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Helping science to succeed: improving processes in R&D

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Bringing drugs to the market remains a costly and, until now, often unpredictable challenge. Although understanding the underlying science is key to further progress, our imperfect knowledge of disease and complex biological systems leaves excellence in execution as the most tangible lever to sustain our serendipitous approach to drug discovery. The problems encountered in pharmaceutical R&D are not unique, but to learn from other industries it is important to recognise similarity, rather than differences, and to advance industrialisation of R&D beyond technology and automation. Tools like Lean and Six Sigma, already applied to increase business excellence across diverse organisations, can equally be introduced to pharmaceutical R&D and offer the potential to transform operations without large-scale investment.

Introduction

Science has greatly advanced our mechanistic knowledge of human disease, but bringing drugs to the market remains challenging and the outcome is too often not predictable [1,2]. As we rely on serendipity for success, efficiency and quality in execution is the most tangible lever to reduce cost and shorten timelines. Consequently, there has been much talk about industrialisation of drug discovery [3], which nearly always meant massive parallelisation, driven by the investment in new, higher throughput, technologies, in combination with automation and miniaturisation (for reviews see [4–6]). As to the organisational structures, centralisation has been a standard answer to gain efficiency by bundling expertise and avoiding duplication both in personnel and in capital equipment [7].

Focusing on the 'hardware of industrialisation', we have largely ignored soft tools, aiming to increase business excellence, successfully applied across multiple industries (for example see [8–10]). Lean, Kaizen, Six Sigma and other tools can be adapted to the drug discovery process, where we have a mixture of transactional and production-like processes. Pushing industrialisation of R&D beyond the latest techniques and hardware, and acting in concert with technological and scientific advance, lean methods bring benefits to organisations where the focus has been on the optimisation of single process steps, often creating imbalanced processes with waiting times at handover points. Starting with the application of lean methods to the production of chemical libraries [11], a setting almost akin to manufacturing operations in other industries, lean thinking is spreading to the whole Hit to CAN (CAN: candidate for first in human) process and beyond [12].

Within this manuscript we will discuss the underlying concepts and illustrate the impact with examples from the Hit to Lead to CAN process, aiming to enhance the fast generation of knowledge in the iterative cycle of lead optimisation, while at the same time creating a continuous improvement culture among scientists.

The evolution of lead optimisation

Iterative cycles of compound optimisation are at the core of drug discovery, initially with chemists and biologists working alongside of short ways (easy communication and transfer of reagents, data and so on) and quick communication channels. From these simple beginnings, the Hit to Lead to CAN process has evolved into a complex task, involving multiple departments within pharmaceutical companies and, through outsourcing and collaborations, external resource [13]. The requirements and set-up of a

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formalised Hit to Lead to CAN process have been described in a number of publications from pharmaceutical companies, focusing on both the scientific drivers as well as the organisational set-up to deliver efficiency [14–16]. The complexity of the task at hand has been driven by the number of parallel projects and compounds (moving from classic medicinal chemistry to parallel chemistry), the centralisation of process steps into separate departments and lately the concept of multidimensional compound optimisation, requiring the simultaneous generation of data for the primary target, selectivity and ADMET early in discovery [17,18].

Centralisation of tasks into separate teams/departments (i.e. compound synthesis, compound purification, compound logistics, screening, reagent generation and so on) has widely occurred across the industry and has been the standard tool to drive gains in efficiency (i.e. cost per data point) and quality through:

- Parallel execution of projects and sharing of resource.
- Utilisation of costly equipment and crucial mass for investment.
- Implementation of unified business processes.
- Focusing expertise and driving discipline excellence.

For example, generation of structure–activity relation (SAR) applying simple *in vitro* assays has evolved at Pfizer Sandwich from a distributed model, where resource and equipment was therapeutic area (TA) based, to an open-access laboratory approach with centralised equipment and TA-based resource using these communal laboratories, to a centralised *in vitro* screening team, generating all SAR data for the TAs. However, with these and additional centralisation efforts in compound synthesis and purification, the iterative compound optimisation has evolved into a highly complex set of interactions of stakeholders with multiple handover points and presents itself as a mixture of information flow (compound logistics, tracking or data, decision points) and production-like process steps (i.e. compound synthesis/purification, production of reagents, compound preparation, screening assay). Taking a step back, it is easy to align with similar processes in other industries and apply tools to optimise quality, reduce cycle time, and increase 'customer satisfaction'. Centralisation undoubtedly decreased the cost per data point, but too often it does not deliver the required speed and business flexibility at the same time, while scale-up and the required process logistics and robustness require skills previously not honed in early discovery. The application of centralisation without addressing these challenges can even be detrimental to the overall performance of business processes.

