesis lead time was also reduced. The importance of tracking, discussing and challenging lead times was illustrated by one of the pioneering teams. This team had restricted its work in progress to 1.5–2 targets per chemist but found that lead times were still too high. Analysis of the data revealed that a lengthy and complicated synthetic route to one of the chemical series was an important contributor to the high lead times. As this series also was found to be less promising from a medicinal chemistry and SAR (structure activity relationship) perspective it was decided to focus on the more attractive and tractable series. In addition, the work in progress was further reduced to close to one target per chemist. As a result of these changes, lead times were further reduced. As illustrated by this example, clear focus on time coupled with visualization of ongoing chemistry facilitated timely decision-making.

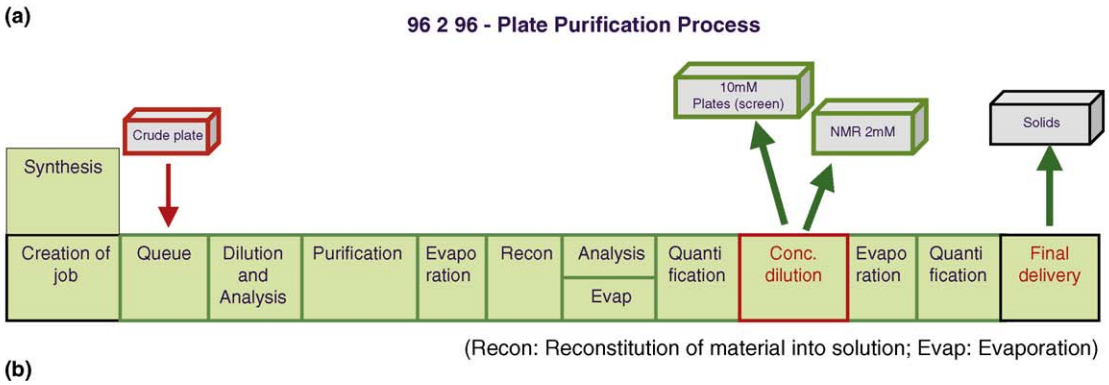
Finally, a number of improvements were made to the supporting infrastructure for chemists to reduce non-value adding activities (waste), thus allowing chemists to focus on science and lab work. These improvements targeted areas such as access to routines useful for chemists, pre-synthesis safety assessment, documentation of synthetic work, stores and stocktaking of reagents, maintenance and upkeep of instrumentation for analysis and purification, as well as sharing of knowledge on how to handle infrastructure in short Tips & Tricks sessions.

Improving analysis and purification

The existing batch plate purification service now faced new challenges, that is, purification of larger amounts of compounds with reduced lead times and maintained quality. Three major areas of improvement were identified by analysis of the subprocesses of the plate purification process (Figure 4a), namely, dissolution of both the crude and purified compounds, re-purifications to meet the quality cut-offs and inefficient use of the instruments in the process. Because dissolution of crude compounds took a disproportionate amount of time, it was agreed that the customer, that is, the synthetic chemist, would dissolve and filter the samples before submission to the purification service. By far the most time consuming and lead time prolonging issue was insufficient quality of the resolution, leading to a need to re-purify compounds, loss of material, and large volumes of collected fractions that needed time-consuming evaporation. Consequently, two major changes were made to improve how chromatography was run. Firstly, 'sandwiching' of the injected samples was implemented to minimize precipitation of the compound in the system before entering the chromatographic column. This allowed an increase in the amount of crude material that could be purified and minimized downtime in the process as well as loss of material. Secondly, use of new chromatographic material allowed some of the purifications to be run at high pH (>9) resulting in stronger retention and less 'on column' dilution of the target compound, which reduced evaporation time and gave an eluted product of higher purity.

In addition to the technical enhancements, the team changed their way of working. Initially, each analytical chemist moved a set of compounds on a plate, or several plates, through all the subprocesses to final delivery. Inevitably, when a problem arose in some part of the process, timely delivery of several plates was affected owing to collisions of work in progress. To circumvent this, the whole process was divided into three main areas for which each team member was responsible for a week, after which time they were rotated. This secured a much better control and operation of the limited set of instruments each person was responsible for during the five days working period, which significantly reduced deviations owing to instrument down time. In addition, rotation ensured that all team members continued to have the knowledge and skills required to operate the whole process. The technical improvements, together with altered working practice, resulted in an improved and more robust batch process overall, which was clearly reflected in reduced and sustained lead times (Figure 4b).

Subsequent to purification, the compounds are analyzed to assess chemical purity, an accurate mass, and a chromatographic lipophilicity measurement. Furthermore, they are also characterized using plate-based ^{1}H NMR spectroscopy. Finally, the process delivers a 10 mM plate of the purified compounds to be used for biological screening, with excess solid material being stored in the compound collection.



