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A case study of lean drug discovery: from project driven research to innovation studios and process factories

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At the operational level, the number of investigational new drugs or candidates for development per dollar spent in research, and the number of patents per year are highly integrated measures of productivity and, thus, difficult to influence at the individual or lab level. Hence, different metrics are needed to assess and thereby improve productivity in research at the individual and group level. This review centers on a case study, including over 70 interviews, in a research department of a global pharmaceutical company as well as over 40 interviews in contract research organizations (CROs) and 5 in small biotechnology firms. For each lab, its value adding process was plotted according to lean six sigma methods and appropriate metrics were defined. We suggest a strong focus on short feedback loops in research as an indicator for efficiency. Our results reveal two categories of activities: creativity-driven ones and process-driven ones, both discussed with respect to the methodology used. The fundamental differences in nature of these activities require different sets of metrics to assess them. On the basis of these metrics, different organizational forms can be derived to achieve a lean research structure: innovation studios and process factories, respectively.

Changing research environment

Productivity in drug discovery is a challenge for pharmaceutical companies. The business environment in which research organizations are evolving has changed dramatically over the past 15 years:

- Regulations and customer requirements for long-term treatments have become tougher
- Complexity of treatments in certain therapeutic areas has increased
- Complexity of targets and compounds has increased
- A large number of generic drug companies have emerged from Israel and South-East Asia. Some of them have even launched generic products although patents have not yet expired (e.g. Protonics, Lautrel, Famvir)

These parameters have made it tougher to reach appropriate returns on R&D investments – less and less drugs per R&D dollar spent are leaving the pipelines. Furthermore, several companies pursue the same therapeutic targets in parallel with a 'best in class' strategy, preventing market exclusivity, decreasing upside potentials of R&D investments [1]. It can be argued that the 'low hanging fruits' have already been picked and the time has come to explore new paradigms. This is confirmed by several global pharmaceutical companies (GPCs) that want to invest ~20% of their R&D pipeline in new biological entities (NBEs). Many approaches have been explored till date to fill this productivity gap, for example:

- Merger and acquisition (M&A) activities
- Inlicensing, outsourcing and off-shoring activities to fill the R&D pipeline and lower cost
- Organizations in franchises, programs or therapeutic areas
- The use of new scientific methods (e.g. fragment-based drug discovery, genomics, proteomics, combinatorial chemistry)
- The use of harmonized stage-gate models across different research sites
- Office layouts facilitating communication and knowledge creation

Increased complexity in research has led to higher levels of specialization and thus a greater need to coordinate specialists from different scientific communities and geographical areas [2].

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The research organization has grown from the 20th century isolated laboratory to a multinational, globally organized 'company within a company' working in a dense web of partners: biotechs for inlicensing, contract research organizations (CROs) for outsourcing, consultants for specific projects or universities for knowledge transfer in early stages.

Organizations are growing and the cost of inlicensing has almost doubled: there is a need to streamline internal operations

A common challenge of large research organizations is to leverage ever-increasing organizational knowledge, especially tacit knowledge that is of paramount importance to be competitive in science-driven industries. Thus, research organizations have reached a size where coordination spoils individual initiative, hindering creativity and productivity of the organization [3]. Managing a large research organization requires more coordination than smaller groups where everybody knows everybody and knows who knows what. With more coordination, formal processes come in place and less freedom is given to personal initiative, a major driver for creativity. To address this tradeoff, companies like Johnson & Johnson with Centocor and ALZA, as well as Roche with Genentech, have kept their biotech acquisitions isolated from their mother company's heavy bureaucracy and politics, in the hope to keep the academic biotech spirit and culture in the acquired company. The two cultures seem to be rather different [4] but still can benefit from each other: the small company stays creative but takes advantage of a large organization's knowledge pool and experience.

Inlicensing, another approach to fill the productivity gap in R&D, has shown almost doubled prices from US$ 77m to 122m in average payments per preclinical asset between 2003 and 2006, including upfront payment, milestone payments, R&D funding and equity investment [5]. The total cost of alliances has also increased because of postinlicensing costs and costs generated as a result of inferior inlicensing conditions for buyers [5]. Thus, inlicensing deals are made earlier with higher risks. Several companies have managed to fill their late discovery and pre proof-of-concept (POC) pipeline, but a larger proportion of projects has failed at POC or in Phase III clinical trials [6], much to the detriment of overall business performance.