A toolbox to increase business excellence

To improve our processes, we have started to develop a toolbox of complementary methods, based on principles taken from Lean and Six Sigma and working in concert (Fig. 1) to build a coherent business system. The methods in themselves have been successfully applied beyond the manufacturing setting within service industries [19], healthcare [20–22], but, more importantly, also within product development [8,23]. Starting with processes associated with *in vitro* screening within the Hit to CAN process, our aim is to improve in three key areas:

- Decrease cycle time.
- Reduce failure rates.
- Increase colleague engagement.

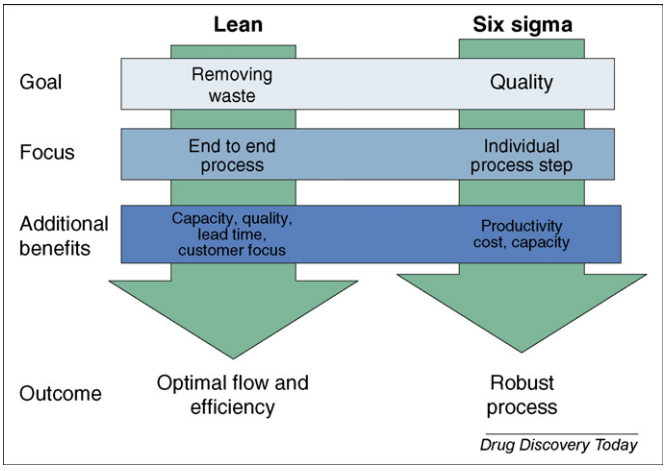

FIGURE 1

Working in concert. Although often applied in isolation, Lean and Six Sigma are complementary and are ideally applied in a modular fashion to address problems for single process steps, as well as the end-to-end workflow.

The focus on these areas is driven by the feedback of colleagues in chemistry and benchmarking across the industry, and success will enable project scientists to test more scientific hypothesis for a given project. Reduction on failure rates has a direct impact on the workload and cost in our department, while colleague engagement is paramount to generate ideas and scientific progress.

Within this concept we try to address basic stability in our operations via workplace reorganisation (i.e. the physical set-up and organisation of laboratories) and work standardisation, introducing principles of the visual workplace and 5S (see below), and building a culture of continuous improvement through the roll-out of the Kaizen philosophy [24]. In parallel, building on these changes, we have mapped all our processes to apply lean methods for process re-engineering.

Start with basic stability

While lean methods are most powerful in eliminating time-consuming steps not adding value and reduce the cycle time of processes, they rely on robust process steps for overall success, and should be first priority.

Within the Primary Pharmacology Group (PPG) we have implemented the basic principles of quality improvement through a number of measures including:

- Standardising work, to improve the consistency of processes and equipment use.
- 5S (sort, set in order, shine, standardise and sustain), a philosophy and method to organise and manage the workspace and thereby increase morale and work efficiency [25].
- Kaizen (kai: change, zen: to become good) projects, which we used to solve problems using the Six Sigma approach.

Standardisation

The standardisation of all work steps is fundamental to all quality improvement. Although powerful and simple in principle, standardisation, to the extent needed in a centralised facility, is one of the key challenges and has not been widely achieved in the early discovery setting. Standardisation is sometimes seen as stifling creativity of scientists. However, rather than restricting ideas, the

