Productivity Challenge of the Pharmaceutical Industry
And
Its Implications for Its Researchers

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Introduction

Despite substantial increases in pharmaceutical Research and Development investments for the last several decades, the number of new molecular entities (NME) approved stayed at the same level. Meanwhile, the pricing pressures from government, other third party payors as well as competitions from generics against branded prescription drugs continue to intensify. The global pharmaceutical industry is facing unprecedented pressure to increase its productivity!

Major pharmaceutical companies have responded with a wide array of strategies to address this productivity challenge. Of these strategies, some are business oriented: including merger and acquisition, in-licensing, redesign of organizational structures and business processes; while others focus on enabling technology solutions: such as genomics, biomarkers, and monoclonal antibodies. A snapshot of any individual company would reveal a combination of a unique set of business and technology strategies aimed at improving its productivity.

Strategic changes create opportunities and, at the same time, brings uncertainty. The emerging forces of change will undoubtedly impact the career and personal life of researchers in the industry, many of whom have not experienced such frequent and dramatic changes. How should the researchers prepare and cope with the changes?

This two-part article attempts to highlight the following:

1. The productivity challenge
2. Survival guide for the researchers

The transformation of the industry will no doubt result in more uncertainty and volatility, it will also present more opportunities for companies and individuals that are better prepared and positioned to embrace the future.

Part I: The Productivity Challenge of Pharmaceutical Industry

Why the productivity challenge?

The global pharmaceutical industry has enjoyed continuous growth in both product revenue and market capitalization for decades. It has been positioned as one of the few recession proof industries based on its performance through multiple economical cycles. The industry has delivered many innovative medicines with tremendous positive impacts on the quality of patients' lives. Generous investments in R&D enabled pharmaceutical companies to build deep pipelines and product portfolios that drive the growth. As a result, the researchers in the industry have enjoyed relative stable working environment that allowed them to focus on research and development activities and largely insulates from external economical pressures and volatilities the industry faces.

In recent years, there have been visible strains in the pharmaceutical business model, to name a few: competition within the industry is intensifying; patent expirations of major products have clouded the growth prospects; pricing pressure from government and third party players are mounting, both from international markets as well as from the United States. More importantly, the outputs from the R&D pipelines have slowed down compared to the size of the R&D investment. For example, the global pharmaceutical R&D expenditure has grown from $2 billion to $26 billion between 1980 and 2000 while the industry outputs remain at the same level through the twenty-year period. FDA approved only 27 NMEs in 2000 vs. 20 NMEs in 1986.

One may argue that it is yet too early to draw the conclusion based on just twenty years of performance, given that the industry's product development cycle spans 10 – 15 years. Since a significant portion of the pharmaceutical R&D resources concentrate on late stage clinical studies, at least the total R&D spent can serve as a useful proxy to gauge the correlation between investment and near term industry outputs. Based on the historical data, it is difficult to see a growth trend of increase in new product approval despite the steady rise of R&D investments.

Another observation that has been frequently used to counter the productivity gap argument is the fact that the current commercial value per approved product is much higher than that of twenty years ago. The industry has taken a blockbuster driven approach, which leads to much higher peak sales revenue per product and faster revenue growth post-launch. A smaller number of products with blockbuster potential generating much greater revenue streams can still deliver a healthy return on investment. While this argument can be used to justify the tremendous rising in development costs in late stage pivotal studies as well as pre- and post-launch commercial costs, it fails to address the productivity deficiency in discovery and early stage development before the blockbuster potential of a compound is revealed.

The rapid rising cost of bring a product to market has been identified as one of the root causes of the productivity challenge. Based on two most recent analyses from Tufts Center for the Study of Drug Development (CSDD) and Boston Consulting Group, the total cost of developing a new prescription drug is nearly $900 million. The new estimate is almost quadrupled the cost of developing a drug in 1987, which was estimated to be

around $230 million by CSDD. This increase is a result of higher direct costs, longer duration of the R&D projects and overall longer drug development cycles. Examples of such factors include additional complexity of the clinical studies, especially during the late phase of the development, as well as the rising regulatory hurdles for approval.