Need for reliable and nuanced performance metrics to create a lean research organization

Lean management has its origin within Toyota and was pioneered by Taiichi Ohno – former head of engineering at Toyota. The aim of lean management is to streamline the value added process at all levels of an organization and eliminate waste. Womack and Jones [7] identified five principles defining lean management:

- Specify the value to the customer by product family. This defines what the deliverable of a process should be
- Identify all the steps in the value stream for each product family, eliminating every step and every action or practice that does not create value
- Make the remaining value-creating steps occur in a tight and integrated sequence so the product will flow smoothly to the customer
- As flow is introduced, let customers pull value from the next upstream activity
- As these steps lead to greater transparency, enable managers and teams to eliminate further waste, and pursue perfection through continuous improvement

In the case of drug discovery, the customers at the lab level are other labs or management, whereas the customer at the level of the entire research organization would be preclinical or clinical development depending on the company. Lean six sigma is based on the same theory, whereas six sigma emphasizes on eliminating variance rather than waste. Although these principles were developed in manufacturing settings they can be applied in other areas as well.

To increase productivity, there is a need for reliable metrics that researchers can positively impact. Defining the value to the customer – the first step in lean management is really what defines a performance metric. Although the customer value might be clear, measuring productivity in research in an absolute way remains challenging and time-critical. The probability of success of a specific molecule is extremely low and the time from start of target validation to market introduction can be more than ten years [8]. Yet, it is possible to define indicators for productivity to answer the question: are we better today than yesterday? Many successful managers rely more on time series than on snapshots. These indicators may vary between different research institutions:

- Universities often use the number of publications, impact factors and amounts of grants
- GPCs use the number of investigational new drugs (INDs) filed per year and dollar, or the number of candidates for development
- External resources like CROs are commonly assessed by full-time equivalent (FTE) cost to measure 'body leasing'. Synthetic chemistry is often measured by the number of synthetic steps/FTE cost. For *in vivo* assays the 'per animal' cost and time are used as performance metrics

All of these metrics have their respective strengths and weaknesses. We focused on operational performance in GPCs and thus excluded fundamental research at universities.

The number of INDs or CDs is appropriate to measure an entire research organization's performance but not that of an individual lab. With today's level of specialization in research, along with matrix-organized research departments of over 1000 employees, only a few persons in the organization can directly impact these metrics through individual action. The performance indicators of their task become blurred. To impact productivity you need to look at the details in each process. The stride for operational leanness must guide every employee's actions for every process step and constant awareness against waste must be fostered. This implies that management needs to empower scientists to design their own process because they are the only ones seeing the details.

With the cost per FTE for an expected performance the total cost of outsourcing to a CRO is often under-estimated because of allocation of internal resources. The overall impact of outsourcing on the progress of a program and the opportunity cost caused by longer feedback loops or knowledge leakage is seldom taken into account. Similarly, when inlicensing a project, only contract expenditures are considered. In both cases, the total transaction costs in the form of due diligence, and the cost of deal identification, business development and strategic alliance teams at the interfaces between different parties, are neglected [5]. Conse-

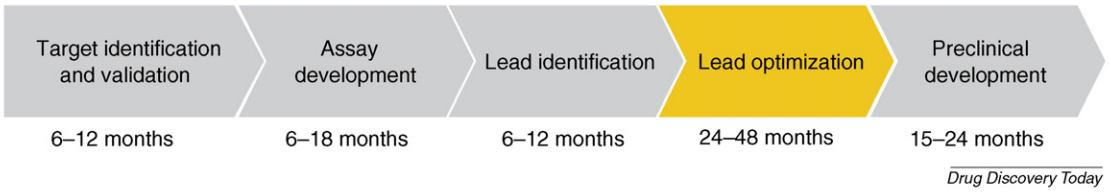

FIGURE 1

Outline of the standard drug discovery process with mean durations for each phase (adapted from [9]).

quently, a need arises for metrics allowing a fair measurement of performance and thus improvement.

Aim and method

The focus of this study was to define precise metrics in early discovery at the lab level. For this purpose we chose the lead-optimization (Fig. 1) phase because it is often closely preceded by patenting, thus time-critical, and it is the last step before the start of preclinical development. This phase typically lasts 24–48 months [9]. We used the case study method as the research method and conducted over 70 interviews within a research department of a GPC. The questions asked were not company-specific but reflected the general research process in lead optimization. All interviewees had previously worked for other pharmaceutical companies to allow generalization of our observations. Areas of medicinal chemistry, pharmacology, HTS and automation, and DM/PK were analyzed.