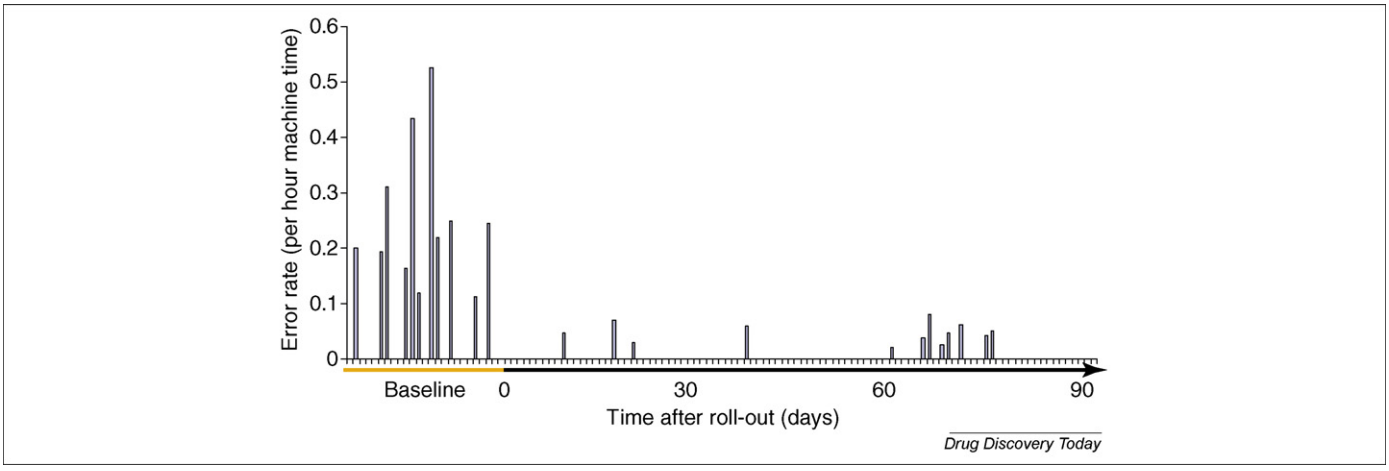

FIGURE 2

Benefits of standardisation. Shown is the impact of standardisation on the machine (liquid handling robotics) error rate as expressed as errors per hour machine time. After measuring the baseline performance (baseline) generic programmes have been introduced at time 0, and the performance followed with reviews after 30, 60, and 90 days.

standardisation of scientific work frees up time for more experimentation. Creating workarounds in processes is not creative or helpful as we usually address symptoms of a problem rather than the root cause.

Standardisation goes beyond standard operating procedures for biological assays and has to touch every aspect of work: training of new starters, programming and use of equipment down to the delivery of consumables to labs. Everything needs definition and, most importantly, simplification wherever possible. Importantly, standardisation does not mean standing still as methods evolve and it is now simpler to update and roll-out a single and harmonised method. Standardisation can be simple and effective even without other changes to the work practice. For example, the introduction of generic liquid handling programmes, instead of scientists writing their own programmes, had a measurable impact of the downtime of equipment within our department (Fig. 2), since only programmes adapted to the capabilities of the equipment were included.