In recent years, FDA becomes increasingly conservative in reviewing and processing NDA submissions, especially if the compound under review has the potential to be associated with certain risk factors such as QTc. In addition, the Agency has also taken more stringent measures to inspect manufacturing process and facilities, which also led to significant delays in new product introduction for several companies. Although the slower approval process is an obvious driver for the industry's near term pipeline drought, it is certainly not the only reason. With a dynamic new FDA commissioner in place, there is evidence suggesting that FDA will likely accelerate the pace of approval while try to recalibrate the balance between facilitating the introduction of new medicines and protecting the safety of patients.

A faster and "friendlier" FDA does not necessarily mean the industry can escape from other drivers of higher R&D costs. At the scientific level, a growing portion of the molecular targets and mechanisms for drug discovery are unprecedented with limited structural and functional information available. This will likely increase the attrition rates of compounds as the researchers try to understand the basic science of these targets and pathways and develop specific drug leads against the targets at the same time.

The productivity challenge of the industry has pushed down the valuations and stock prices of companies in the sector, in fact many companies have made news headlines for their poor finance performance and bad management decisions. Clearly, it is increasingly more difficult to generate a positive return on investment (ROI) on R&D. If the factors leading to the productivity deficiency are not addressed, the R&D cost will likely to rise continuously, until a point where most of the companies won't have sufficient resources to invest in R&D and drive growth in pipeline and product revenue.

Strategies to address productivity challenge

The productivity challenge of pharmaceutical industry is not an overnight problem, there won't be any easy and quick fix either, due to the long product development cycle time. Many companies have recognized the strategic importance of this issue and have taken a wide array of approaches to address it. In general, these approaches fall into two broad categories: business approaches and technology approaches.

<u>Business Approaches</u>

Merger & Acquisition

M&A has been a strategy of choice for many current pharmaceutical companies as well as their legacy organizations. Examples include Pfizer, Glaxo SmithKline, Johnson & Johnson, Bristol-Myers Squibb, Novartis, Aventis, AstraZeneca, etc. In theory, M&A allows the merged companies to expand market presence, reduce overhead costs, expand and streamline pipelines by combining scientific expertise and eliminating overlapping projects, as well as leveraging scale to reach critical mass of investment in specific areas. The consolidation of the industry has been a constant theme for the last decade, which resulted in multiple mega-mergers as well as the disappearance of over half of the original players in this sector. Nevertheless, integration of two companies of different culture and business processes is a complex, difficult, and lengthy process. While delivering merger-related cost savings can increase the confidence of shareholders in the near term, simply pooling the resources of two companies facing the same productivity challenge, however, does not necessarily offer the right solution. The real synergy in R&D should come from improvement of productivity on an increased scale based on the best thinking and practices from the legacy organizations.

In-licensing

While M&A allows companies to expand their pipeline and product portfolio in a compressed time frame, many companies would prefer to avoid the intense scrutiny of anti-trust authorities and the large scale changes and disruption associated with post-merger integration. In-licensing product candidates at various stages of development is another strategy that provides the companies an opportunity to fill the gaps in their pipelines. Although licensing is a standard business practice for almost every company, committing substantial financial resources to strike the deals as well as sufficient internal R&D capacity to support the development of in-licensed product candidates is an explicit strategy that some companies focus on. One such example is Glaxo SmithKline (GSK). During the last two years, GSK has in-licensed over 20 product candidates at preclinical and clinical stages to complement its internal pipeline. Compared to M&A, licensing is a more flexible and targeted strategy. Of course, the obvious drawback is that the substrates are limited, especially for late stage product candidates. Too many companies chasing a small number of available compounds can dramatically increase the cost of licensing.

New Organizational Structure and Decision Making Process

The typical pharmaceutical R&D organizations today are characterized by multiple layers of managements over functional and geographical business units. Since the basic unit of the R&D process, the project team, is usually cross-functional, it becomes a delicate balancing act between encouraging collaboration and project ownership within the team while maintaining efficient management of people and resources. In addition, how to facilitate effective decision making and resource allocation

across multiple governance bodies in a highly matrixed environment is a strategic issue that every R&D organization encounters.

Since the decision making and resource allocation process is driven by the company's culture and overall strategy, this is an area that companies have taken very different approaches: Lilly uses heavy weight product teams to drive the development of the compounds, GSK has established CEDD (Centres of Excellence for Drug Discovery) using a therapeutic area (TA) based approach to allow competition for resources among different TAs at the early development stage, while Novartis is moving towards Disease Area business units as a framework to streamline investment within specific TAs. The underlining theme of all these organizational structure redesigns is to decentralize decision making, create strong incentive of project ownership, and overcome the bureaucracy associated with big organizations. Another critical driver of these changes is to allow better integration between R&D and commercial organizations and alignment of strategies from both sides.