Applying the lean approach, we asked for the deliverables of each individual at his or her level of hierarchy. Then the process from trigger to delivery was plotted with the employees. The appropriateness of different metrics was assessed on the basis of its impact on the number of candidates for preclinical development.

The level of hierarchy varied from senior vice president to bench scientist. Additionally, over 40 interviews were performed at CROs in China and India as well as in 5 European small biotech companies to understand how processes look like when separated from the rest of the organization and how they were measured.

Results

Typically, for the development of NCEs, pharmacologists, medicinal chemists and biologists are needed as a core team from target validation to start of preclinical development. In this case, specialists were located within their departments and a team of three project leaders from medicinal chemistry, biology and ADME/PK managed the program. Hence research had a matrix organization within each therapeutic area. Some support functions acted across therapeutic areas.

The aim of a project team in lead optimization was the generation of structure activity relationships (SARs) between the developed lead and the target. This was achieved with a multicriteria prototype cycle similar to other industries. A stage-gate model was in place with a set of prospective criteria, which defined nominal values of properties a compound should have to reach the 'start of preclinical development'.

The SAR feedback loop was composed of four phases performed by different specialists at different locations. Medicinal chemists designed and synthesized molecules, biologists or pharmacologists tested molecules and more-senior scientists supported the team with the interpretation of the data generated by the assays. This assumed that assays had been developed before the start of lead optimization or were developed in parallel and were ready to use when needed by the team. The speed of this feedback loop was more or less directly proportional to the knowledge creation rate within the team. As long as there was no feedback the team was left in the dark. They did not know if their last hypothesis had to be rejected or not. These loops were run in parallel, such that a synthesized compound was tested for several properties at the same time in different testing groups and several compounds were tested for the same property at the same time. Some steps in this cycle depended on the output of the step before and were, thus, input-dependent; some did not.

The process delivering the needed data for each criterion was plotted (Fig. 2) and the performance of the teams for each process was measured.

From the end of lead identification to the start of preclinical development the teams performed multiple iterations along the SAR process (Fig. 3).

Each step represented a different activity and required:

- Different skill-sets
- Different metrics [10]
- Different organization structures

Two types of processes were identified: input-independent and input-dependent ones

Input-independent activities had a standard process and could be measured with process quality, on-time delivery, variance of delivery times and turnaround times. The teams responsible for these steps should focus on process innovation and, thus, be recognized accordingly. In Shanghai several CROs have been successful (e.g. Wuxi Pharmatechs or Chempartner) delivering to most western GPCs. These CROs focused on well-defined activities and generated the highest turnover per capita [2]. Daily work was standard, did not require too much creativity but needed people who liked repetitive process, continuous improvement and delivered according to given specifications. It is important not to overstaff the teams with over-qualified personnel.

Synthesis is performed by bench scientists. Sometimes a scientist designed and synthesized the molecule, sometimes a senior scientist designed the molecule and a junior scientist synthesized