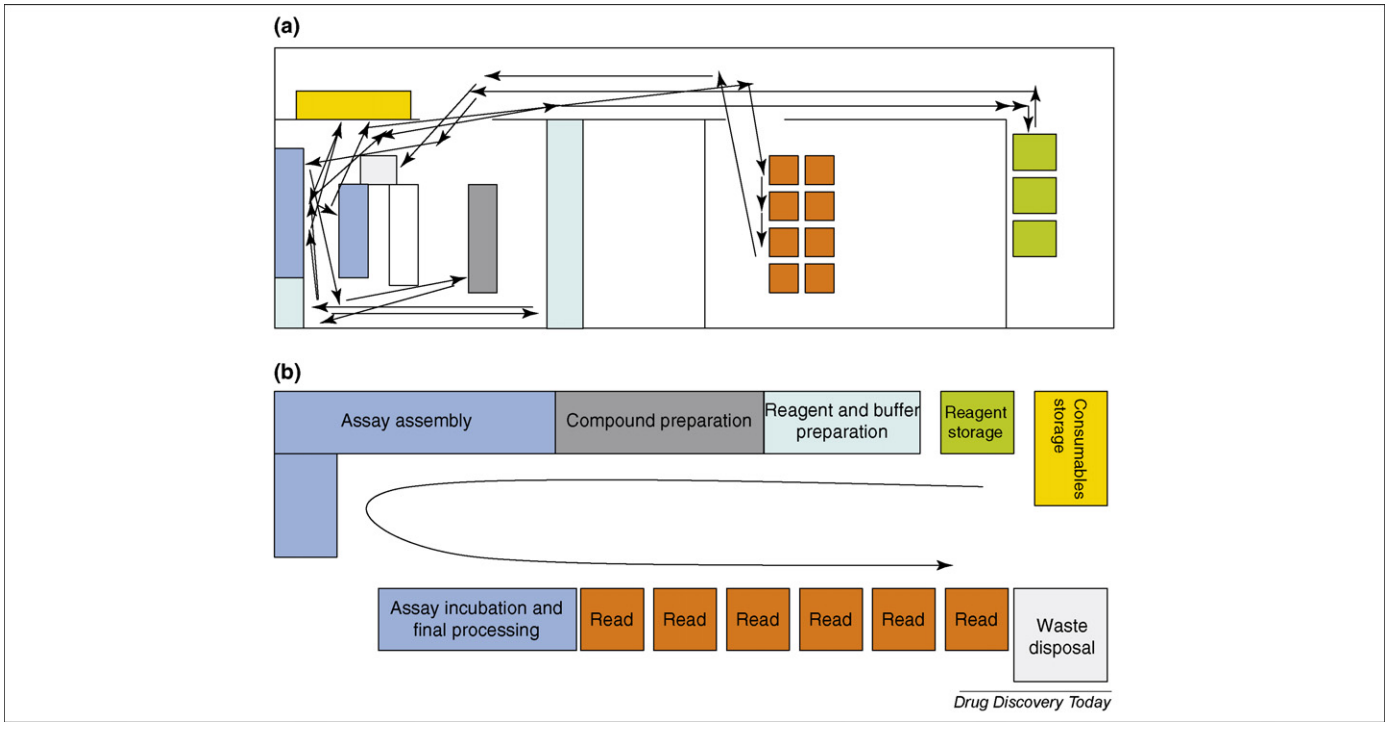

FIGURE 3

Workplace reorganisation. (a) Original laboratory layout. The classical laboratory set-up is not aligned with workflows and in the example, outlining the workflow for a typical radioligand binding assay in our laboratories, work was spread over multiple areas in different laboratories resulting in extensive transport of samples and a convoluted workflow. (b) Optimised layout for a screening work cell. Grouping work by assay type, equipment needed is placed in close proximity and following the 'natural' flow of work from deliveries and storage to waste disposal (drawings are not to scale).

5S and workplace reorganisation

Scientists and laboratory staff are interested in experimentation rather than workspace organisation and housekeeping. Our focus on workplace organisation with examples taken from the manufacturing settings within Pfizer and implementing 5S was a considerable culture change, but brings immediate benefits as a large amount of time, energy and motivation is lost through a lack of workspace organisation. The key steps, with examples from our setting, are:

- *Sort*: removing unneeded equipment and supplies gives more space to work in (as a byproduct there is in our experience considerable cost-avoidance because of re-use of equipment and consumables across the organisation).
- *Set in order*: saving time by arranging workbenches logically and consistently, while labelling reduces misunderstandings. Laboratory reorganisation focuses on the overall layout, following the natural workflow and reducing unnecessary movement.
- *Shine*: improving housekeeping regimes with additional benefits, through the reduction of safety incidents particularly for preventing leaks and spills.
- *Standardise*: generating systems to help maintain the workplace as part of the regular work.
- *Sustain*: regular audits, updates and further improvements are key to prevent sliding back.

The layout of many scientific laboratories does not foster efficient workflows, as a multitude of tasks is supported and spread out across different areas and laboratories, leading to excessive transportation and convoluted workflows (Fig. 3). Grouping screening assays by technologies, characterised by similar processing steps and equipment used (i.e. setting up 'product families'), presents the opportunity to set up work cells dedicated to specific assay types, bringing equipment closely together and following the 'natural' flow of screening tasks.

