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Does process excellence handcuff drug development?

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R&D expenditures in the pharmaceutical industry have been increasing, whereas the number of new drugs has stagnated. The patent cliff and increasing pricing pressure from payers urge for greater effectiveness and efficiency throughout the industry, including R&D.Good processes are at the heart of increased efficiency, while carefully maintaining and expanding freedom for scientific exploration and innovation.Primary targets for process improvement are service platforms, administration and interactions with suppliers, which are already applicable during the early research phase for new products. Further down the value stream, developments such as quality by design (QbD) promise increased flexibility in manufacturing processes on the condition of increased process understanding and control, based on mature process governance and management.

Introduction

For more than a decade, the pharmaceutical industry has been struggling with decreasing approval numbers. At best, the figures provided by the FDA indicate stagnation at 20–25 innovative new drugs annually [1]. This is particularly remarkable because the industry's R&D investment has increased by 12% on average year-on-year since 1970 [2] (Fig. 1).

A recent study estimated that it takes nearly US$ 1.8 billion over a period of 13.5 years to develop a new drug [3]. For the past 50 years, these costs have increased significantly faster than the general inflation rate [1], despite all the scientific advances made during that time. During the 1980s R&D investments by PhRMA-member companies climbed in relation to sales revenue from an average of 9.0% (1970–1980) to plateau at a new level of 16.6% (1992–2009) [2]. Taking into consideration the length of the drug development cycle, there is no indication that dedicating a larger share of revenues to R&D helped the industry increase the number of new drug approvals. Making things worse for the industry, payers are continuing to increase the pressure to reduce the retail prices of new and existing products. As a result, the annual growth rate of net sales shows a distinct downward trend for the past decade and could even become negative, despite the growth rates in emerging markets. Based on this, it might not be sustainable to increase R&D investments or even maintain them at current levels. In fact, 2008 and 2009 both saw lower absolute R&D investments compared to the previous year (2007) – for the first time since PhRMA began reporting these figures in 1970.

Responding to this combination of stagnating productivity and rising cost pressure, the industry is pursuing two complementary strategies: increasing the economic power of companies through market consolidation and attempting to increase productivity in the remaining companies.

Market consolidation: mergers and acquisitions

The past few years have been characterized by massive consolidation among pharmaceutical and biotechnological companies. The acquisitions of Genentech by Roche, Wyeth by Pfizer and Schering–Plough by Merck are just the most prominent examples from an extensive list [4]. A recent analysis of pharmaceutical industry productivity in terms of new drug applications indicated that the strategy of strength through mergers and acquisitions could well fail to increase the involved companies' productivity and might even harm the industry as a whole [1]. Some analysts have issued warnings that the recent reduction of the pharmaceutical workforce – in particular shedding 'old hands' from R&D, manufacturing and QA – is leading to