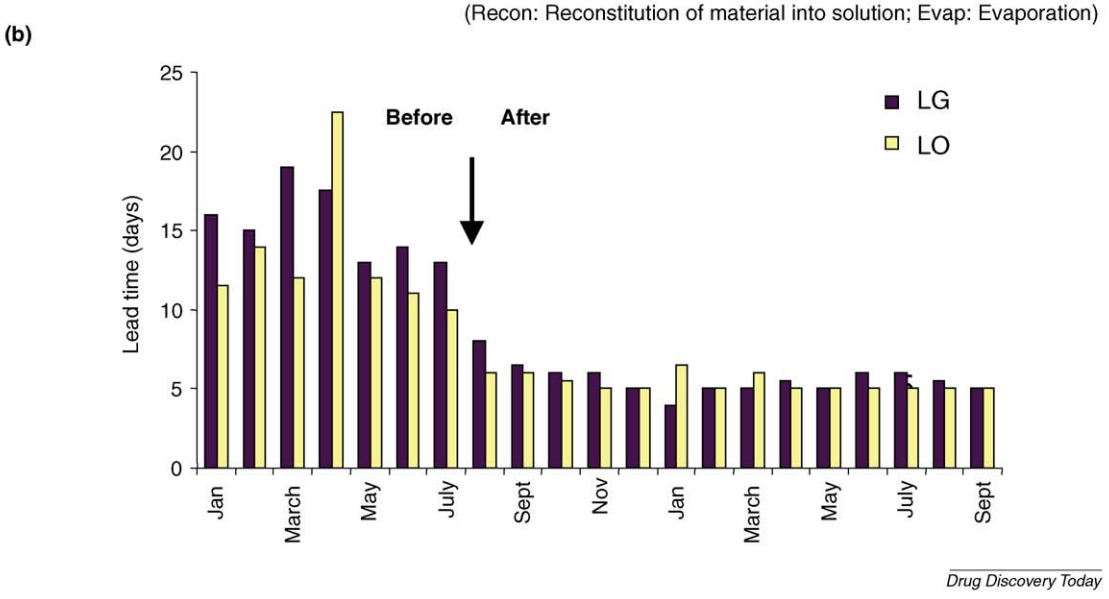


FIGURE 4

(a) The 96 2 96 plate purification process used for purification of compounds from the lead generation and lead optimization phases in drug discovery. The process delivers 10 mM solutions ready for biological screening, 2 mM solutions for plate NMR analysis and solids to the compound collection. **(b)** Lead times for purification of compounds in the 96 2 96 process before and after major improvements were implemented. LG: lead generation compounds; LO: lead optimization compounds.

Additional considerations when 'thinking lean'—customer focus

In addition to the production of a physical sample, we realized that the knowledge of how to make a compound is also a key output from the synthesis process; therefore we recognized intellectual property and process development chemistry were additional important customers. The quality of the knowledge-based outputs to these customers was improved as follows: first, experimental procedures were recorded in the corporate electronic laboratory notebook in a 'patent-ready' format for each new reaction. Secondly, 'process chemistry ready' procedures were made available for the most common chemical transformations, such as amide bond formation. This encourages chemists to choose reagents that are suitable for later scale-up in the first instance, rather than using reagents that would need to be replaced at a later date. Finally, with the new emphasis on speed of delivery from chemistry, it became necessary to consider investment in improving the synthetic sequence and its robustness in order to enhance the rate of progress in the discovery phase of the project. In addition to facilitating reductions in chemistry lead times, early investments in route development offered potential downstream benefits to process development chemistry in terms of speed and cost of later synthetic campaigns.

Objective-setting, reward, engagement, and motivation

The change from individual-based working practices to team-based work sharing precipitated the need to re-consider recognition, reward, and performance management in this new environment. This resulted in the introduction of standardized objectives for chemists and LO chemistry teams, which were then complemented with objectives specific for the individual chemist or team. Assessment focused not only on what was done but also on how it was delivered. In this way, we tried to ensure that the recognition and reward framework was well aligned to the new ways of working we wished to encourage and acknowledge.

We believe that a crucial success factor in Lean Sigma methodology is that the team which makes the improvement recommendations comprises those involved in the work on a day-to-day basis. The lab scientists who work within the process have the necessary level of credibility with their peers to make recommendations for

change. Additionally, they spent considerable time and energy communicating with the rest of their peers throughout the process, both formally through presentations, but also informally in the tearoom or in the lab. It is our belief that the same recommendations would have been much more difficult to implement if they had come from managers not involved in the core synthesis process.

One important element of team motivation is for the members to work together to achieve a common goal within a clear team context. The team-based visual planning boards provide a transparent overview of all the ongoing chemistry work in the project. Thus, it is readily apparent when progress is made, which by itself can be very motivating for teams. When the first data began to emerge showing the dramatic reduction in lead time as a result of the changes implemented in the synthesis process, there was a palpable sense of team pride in the results. As a consequence, commitment to the new ways of working has been sustained over a period of 12 months.

Conclusions

Although the design and synthesis of novel drug candidates is inherently innovative, requires true scientific research, and experiences low levels of success, it is nevertheless possible to describe the underlying work in terms of processes [3]. When placed in the hands of research scientists, Lean Sigma offers powerful tools and interventions that have given rise to dramatic and sustainable improvements in speed, consistency and quality of work. It is, of course, people who have the insights and inspiration to solve the many difficult problems a typical drug discovery project encounters. This human aspect of Lean Sigma often goes unreported. A sense of pride in what has been achieved, and a new confidence in being able to solve other bigger problems has emerged in those people who have been involved in improvement projects and perhaps that is just what the pharmaceutical industry needs.

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