Kaizen

Learning from the Toyota principle we need to engage scientists at the ground level in solving problems and celebrate the day-to-day inventions for ongoing motivation. Key to success is to tackle problems relevant to the daily work, to make working in the laboratory easier (too often all processes put in place tackle business needs while not addressing workability). The approach implemented in PPG uses Six Sigma-derived principles to foster teamwork across disciplines, introduce a structured approach to problem solving and illustrate principles of cost and benefit.

Six Sigma is a structured, data-driven approach to problem solving using a defined cycle of Define, Measure, Analyse, Improve and Control (DMAIC) to improve an organisation's products, services and processes by reducing defects (Fig. 4). Going back to work at Motorola [26] in the 1980s, the term Six Sigma describes processes with a failure rate of 3.4 per million opportunities, but this can be misleading – the desired quality level should be defined based on the actual needs and resources. The most important

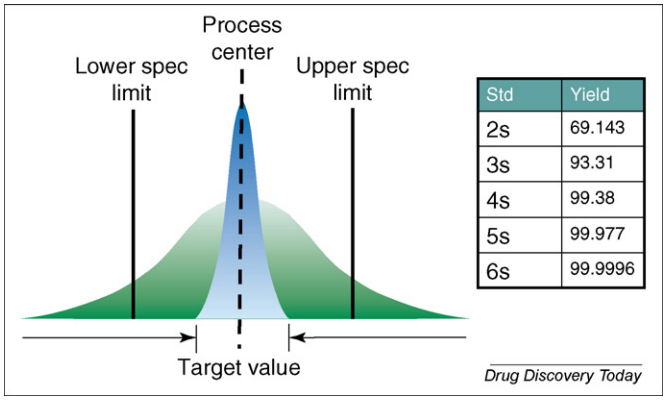

FIGURE 4

Six Sigma is a method that focuses on the reduction of unwanted variation in products and processes with the target performance of 3.4 defects per million opportunities.

- Applies a universal, structured problem-solving method: Define, Measure, Analyse, Improve and Control (DMAIC) that helps to identify the root causes in complex problems.
- Customer focus: customer defines defects and elements crucial to quality.

Shown is the process yield (i.e. the percentage of process output within the upper and lower specification limits) for different process sigma levels.

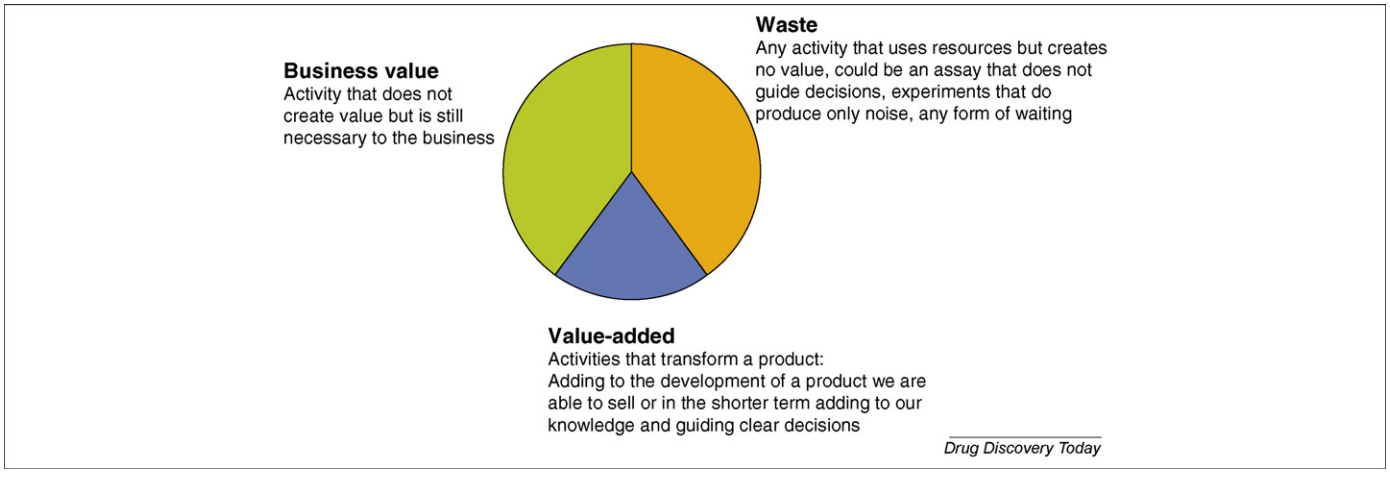

FIGURE 5

Lean principles. Lean methods focus to increase flow and eliminate waste in processes by identifying and concentrating on value adding activities as defined by the customer. A key tools is the application of value stream mapping for current and future states.

characteristic of Six Sigma is the systematic approach to quality improvement it provides, using the DMAIC structure.