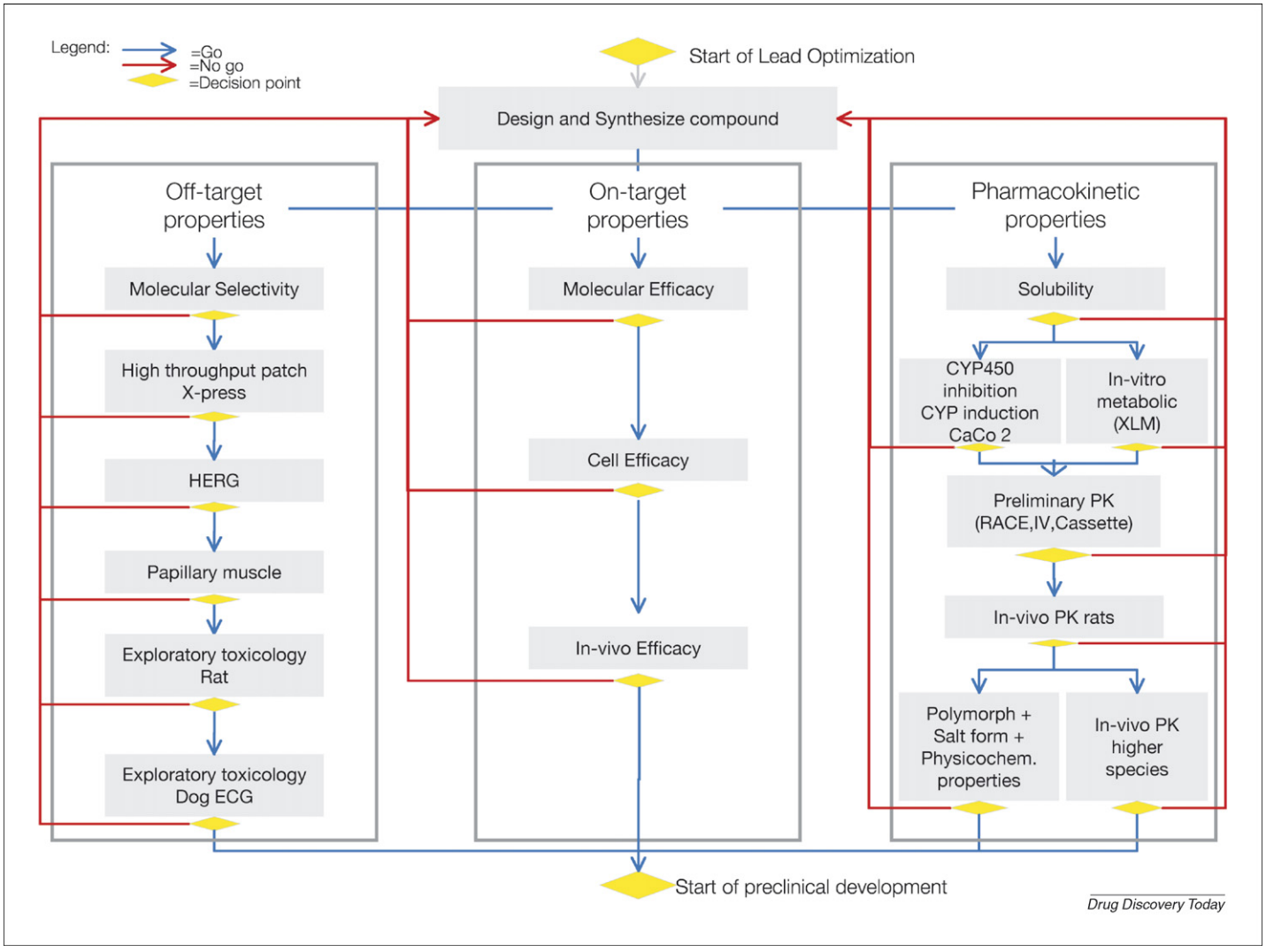

FIGURE 2

An example of the multicriteria lead-optimization process. Each molecule needs to fulfill a set of criteria. The leading group decided in what order criteria were tested. The process outlined shows the standard screening strategy that was used. If a molecule met the prospective criteria defined in the stage-gate model, it was tested for further properties. If it did not meet the expectations, interpret the results and redesign new molecules initiated a new iteration of SAR. When a molecule met all prospective criteria it became a candidate to start preclinical development.

it. There was a standard component and an innovative component requiring complex problem solving in this step. The standard synthetic part could be measured by the number of chemical steps per week because it reflected output, complexity, cost and time. These were the aggregated customer requirements – being the testing groups and the team leaders. Complex synthesis was assessed ad hoc by a lab leader to estimate its equivalent in standard steps because this process often needed literature research or help from other specialists in the area.

Testing was independent of the molecule tested to a certain extent. Testing does not generate new products. But there is innovation at the testing process level. It can, therefore, be measured by:

- Process quality assessed by the internal customer (data quality and methodological rigor)
- Variance and mean turnaround times
- FTE cost

These were the values defined by the internal customer – being the medicinal chemists and the team leaders. After the process had been plotted and had been defined as input-independent we asked how long each step in the process took to compute a theoretical turnaround time. Thereafter, we retrieved historical data to analyze what the turnaround times really were. The gap between the theoretical and practical turnaround times could be considered as waste (Fig. 4). In a second phase, variance was analyzed to understand the stability of the system.