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2011.02.010

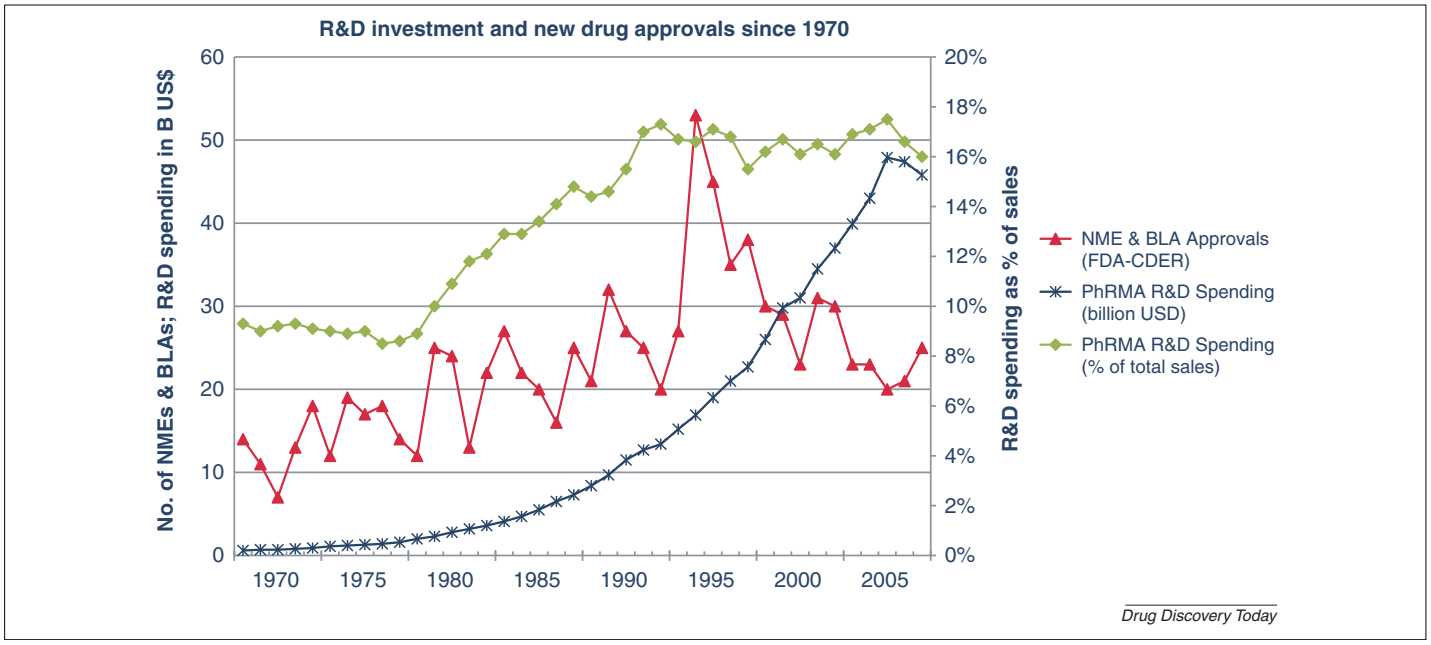

FIG. 1

R&D investments by PhRMA-member companies [2] and approval of new drugs (New molecular entities (NME) and new biologics applications (BLA)) [data provided, with permission, from Ref. [1] since 1970.

unrecoverable loss of drug development experience and could compromise the future ability of the industry to provide safe and effective drugs [5,6].

Increasing productivity

Two independent studies, one led by the FDA and another by the EFPIA (European Federation of Pharmaceutical Industries and Associations), analyzed the reasons for the industry's lack of productivity. Concordantly, they prioritized three areas with the highest potential to benefit from change [7,8]:

- Predictivity of safety evaluation.
- Predictivity of efficacy evaluation.
- Industrialization of development and manufacturing processes.

The studies further mention knowledge management and education and training for scientists and technical staff as being important measures that would support sustained improvements.

Public–private partnerships were launched based on the two studies: the Innovative Medicines Initiative (IMI; http://imi.europa.eu/) in Europe and the Critical Path Institute (C-Path; http://www.c-path.org/) in the USA. Both provide a framework for multiple projects addressing specific aspects of drug development. One example of a successful project is the Predictive Safety Testing Consortium (PSTC; http://www.c-path.org/pstc.cfm), which published a series of articles reporting on success in improving how the safety of new drug candidates is evaluated, with respect to drug-induced kidney damage, at the early stages of new compound development. The group described a panel of safety biomarkers [9] and collaborated with the FDA to define a methodology and process for qualifying new biomarkers for routine use and regulatory evaluation [10,11]. Remarkably, the qualification of these preclinical biomarkers marked the first time that the FDA had approved a technology, protocol or method to test a drug [11,12].

Innovation versus standardization

A recent analysis of factors influencing drug development productivity shows that two factors have the highest impact on overall success and productivity [3]: having the best possible scientific understanding of a particular drug and target; and having the ability to filter out candidates early on that will fail in clinical trials because of safety or efficacy issues. IMI and C-Path are both very much in tune with this assessment. However, the study also shows the huge influence that immediate cost and cycle times of individual phases of development have on the total investment per successful New Drug Application (NDA) or new Biologics License Application (BLA). Cost and cycle time directly reflect the quality and efficiency of the underlying processes. According to the model, a mere 5% increase in efficiency would translate to savings of >US$ 150 million per newly approved drug. This amount corresponds to the out-of-pocket cost of funding eight projects from target through preclinical testing, thus directly impacting the pipeline.