Six Sigma is often perceived to be complex and time-consuming, and the training courses alone typically last two to four weeks. For simpler problems, however, it can be applied in a few days using a carefully selected subset of the tools while retaining the DMAIC structure. Our implementation of Kaizen applies the basic (but shortened) principles of Six Sigma, starting with a sound definition of the problem. Put simply, we should not come to a meeting with the solution, but truly explore the underlying problem and bring together the different disciplines/colleagues involved in the work. Following this 'definition' is measurement, that is, what is the scale of the problem and its localisation, to make diagnosis easier. Although this can be time-consuming, more often it relies on data already available or even an estimate based on interviews with colleagues. The 'analyse' phase thoroughly explores possible causes, applying simple tools like fishbone diagrams. The joint discussion for improvement prioritises possible solutions according to expected benefit and the ease of introduction, while implementation of solutions is followed by a control phase measuring the impact of the changes and ensuring that the problem does not recur. Our approach to Kaizen is scaleable from a two-hour meeting involving a small set of scientists for the initial phase, to a full Six Sigma project within or across departments. The most important principle is that the discussions involve those already doing the work and hence the solutions are designed from the bottom up.

Lean: reducing cycle times and improving flow

Lean is a method to eliminate waste in processes by identifying and concentrating on value adding activities as defined by the customer (Fig. 5). Crucial for success is a clear definition of the boundaries of the process with a definition of the suppliers, inputs, process, output and customer (SIPOC). The projects themselves are scaleable, from focusing on single work groups to processes looking at the entire workflow within a company. Underlying all projects is the detailed mapping of the current process ('current state value stream map'), annotating the single process steps with waiting and processing times, failure rates and so on, and evaluating all steps for their 'value adding' contribution. Waste is defined as anything that is not directly adding to customer value. For compound optimisation, the final product is knowledge and the answer to a scientific hypothesis, namely, that a modification of a chemical structure has a predictable impact on its biological activity. All activities contributing directly to this are adding value, other activities can either be classified as pure waste (e.g. waiting time, see Table 1) or business value (i.e. an activity that is not directly adding customer value but is still needed to run the business, for example, compound tracking). Once scientists are in a 'lean thinking mode', multiple opportunities to increase the fraction of value adding work can be identified in almost every process and cycle time is reduced in parallel by removing unnecessary steps. It should be noted that even optimised processes rarely show value added fractions beyond 25% of the overall time, so expectations have to be realistic.

After the initial process mapping, a 'future state map', that is, the process as envisaged in the future is drawn, and a detailed implementation plan for a pilot project is established. Pilot projects usually run for 90 days with benchmarks after 30, 60 and 90 days before full implementation, or further modification based on the learnings. As demonstrated by an example from our *in vitro* screening efforts (Fig. 6) the impact of lean process re-design can be dramatic. By eliminating/parallelising process steps and moving away from the 'one scientist one assay' paradigm, we have, in this example, been able to reduce the assay cycle time from compound receipt to data publication on average by ca. 40%, while at the same time improving capacity threefold by removing unproductive waiting time.