For input-independent activities we suggest the process performance index derived from Wiendahl's bottleneck equation (where # = number of) [11]:

$$P = \frac{\text{of assays}}{\text{FTEs allocated to the assays} \times \text{average turnaround time}}$$

Input-dependent activities were more awkward to measure because there was no standard process. Expertise was needed in order to react according to the input given. These processes may be

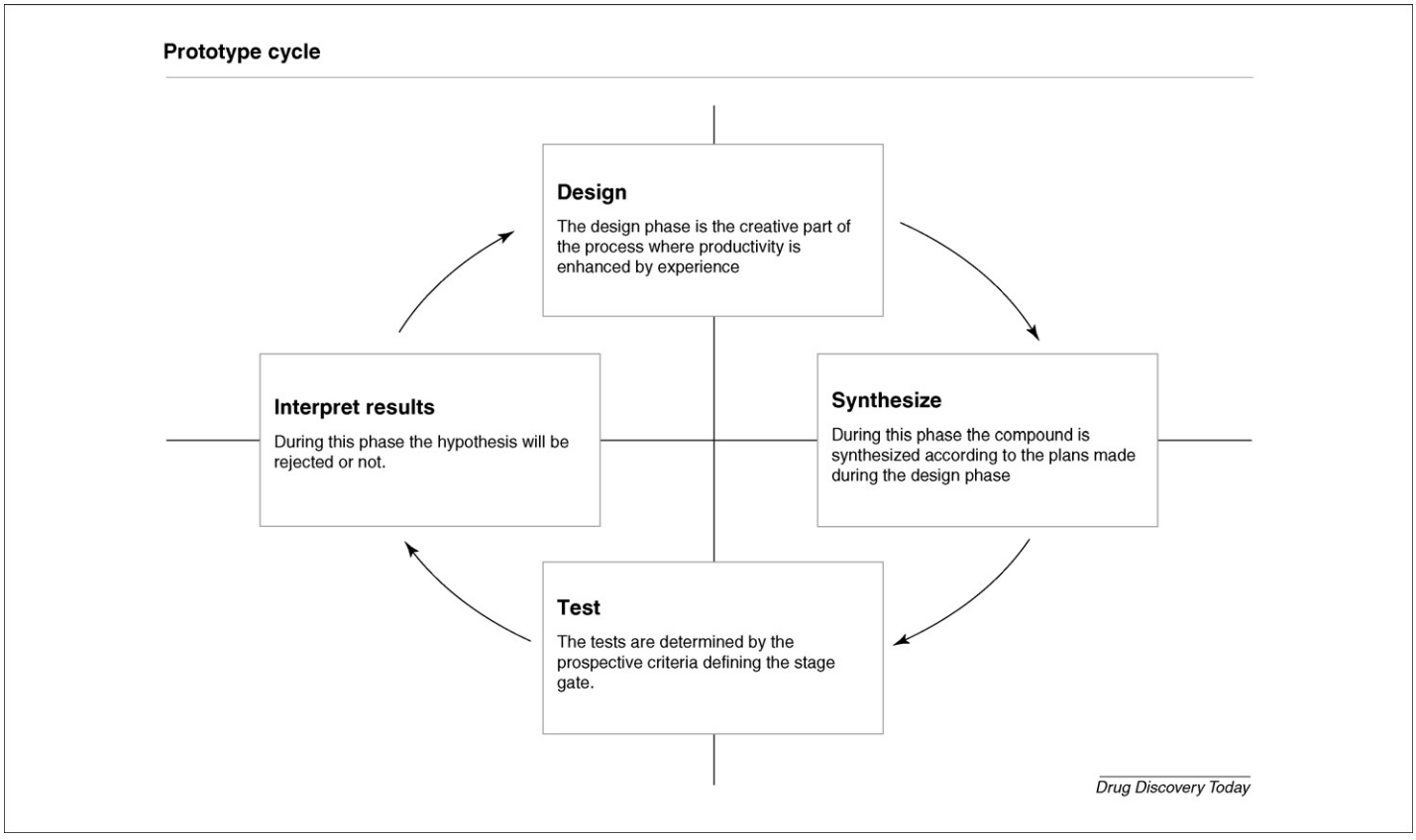

FIGURE 3

An outline of the four-step iterative structure activity relationship (SAR) cycle. Hypothesis-driven research is commonly performed according to this cyclical model.

assessed by a peer review. Time-based value benefit analysis could be used to illustrate the advancement of the project (see example below). With this method all criteria were weighted according to the impact on the probability of success to reach the start of preclinical development and an aggregated score for each compound was calculated. The evolution of this score over time reflected the advancement of the program.