Innovation and standardization are generally considered to be mutually exclusive but, in reality, they are not. To comply with the scientific method and to produce valid results, all scientific work, including early research, must be repeatable. To achieve this, the experimental set-ups and conditions must be completely and comprehensively documented and systematically optimized. In addition, the cliché of a genius achieving a breakthrough single-handedly holds less truth than ever these days [13]. That said, workable and reliable rules for collaboration are essential whenever division of labor is a key success factor. Thus, process thinking and innovation are not opposites; rather, they are complementary when dealing with a series of actions and events that is meant to be reproducible, and they lead to reliable results – and at any interface between people or functions. Naturally, certain processes are more amenable to standardization and optimization than others. Although there is ongoing and very active debate over whether innovation can be captured in a formal process at all, discussions over the past five years have shown that other aspects of R&D can certainly be looked at in a process-centric manner [14–16]. Optimized processes provide many benefits, including reduced administrative efforts, increased transparency of agreed services and quality and shared best

practices. Administrative processes in day-to-day work should become so streamlined as to be hardly noticeable and leave more room for core tasks. Additional standard processes in R&D involve, for example, internal technology and logistics services or the clinical supply chain. Bad processes can be a major drain on work motivation and are probably to spur evasion strategies, cannibalizing the intended gains.

Transparency and collaboration

One important goal of implementing and enforcing processes is achieving qualitative and quantitative transparency on process performance. By definition, a good process will ensure effective and efficient delivery of a high-quality product. Much of the confusion about process improvement is related to defining the process as such – at various levels of detail – and the elements that can be subject to systematic continuous improvement (CI). Although a CI project is unlikely to define a strict business process for innovating the best chemical synthesis route, it should be able to ensure that there is a mechanism for efficient information exchange and workload distribution between medicinal chemists [17]. Common to all systematic CI methodologies is the fact that they have defined a way to look at a business process from end to end and then specifically focus on those parts of it that can be improved and would benefit most from any improvement. Critics of business process management (BPM), Lean- or Six-Sigma regularly state that many of the changes introduced during a CI cycle can simply be seen as applying common sense [18]; however, it should be considered a methodological strength to sample, evaluate and integrate systematically the knowledge and experience of the process participants and process owners to achieve improvements in a data-driven and transparent way.

BPM projects are typically structured into four phases: strategy, design, implementation and control (Fig. 2). The formalized approach avoids rushing to the seemingly obvious solution instead of conducting a thorough investigation. Experienced CI field practitioners avoid the common pitfall of overwhelming project teams with methodology-specific jargon and regularly combine tools from the different 'schools' to achieve the best results for their projects. Depending on the individual project, business process implementation can be supported or (partially) automated through IT, for example through service-oriented architecture (SOA) technology.

Because nearly all aspects of industrial drug R&D interact with or are dependent on IT systems (Electronic Lab Book, Laboratory Information Management System, Document Management System, Clinical Trial Management System, Electronic Data Capture and Product Lifecycle Management, etc.), the proximity of BPM to IT – and integration and automation in particular – is a definite strength. BPM provides a