New Business Process

One of the major innovations of the last two decades for R&D business process is the emergence of outsourcing to complement the traditional vertical integration model of the pharmaceutical companies. An entire sector, Contract Research Organizations (CROs), becomes a vibrant component of the R&D. The outsourcing partners help the pharmaceutical companies to mitigate risk, reduce cost, and more importantly, focus on investing and developing unique in-house expertise that will sustain their competitive advantages. The strategic flexibility provided by outsourcing is a key lever that can help to improve the overall R&D productivity. Of course, working with external partners will also increase the complexity of project management and coordination. To fully capture the value and leverage the flexibility of outsourcing, the business process will need to be refined to provide the necessary interfaces and support mechanisms.

Technology Approaches

Technology is at the heart of pharmaceutical R&D. Ultimately, it is the advancement of science and technology that will allow us to unlock the secrets of the genome, address the R&D productivity challenge, and develop better medicines. However, we need to set the right expectation for what technology can and cannot deliver. Despite the optimism on the transforming power of genomics, proteomics, and pharmacogenomics, there is a clear recognition that these technologies are still in their early stage of development, and that, in the short term, they require substantial investments that may not generate adequate returns. Based on a cost analysis of genomics by McKinsey & Company, genomics will increase the overall pharmaceutical R&D costs significantly in the next five years. The benefits of genomics and other enabling technologies will come, but likely over a much longer time frame. For pharmaceutical researchers at the cutting edge of innovation, technology seems to be naturally the preferred (and sometimes the only) solution to overcome the productivity

gap. It may be difficult for them to realize that the significant investment in platform technologies is a key factor that contributes to the overall cost increase of developing a drug in recent years.

Since many enabling technologies have the potential to improve R&D productivity in some capacity, the discussion on technology approaches in this article will be limited to two examples (namely biomarkers and monoclonal antibodies). These examples are chosen not based on their technical merits, but due to their direct impact on improving the R&D productivity. For discovery research and clinical development, biomarkers are becoming an increasingly important tool to provide early signals on the safety and efficacy of compounds. Proper use of biomarkers can speed up decision making, reduce the cost and time associated with preclinical and clinical studies. Another platform technology that has gained wide acceptance by major pharmaceutical companies and biotech companies is monoclonal antibody (mAb). Compared to small molecule drug candidates, mAbs usually have more straightforward lead generating and optimization approaches, relatively well characterized safety profiles, and, as a result, better attrition rates. Of course, manufacturing capacity and cost currently remain key constraints for the late stage development of a successful mAb product. As more mAb products launched and more manufacturing capacities become available, mAbs will become a major product class across multiple therapeutic areas.

Summary for Part I

The productivity challenge of pharmaceutical R&D is well recognized within the industry. An individual company may combine a different and unique set of business and technology strategies to try to improve its productivity. Taken GSK as an example, it has established the autonomous CEDDs to improve the early development process. It also committed significant resources for in-licensing compounds over a short time period to fill the pipeline gap. In addition, the company has invested heavily in genomics and pharmacogenomics over the last decade. Given the patent expiration of Augumentin and the projected slow growth of other products in the market, GSK has to aggressively respond to declining stock price and investor confidence. Similarly, most of the major pharmaceutical companies are confronting with the same set of issues. As discussed, they have also developed and implemented various strategies to drive pipeline and product portfolio growth. It is still too early to tell which strategy is effective and will prevail in the long term. The forces of change will continue to shape the structure of the industry and the underlining business models, processes and strategies. One will hope that the companies that are more agile, adaptive, and innovative in response to the R&D productivity challenge will have a better chance to harvest the fruits of genomics, proteomics, and pharmacogenomics and eventually develop personalized medicines for every disease.

Note: Dr. Steve Yang's experience includes R&D strategic planning, portfolio management, corporate development, and merger & acquisition integration. Prior to his

current position at Pfizer, he has worked at a start-up biotech company and a management consulting firm. This article is based on author's personal opinion and does not represent Pfizer's view points.