



## PERSPECTIVE

# Success factors in drug discovery and development

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**Abstract:** The article aimed to give a personal perspective on drug discovery and development. The author has worked both in Big Pharma as a scientist and manager and more recently also in start-up biotech companies. Drug companies have played a major important role in improving population health and will continue to do so. The hurdles and costs for drug development have continuously risen without a parallel enhancement of productivity. There is no single explanation for this and the article outlines success factors and hurdles for effective drug development. Aspects of the external and internal environments that influence Big Pharma productivity is outlined and discussed.

**Keywords:** pharmaceutical industry, productivity factors

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## Introduction

The international pharma industry faced a productivity crisis during the last two decades which has been outlined in many publications<sup>[1]</sup>. The number of new drug (NCEs) approvals and introductions into the market has fallen, despite increasing R&D investments, clearly not a sustainable situation; fewer new drugs need to carry the costs of the failures. Furthermore, it has been estimated that some 300 000 employees have been laid-off as a consequence of the productivity shortfalls<sup>[2]</sup>, R&D units have been closed as part of a necessary consolidation and therapy areas have been abandoned. The big losers in this drama are naturally the patients to whom new drugs can't be offered. Despite advancements in healthcare, many diseases affecting large numbers of patients stand without effective treatment. During the last two years an increasing trend in new drugs approvals can be observed. This is very positive and is mainly reflected in orphan indications and hence smaller patient segments, which historically were less in focus by Big Pharma industry, but now will benefit from this development.

The author has been witnessing and been part of block-buster successes as well as the downsizing of the industry, by working as both as scientist and manager in Big Pharma industry and the last years in small biotech companies. The article aims to give reflections on his personal learning and perspectives on the industry's developments.

## Role of Drug Companies in Improving and Maintaining Population Health

Drug companies have delivered major contributions to patient and population health. This purpose is and will be of major importance, since only this industry possesses the complete set of capabilities, e.g., chemistry, biomedical and pharmacological science, drug metabolism-, analytical-, formulation-, clinical trials- and regulatory competence to discover and develop novel drugs. Since major unmet medical needs remains, future novel drug treatments need to contribute to population health.

The purpose of the pharmaceutical companies, to contribute to patient health, is an important driver for scientists and staff working within the respective or-

ganizations. This is contrasted to the often-given media picture of a profit-hungry industry making money out of sick people's misfortunes. Part of this picture may stem from the perceived view of big pharma companies having focused to "blockbuster" drugs, whilst leaving out smaller segments of medical need. This strategy is now changing and smaller indications as well as orphan drugs will hopefully be pursued. The fact is that most scientists come to industry to make a difference to human health. Another fact is also that companies and their employees have been richly rewarded for the contributions and rightly so, whilst there is great risks involved both for the scientist and manager, as well as for the investor. However, working with sick people as a customer comes with a great responsibility in terms of care for the individual patient and contribution to society. This responsibility goes far beyond profits, which are only a mere expression of success.

## **Influencing Productivity Factors in the Pharmaceutical Industry**

### **Fundamental Factors**

Complex Diseases: Patho-physiology and what we don't know

Despite all rapidly developing science most human patho-physiologies are not easily described. With the exception of monogenic diseases, for which there is normally little cure, and infections, our understanding of exact disease progression is often limited and constitutes a major hurdle for rational drug discovery and development. The interplay between our individual genomes and lifestyles is very complex. Despite these difficulties there are medical areas where novel drugs have contributed to better treatments, e.g., in autoimmune diseases, cancer, etc. However, to find a single target approach to the complex multifactorial diseases is normally very difficult because the compensatory mechanisms of the human body are forceful. On the other hand, in the event that most of the central biological processes are targeted, the side-effects are likely to come into play.

Preventable Diseases: Our stone-age body in the westernized lifestyle

The westernized lifestyle, which came to societies in the wake of industrialization of farming and production, is, in relation to health aspects, characterized by inactivity and overeating. As our bodies show a high

level of phenotypic plasticity in response to the prevailing environment, this has fundamental effects on disease patterns. Hence, for many of our major diseases (e.g., cardiovascular, obesity, diabetes type 2, some cancer forms and osteoporosis) a major contributing factor, in addition to genetic background, can be described as a mismatch between this new environment and the inadequate adaptation of our bodies to the challenge.