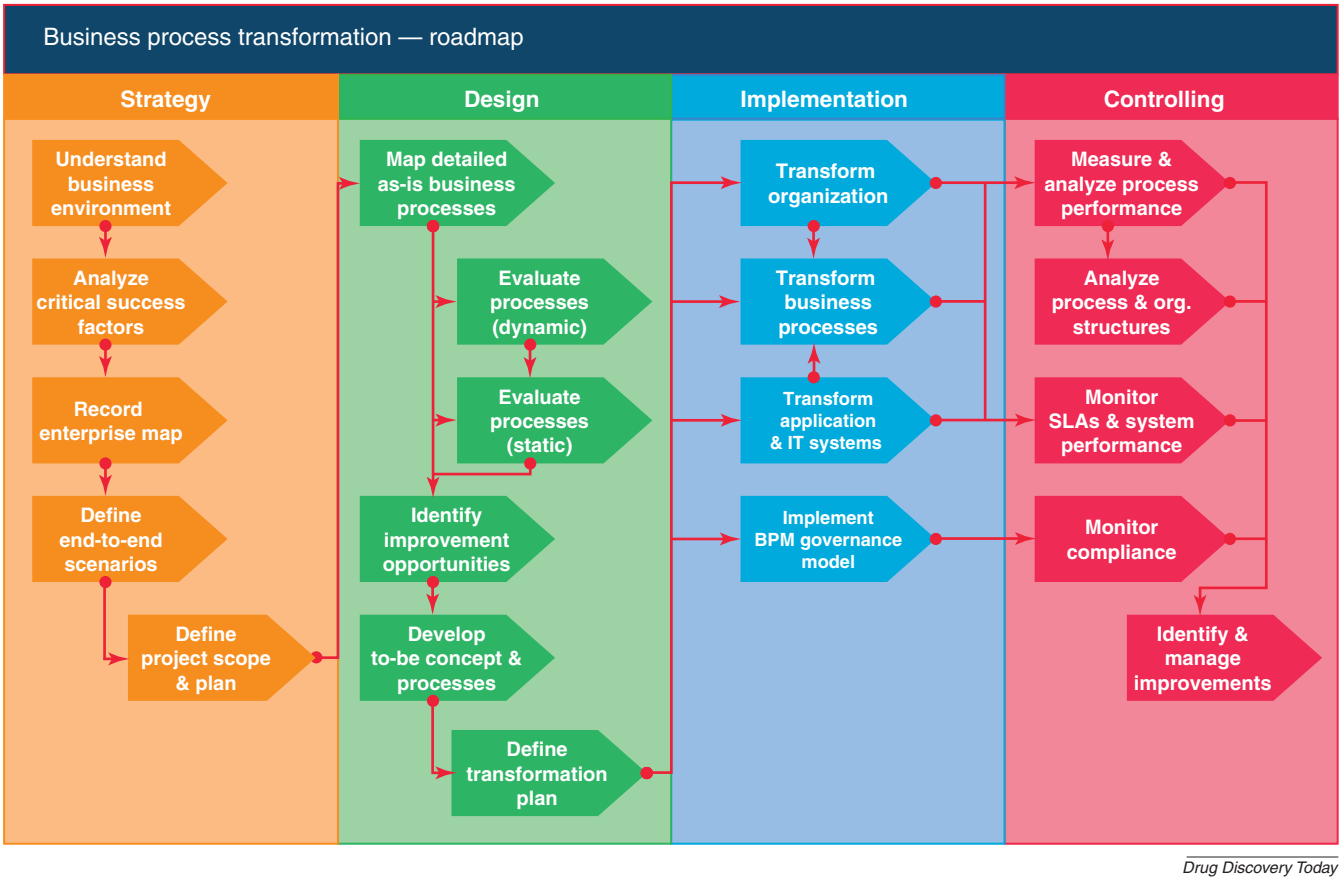

FIG. 2

ARIS Value Engineering methodology for business process transformation supported by BPM. Business process management (BPM) is a management discipline focused on systematic and continuous improvement (CI) of business processes and on maintaining them in a state of control. The intimate integration of IT to support process control and maintenance, and automation aspects, gives the approach a broader scope than most CI methodologies like Lean or Six-Sigma. Typically, a process-transformation project is structured in four phases: strategy, design, implementation and control. Following the principle of CI, these phases should be seen as a continuous cycle that could be entered at various stages.

systematic approach to collecting and describing processes, their timeline and associated responsibilities, IT systems, input and output, and interfaces. This ensures that the process description is comprehensive and consistent, for example with respect to nomenclature for roles and systems, and is therefore meaningful in a context beyond the isolated project. SOPs, regulatory documentation and training materials can be generated, in an automated manner, based on such process descriptions. Process understanding captured during the process documentation is a prerequisite for the service-oriented integration of IT systems to streamline process flows and address weak points and bottlenecks [19]. From the start, CI projects should directly involve process owners and process participants in describing and modeling the business process in question, as well as evaluating the process and defining improvements. This transparent and collaborative approach values and levers the team's experience and domain knowledge and lays the foundation for sustainable increases in efficiency and quality. It is important to stress that process transparency is not tied to process rigidity. Particularly when applied to R&D processes, the former clearly contributes to collaboration and success, whereas the latter serves only to maximize frustration and strangle innovation. CI taken beyond the buzzword level will – analogous to the scientific method – systematically use information about the past and current state of a business process to understand it and make predictions about its response to manipulation. In other words, it will develop process understanding as a basis for optimizing quality and efficiency.