TABLE 1

Lean waste categories with examples from the Hit to CAN process

Lean waste types	*Hit to CAN examples*
Defects	Incorrect data (shift in results) Noisy data
Overproduction	To high *n*-numbers Extra compound/reagents requests 'just in case'
Extra processing	Customer queries to compound logistics Lost samples
Waiting	IT systems down Missing information No compounds, no reagents
Inventory	Batch processing at single day of the week
Motion/transport	Multiple hand-offs Transport of waste to chemical stores
Underutilised people	Limited employee authority and responsibility for basic tasks Inadequate business tools

Improving flow

A key concept within Lean is the batch size, that is, the number of components worked on in parallel (i.e. a group/batch). Working in batches is a hallmark of 'efficient' processes in many areas of work beyond R&D as the joint processing of multiple samples brings down the cost for the single sample. The concept has been further driven in early discovery by the introduction of large-scale automation which, for best utilisation and minimal set up time, requires large batches. Although this approach will reduce cost for the single sample, batch processing increases waiting time and the impact of system failure is increased with batch size. The different needs of single samples (or projects) versus the centralised facility highlight the need to holistically plan process improvements beyond single departments to benefit the overall workflow of the company.

Sometimes seen as counterintuitive, reducing the batch size can decrease cycle time (i.e. the time needed for one cycle of the process to complete) while at the same time reducing the impact of, for example, equipment or other process failures.

For example, the reduction of batch size in our compound processing unit has enabled the same day turnaround from compound preparation to screening results for a third of projects. Instead of accumulating the compounds for big overnight runs on equipment designed to run large batches for multiple projects, we have switched work to smaller, distributed equipment producing dose/response plates for just one project at a time. As a result, we can now achieve a one day turnaround from compound receipt