Approaches to novel drug discovery in mismatched diseases must take lifestyle factors into account. Continued exposure of the human body with excess energy in form of carbohydrates and fat, inactivity and smoking will strongly limit the long-term success of drug treatment. The pharmaceutical industry needs to take a more holistic responsibility by engaging with medical professionals and political decision makers in the fight towards a healthier lifestyle. The problem is on the agenda through the United Nations 25x25 approach which is partly building on education and, if successful, it will have a major impact on non-communicable disease mortality<sup>[3]</sup>.

### **Internal Factors**

Ownership Structures and Influences: ROI, endurance and passion

The role of the ownership structure of the pharmaceutical industry has been debated and proposed as a major factor for the maintenance of corporate identity and resilience<sup>[4]</sup>. Drug discovery and development requires long-term and passionate view on investment, whilst this is a very lengthy and risky endeavor. Hence, it has been questioned if past and current ownership structures are the proper owners to maintain a long term view and to accept lower margins over long time. Clearly the contraction of the big Pharma industry has been a global event over the last two decades, with enormous loss of talent as a consequence of all major pharma companies has been subjected to endless mergers and acquisitions (M&A). In contrast, companies with different ownership structures, such as foundations, not-for-profit organizations and companies in private ownership, have been able to survive periods of diminishing returns and to pursue strategies with less external accountability.

The Game R&D Plays: "One in twenty"

Three decisions in the history of a novel project dictate its fate. The first is the selection of the target, the second is the selection of the molecule and the third is

the selection of patients. From these decisions onwards the rest is documentation of the resulting effects and side effects.

The pharmaceutical industry is different to other engineering industries in as much the ability to predict if a novel project will translate into a successful product is very low. It has been estimated that 93% of candidate drugs fail to reach approval, let alone be successful in the marketplace<sup>[5]</sup>. Despite the emergence of new technologies, increased development investments and longer development times productivity has fallen. The major contributing factors for failure are lack of efficacy and toxicity/clinical side effects<sup>[6]</sup>. The industry has rapidly introduced novel strategies to rectify this situation, impressive advances in novel platforms, technologies and ways of working have been introduced. Some examples include the following:

(i) Advances in biomedical science platforms such as genetically engineered animals, stem cell approaches, bioinformatics platforms and predictive science methodologies all aimed to improve and verify correct target selections. Recently, evidence has been provided that compounds co-developed with a biomarker have been associated with higher success rates. The concept of biomarker monitoring for efficacy and safety could bring significant contributions to overall success<sup>[7]</sup>.

(ii) Novel platforms for drugs include, in addition to small molecules, biologicals (proteins, peptides, antibodies, and modern vaccines), RNA-interference molecules, cell therapy and gene therapy approaches. Particularly the more recent introduction of antibodies has been successful.

(iii) Platforms for drug discovery include miniaturization which expands the capacity of bioassays and chemical synthesis, profiling technologies such as transcriptomics, new imaging methods and ultra high throughput assays.

Novel Project Strategies: Targets, new chemistry and big project portfolios

The technologies introduced above provided a means for rapid target selection and testing of large number of compounds. The fundamental strategic change of direction was based on the principle that a multitude of early development projects would mitigate for loss seen later in the development process. In this context, the principle coined by Sir James Black “the best way to create a new drug — is to start with an old one” was no longer in fashion. The new ways of working bro-

ught forward chemistry and novel molecules, however, at the expense of solid human target validation. Industry paid a very high prize for this novel strategy in terms of development failures. Furthermore, it is also disappointing to note how little impact the introduction of novel technologies have had on improvement on success. In many companies the re-introduction of more integrated experimental models showing physiological responses have been increasingly used in early drug evaluations.

Hindsight makes analysis easier and looking retrospect, the human target or treatment paradigm validation plays the most critical role in the success of a novel project in view of the author. The highest level of approach validation is based on existing drugs demonstrating clinical effects in the appropriate patient population. A relevant example is pharmacological treatment of peptic ulcer disease. The over many decades prevailing treatment paradigm, inhibition of acid secretion, clearly improve the 4-week healing rates of duodenal ulcers over placebo. Furthermore, progressively more effective suppression of acid secretion by anti-cholinergic, H<sub>2</sub>-blockers and proton pump blockers further enhances healing rates. However, the fundamental cause of disease is not improved as evident by the high 2-year recurrent rates after cessation of treatment. It was not until the understanding of *H. pylori* as a causative agent of the disease was discovered and its subsequent eradication by a combination of proton pump blockers and antibiotics that the disease could be ultimately cured.