Technology platforms

Over the past two decades, biomedical research has seen the advent of a whole range of technology platforms, including HTS and high-content screening, microarrays and whole-genome sequencing – all of which introduced previously unknown requirements for capital investment, technical sophistication and data-analysis complexity. As a result, many organizations host and run the new technologies at centralized facilities, often in competition with external service providers. For these groups, good processes translate into shorter cycle times from sample to report, and more-satisfied customers who can rely on receiving a high-quality product according to agreed criteria, including delivery date, depth of analysis and level of documentation. In turn, the service facility, based on predefined interfaces, can be certain to receive required input materials, such as samples, and necessary documentation in plenty of time, avoiding unnecessary delays. Taken together, this will facilitate better planning and more-efficient use of resources [20]. The Broad Institute's sequencing group adopted a process-centric mode of operation early in the 2000s and is now probably the most productive – and innovative – sequencing technology centre worldwide [21].

Clinical supply chain

The growing complexity of clinical trials is making it more challenging to provide the required materials. Manufacturing processes and final product descriptions are still in development at this stage. Guiding and documenting changes with process-driven product lifecycle management can be a key element in maintaining transparency and supporting compliance during this crucial phase. Electronic batch documentation linked to a workflow-driven release process for manufacturing process changes can be implemented during manufacturing ramp-up. Particularly during the later phases of clinical testing, this can play a major part in achieving better availability and shorter time to patient. Further cost and quality advantages can be realized by optimizing planning and logistics processes.

The process of process development and quality by design

Recognizing that pharmaceutical manufacturing needs a regulatory framework that would facilitate incorporating tools to improve efficiency and quality, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH; http://www.ich.org/) – joining international regulatory bodies and industry associations – developed new guidelines [Q8 (R2), Q9, Q10] to transform the conventional quality by testing approach into that of quality by design (QbD). The goal is to foster innovation and the application of the scientific method to drug manufacturing. Implementing QbD is expected to deliver more-reliable 'built-in' product quality and more-robust manufacturing processes, along with the opportunity for CI as knowledge and experience accumulate [22]. However, the success of a QbD implementation depends heavily on the efficiency and quality of the business processes used to design, document and govern the manufacturing process and its changes throughout the product lifecycle.

Pharmaceutical quality system

ICH Q10 describes the requirements for establishing a pharmaceutical quality system (PQS), defined as a quality management system for pharmaceutical companies. As part of the PQS corporate management is required to participate in the design, implementation, monitoring and maintenance of processes, assuring quality within their area of responsibility. The document strongly emphasizes knowledge management, training and scientifically rooted risk management as crucial supporting elements. Process models are specifically referenced for their value in maintaining and communicating all relevant information, along with their function as a meaningful foundation for CI efforts. BPM software systems can be used to define and drive workflows for Corrective and Preventive Actions (CAPA), change management, review, sign-off and training based on roles and responsibilities.

Connecting process models with process-supporting IT systems makes it possible to measure process parameters and performance. Analysis of the data reveals process bottlenecks and weak points or uncovers side tracks that could compromise the process goals or regulatory compliance. BPM-enabled surveillance of processes that affect product quality or the effectiveness of the PQS can be combined with dashboards or alerting functions to empower management to fulfil their regulatory supervision duties. This way, process governance and compliance management are becoming self-documenting – greatly supporting regular training and periodic audits.

Summary

Annual R&D investments >16% net income put the pharmaceutical industry far ahead of any other. However, analysis of the cost of bringing a new drug from idea to market and the current rate of new drug approvals show that success rates for developing new products are lagging far behind deflating cost. It is extremely unlikely that the pharmaceutical industry's current productivity crisis can be overcome through scientific innovation in the biomedical field alone. Instead, companies will have to address both dimensions of productivity – effectiveness and efficiency – in concert and aim to optimize them. BPM provides the methodology and tools to increase and protect opportunities for innovation, define transparent processes and optimize them through CI. Even moderate increases in efficiency in drug development translate into significant savings that can be used to fund additional innovation projects. Opportunities for BPM projects can be found across the entire value chain from early development to manufacturing. The scenarios discussed here increase efficiency by automating administrative tasks,

increasing transparency of processes and interfaces between functional units, and orchestrating CI. The process documentation generated as a by-product of BPM is an important contribution toward achieving and maintaining regulatory compliance.

Conflicts of interest

The author is an employee of Software AG. The author declares no competing interest influencing the views presented in the article.

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