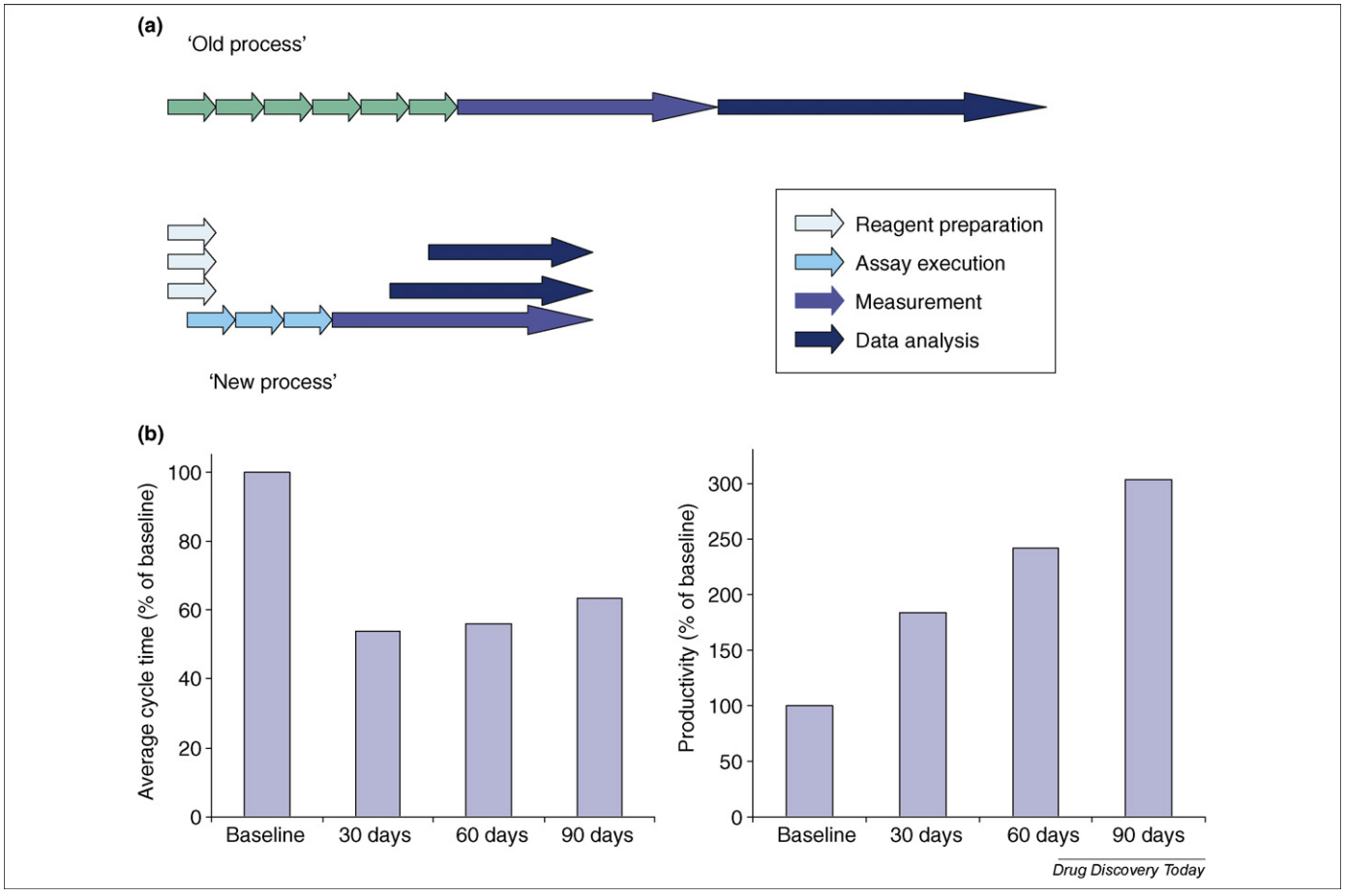

FIGURE 6

Lean process re-engineering. (a) Schematic representation of a simple example of an *in vitro* screening process:

- 'Old process'
  - Uses one FTE, overall five to six FTE work days.
  - Wet work process one time a day.
  - Working day limits assay frequency.
  - Sequential.
  - Unbalanced process steps.
  - Single scientist owns data analysis.
- 'New process'
  - Parallel process steps.
  - Dynamic use of FTE (when needed >1 at the same time).
  - Shared, distributed data analysis.
  - Shorter wet work provides opportunity to run assay twice a day (batch size reduction capacity increase).

(b) Process performance with respect to cycle time and capacity before and after re-engineering.

to publication of assay data for simple biochemical assays and a reduction of the cycle time by one to three days for cell-based and other multi-step assays.

The challenges of implementation

Although specific to our laboratories and experience, the examples within this manuscript should give an idea of the untapped potential for process improvement in scientific laboratories in general, but, while simple at its core (as demonstrated by the mundane solutions outlined here), increasing business excellence through the described methods is not a magic bullet or, indeed, easy to achieve [27]. For success, the effort needs to be sustained and accompanied by a cultural change within the organisation and needs the visible commitment, support and leadership from senior management. A key hindrance in lean application within research is the inability or unwillingness to see work as a process [10], failing to recognise parallels and general principles and to overemphasise the scientific aspects. With the origin of tools firmly in manufacturing, some of our colleagues have been sceptical at the onset of this experiment. How can principles applied in manufacturing have a place in scientific research? We ourselves have worried about the complexity of the problems at hand. In reality only a fraction of the problems and delays encountered were because of the underlying science. Greater than 90% of problems are because of ill-defined, unclear processes and a lack of training found in many workplaces. In other words, misunder-

standings, absence of clear guidance and pressing the wrong button on a new reader are more often at the root of a failed assay or experiment than the lack of activity in a new enzyme preparation. Reduction in error rates alone can result in a substantial improvement in overall cycle time.

Conclusion

The application of Lean becomes more complex beyond manufacturing, but the tools remain the same and the improvement opportunities are just as tangible. Although the underlying scientific endeavour is unique, challenges encountered in pharmaceutical R&D, as exemplified by the Hit to Lead to CAN process, are pertinent to many manufacturing and development organisations and methods are applicable to all activities (examples at different stages of maturation within Pfizer include manufacturing, outsourcing processes, supply chain management, pharmaceutical sciences, finance, human resources). Recognising the similarities rather than differences across industries we can learn and adapt tools applied across diverse organisations. Looking beyond pharma will enable us to develop a toolbox of methods to improve business excellence, help science and scientists to succeed and drive commercial success. Although it is not possible to guarantee 'better science' and more NCE's as a direct result, shorter timelines and processes using less resource and with higher quality will be tangible outputs from this effort.

Lean/Six Sigma, and other methods described here, are not magic bullets. As underlined by the most extensively documented and copied Toyota production & development system, successful implementation rather than the idea in itself is the challenge. Introducing a culture of innovation and continuous improvement needs a sustained effort by all organisational layers and is not a one-off easy fix. However, the results for the business can be dramatic and make use of our most valuable capital, the energy and ideas of scientists in drug discovery.

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