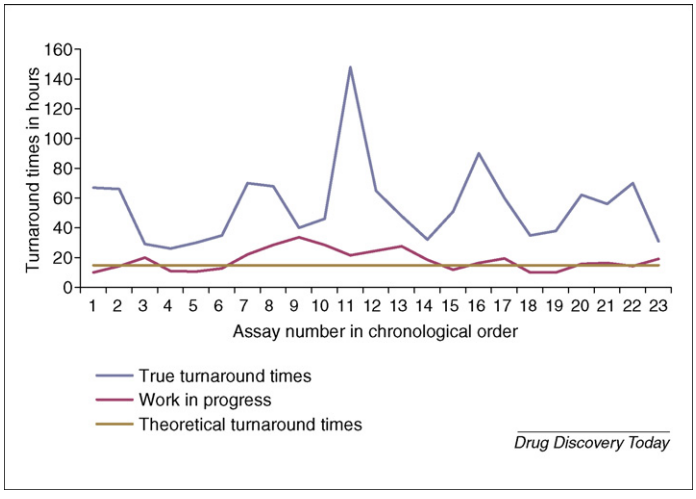

FIGURE 4

Measurement of assay turnaround times (assays ordered chronologically). Illustrated is an example of lead-time measurement from request to delivery of data. A baseline illustrates the theoretical minimal duration, and a third line illustrates the amount of work in progress. If the amount of work in progress and turnaround times are strongly correlated there is a bottleneck because of lack of resources. If there is no correlation, the process is in need for improvement within the lab.

Interpretation and design depended on the outcome of testing; they were therefore input-dependent and required product expertise and creativity. To measure performance of this step, senior scientists and external experts would assess impact on project success in a peer review [e.g. if the team tried to optimize the exposure of a compound, the IC_{50}[1] could be measured over a sequence of compounds. We used a moving average as a filter for serendipity and analyzed the trend of progress within the program. The steepness of the graph was a sign for progress within the team (Fig. 5)].

As a support to assess the group the peer reviewer could use this kind of chart. By combining several weighted parameters, a value benefit analysis can be computed.

Because internal laboratories depended on the quality and time of delivery of other internal or external laboratories, these factors had the highest priority. With long lead times and high variances the system cannot be stabilized and loses efficiency. This is the foundation for six sigma and lean management. Lack of efficiency in the system delays market introduction and therefore creates opportunity cost through lost patent time. Therefore lead-time needs more attention than cost when burning rates and market potential are high, which is often the case for GPCs. Cost is highly

[1] According to the FDA, IC_{50} represents the concentration of a drug that is required for 50% inhibition *in vitro*.

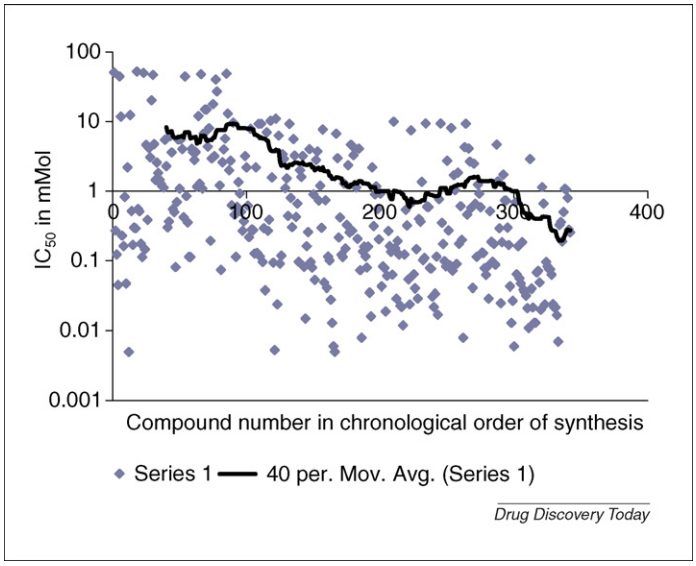

FIGURE 5

Inhibitor concentration 50% (IC_{50}) in Mol over a sequence of compounds. A one-dimensional value benefit analysis chart. The faster the team reaches the nominal value the higher the productivity. If this nominal value is reached in just a few cycles, fewer resources will have been allocated to reach the results. The steepness of the moving average curve indicates the level of progress made over time for one criterion. By aggregating multiple weighted criteria, a peer reviewer gets an idea of the overall progress of the group.