We learn from this that:

(i) progression to effective treatment/cure is a long-term endeavor over many decades,

(ii) several treatment modalities are normally introduced to effectively treat a disease,

(iii) fundamental understanding of disease pathophysiology is the most important factor for treatment success as well as human target validation. This has often been absent at the onset of many drug projects.

Global Reach: Consequences for scientists and entrepreneurs

For the successful companies globalization is necessary to provide for access to markets and new product opportunities. This means operation over many global corporate functions, cultures and co-workers. Functions like R&D need to be managed globally, with the consequence that the same global standards, operational procedures, review and evaluations, budgets, etc

are instituted. In the growth transition from the smaller, fast moving unit to the globally governed one, decisions move to higher organizational levels and take longer time, workflow is standardized and idea generation steered by corporate strategies. In a big Pharma company, some 100 different projects may run in different phases of development and with geographical spread. For an individual project leader to navigate the different strategy reviews and decision bodies, he needs to, in addition to ensure proper presentation of the subject matter, consider the in-house political landscape, lobby with stakeholders and advise on formal report progress.

In order to generate economy of scale, Big Pharma companies often place central functions in large centers of excellence. The consequence for the individual scientist is that they often find their job role being narrowed down to do a single task and distanced to project work. The possibility to influence his or her own work becomes very limited. In this landscape it is clear that conditions for creative drug discovery are not optimal.

**Big Pharma People Management:** Counter to an innovative climate?

To align big pharma company objectives to the individual level, these are cascaded in elaborated processes to staff. Fulfillment of these objectives forms the basis for evaluation of staff performance and subsequently salaries and other compensation. The problem with “people management” in a big Pharma setting is that it is not motivational and aligned to real drivers for scientists at different levels. The inherent risk of drug project failure and hence missing personal objectives drives co-workers to risk adverse behaviors and to become street-smart. Furthermore, due to the complexity of large organizations, skilled scientists soon find themselves devoting much of their time to meetings instead of research. Ironically in many big Pharma companies it is often more rewarding to take on an administrative career than to stay with science.

Scientists come to big Pharma industry because they want to make a difference to patients, to do good science in quality facilities and expect a good compensation. For them to be engaged in this task they need to be given the possibility to strongly influence their own work, pursue ideas and to grow in their skills and take on more advanced duties. Success is to be associated with and being able to influence important drug projects to succeed.

**Small Biotech and Start-up Companies:** The solution to innovation?

Part of the personnel being laid-off from big Pharma find themselves starting new careers as entrepreneurs in small biotech and start-up companies. The business ideas may build on an academic discovery, repositioning or reformulation of a known drug or research projects of little strategic importance to the Big Pharma company. This is sometimes known as “open innovation”. These companies usually focus to one or few projects, lack the broad expertise, are flexible and fast in decision making, steered by results and the funding situation and show a high entrepreneurial commitment. The smaller company critically depends on external CRO competence and problem solving, such as deficits in compound quality often remaining too long in development. The customer to these companies is often Big Pharma.

### **External Factors**

**Socioeconomic Gains:** What health care decision makers want

Many important drugs are becoming generic. This raises the hurdles for new drug development and the pressure on the industry to innovate with advantages for patients and for society becomes increasingly higher. Furthermore, as health care providers are struggling with budgets taking an ever-increasing part of taxpayer money, compensation for new drugs are critically reviewed.

### **Conclusion**

There is no simple recipe for successful drug discovery and one successful drug is no guarantee for a maintained pipeline. No pharmaceutical company is immune towards patent expiries, negative price pressure and failing drugs. To summarize some of the learnings:

The productivity, e.g., successful drug introductions, will continue not to be planable due to the biological complexity and lack of knowledge of patho-physiology. Methods such as biomarkers, that can select patients that are more amenable for treatment, should be prioritized.

Drug development has to take the strong phenotypic influence of the westernized lifestyle into consideration as disease patterns are rapidly changing. Big Pharma should engage more forcefully with medical professionals and politicians to massively inform the populations as to the importance of a healthier lifestyle.

The passion and resilience of Big Pharma ownership together with the formation of a creative culture that fosters entrepreneurship and freedom to explore novel ideas is of fundamental importance.

Cost for health care will rise and the pharma industry has to get accustomed to operate to lower levels of return on investment. This will also improve Big Pharma reputation in the eyes of the society.

Finally, drugs are discovered by scientists and their associated teams. Management need to better understand their needs in terms of freedom to explore ideas and necessary funds, rather than managerial strive to control.

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