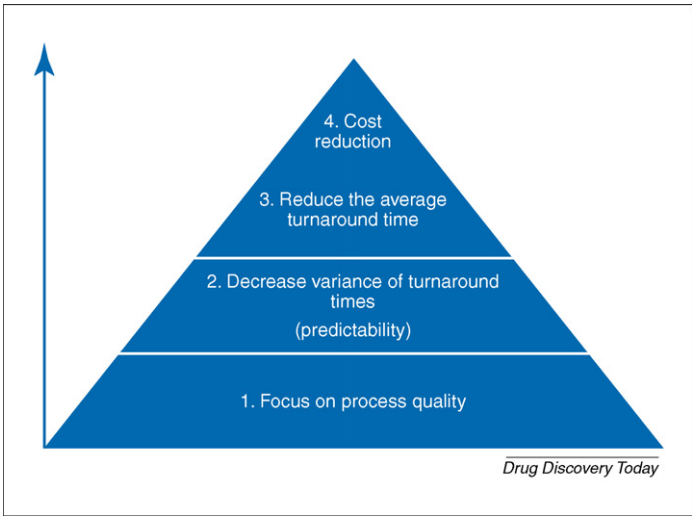

FIGURE 6

Implementation of a process-driven organization. To reach a lean organization, in a process-driven function, the first priority is to bring the process cycle times and quality under control. The next step is to reduce cycle times and, as an effect, costs will go down with mastered processes. Internal customers know what to expect and when, and can therefore plan their processes much better.

flawed since it does not reflect the total cost of operations and FTE cost does not reflect the total cost of outsourcing. Hence, we suggest focusing primarily on process quality, then on variance of turnaround time and only then on speed and cost (Fig. 6).

Implications

Research combines two broad families of activities: process-driven ones and creativity-driven ones. Owing to the different nature of these activities they need different staffing and different indicators. This implies that standard synthesis and testing can be organized like factories, which is the case for CROs in China working in shifts [2]. The most successful CROs that were visited focused on processes and on process improvement, and let the customer take care of the creative part. Interpreting results and designing may be organized like innovation studios, where informal knowledge exchange takes place within small teams of experts: this comes close to the well-known ambidextrous organization [12].

Following Sams-Dodd's [13] organization model, one possibility would be to have a multidisciplinary crossfunctional core team located in the same physical space, interpreting results and designing the next generation of molecules, the old pharmaceutical lab. As seen in today's small biotechnology firms; somewhat informal and multidisciplinary organizations run by highly educated and milestone-oriented scientists, with little coordination compensated by large individual initiative. This is what we call an innovation studio.

Around the core teams are process-oriented data generating teams located by function, providing feedback to their innovation

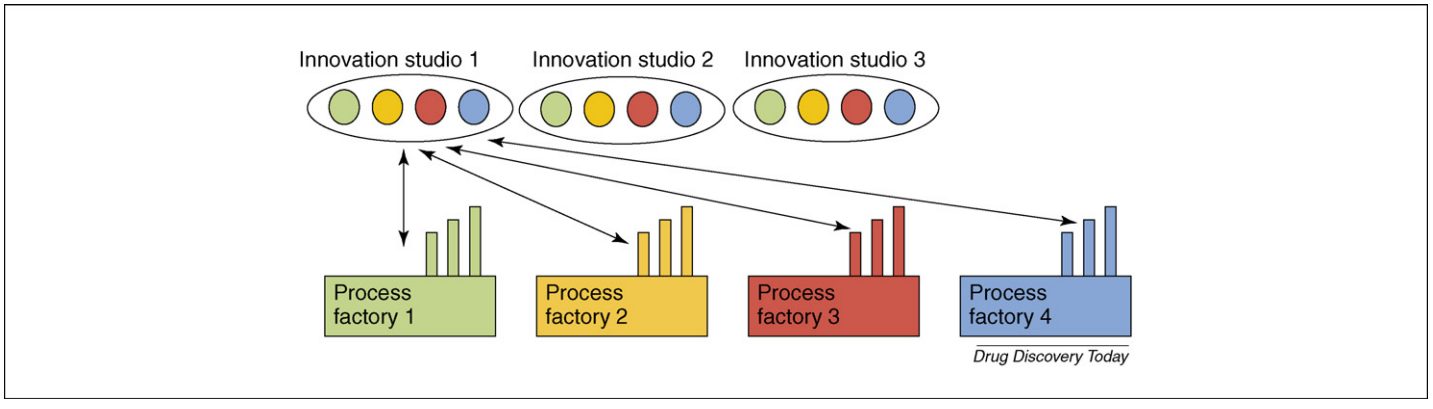

FIGURE 7

Innovation studios and process factories. Each innovation studio is responsible for a program in discovery. Its team is multidisciplinary and creativity-driven. The team interprets data, defines the hypothesis to be tested and is responsible for the screening strategy within the program. The aim of the innovation studio is to be a place for intense knowledge creation about the SAR. The process factories are process-driven within a core technology. They are responsible for generating data to support or reject hypotheses defined by the innovation studios.

studios as quickly and reliably as possible. These teams are specialists for specific technologies (e.g. HTS, combinatorial chemistry, assay development, computational chemistry, medicinal chemistry synthesis, *in vivo* PK, LCMSMS or NMR). They cannot be present in the core team because economy of repetition prevails and heavy investments are needed for equipment and know-how. We call these groups 'process factories'. These 'factories' support all innovation studios. They are organized, staffed and measured like factories: quality, predictability, turnaround time, and cost. Their efficiency is driven by automation, routines and repetition. We will show the impact of this system on motivation in further research.

The system as described needs some rules to function. Process factories run best according to a defined schedule and capacity. Therefore each innovation studio needs to book a slot for a set of compounds to be tested or synthesized. With ad hoc scheduling and no planning, variance is increased and predictability becomes flawed or inexistent, which results in low customer satisfaction. This is where the system has its limitations; it relies on steady-state processes and flexible working hours. Unpredicted occurrences create peaks in demand and can only be coped with if a certain amount of overcapacity is readily available.

Conclusion

We acknowledge the existence and need for two areas in research. A place for production and a place for knowledge creation as described by Kodama [14]. Thus, two different cultures emerge. One culture is where product innovation dominates with a collective sense of identity and fundamental purpose as a frame for collaborative action [14] and the other culture is where production style work and continuous process improvement prevails:

- *Innovation studios*: driven by an integral understanding of the mechanism of action and the SAR, focusing on technologies in the product innovation stage [15]
- *Lean process factories*: driven by routines with technologies having often reached a process innovation stage [15]

This type of organization (Fig. 7) focuses on time, fast cycle times, short feedback loops and, thus, high knowledge creation speed. Emphasizing the core competences of each organizational unit:

- The process factory focuses on innovation through continuous process improvement. Technology specialists are needed in these groups to improve the processes, and BSc or MSc scientists are needed to execute the process
- The innovation studio performs innovation through creativity driven by broad expertise and integral understanding. Senior scientists with strong academic backgrounds and expertise are needed in these groups

As suggested, a change in organization certainly has an impact on intrinsic motivation, one of the most important drivers for productivity in science-driven companies [16]. When doing case studies with groups that were already organized as process factories, we observed a strong team spirit, quick response to e-mails, a strong focus on productivity improvements and a high level of enthusiasm. Whereas, in other teams with little focus on process improvements the impact on project success and publications for personal advancement were emphasized, and we noticed a weaker team spirit prevailing in these groups. One explanation for this discrepancy came from one service providing team. According to them there was little space for individual contribution, which strengthens the team cohesion.

This repeated observation highlights that process orientation and productivity measurements are neither creativity nor motivation killers. Instead, omitting to make the differentiation between creativity- and process-driven activities might lead to over-qualification in some areas. This leads to overpay and frustration because the task is not stimulating and challenging enough. To be stimulating a task requires a variety of skills [17]. Yet efficiency and process orientation seems to impact scientists' motivation in different ways. Some perceive it as positive some as a means of control. This is the topic of further research. Focusing creativity on products on one hand and on processes on the other hand seems to work in pharmaceutical R&D – the same way that it does in the car industry. We acknowledge that this study is based on an in-depth study of many teams at one GPC and that other organizational forms might address the same concerns as the ones highlighted in the introduction. By differentiating activities, the method presented delivers objective performance metrics at the laboratory level in drug discovery that each individual can understand and influence and that aims at the overall goal of research. The system allows the cohabitation of creativity- and process-driven tasks, of exploration and exploitation [18] that, in our opinion, is key for efficient research. The system is based on a standard drug discovery process for new chemical entities. Yet it could be adapted to biological entities as well; since we founded our method on a need for fast feedback loops to drive efficiency in hypothesis-driven research.

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