Pharmaceutical industry; Where it is now and where it is heading

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This article overviews a recent trend of market performances of US pharmaceutical companies and a new paradigm shift in drug research with emerging technologies in terms of their potential effects on future industry performance and health care practice.

Introduction

Financial performance expectations for US pharmaceutical industry by analysts at Wall Street could be viewed unrealistic. That is, a recent interview with 15 financial analysts indicated expected average annual earnings growth for US-based big pharmaceutical companies of 12-15% from year 2000 to 2005. In reality, however, average annual sales increase for those big pharmaceutical companies during the same period is expected to be around 8%, whereas annual market growth is forecast at 6%. Obviously, a big pharma is unlikely to get anywhere near those expectations. With simple calculations, at least 5-6 new chemical entities (NCE) are required to be added on its current product portfolio every year for big pharma, in order to generate 10% annual revenue growth, assuming each NCE yields $150 million sales a year. Make things even worse, R&D productivity of those big companies are low, reflected by the fact that fewer than one NCE per company enters the market annually with more than half of all those new product introduced coming from the companies with sales under $800 million. Consider that it takes about $800 million (some say more than $1 billion) and 12-14 years to produce one NCE, and the average NCE is estimated to generate around $350 million sales at peak-some 8 to 11 years later after launch. The ever-increasing pressure from financial community for higher return and growth of pharmaceutical industry and the enormous cost burden for new drug development forced big pharma move into more efficient and faster drug development approaches.

Paradigm shift in drug discovery and development processes

1. Rational drug design, its hopes and limitations;

As part of efforts to streamline drug discovery process and increase in its success-ability, for many years, scientists both in and out of pharmaceutical industry have been talking about "rational" drug design based on molecular mechanisms and biochemical events. This discussion began with understanding of three-dimensional structures of proteins with improvement in crystallography technologies. The argument was that it would be easier for medicinal chemists to design molecules that would interact more efficiently in an active site of protein once its three-dimensional structure was known. However, this approach was not able to deliver on its promise due to a couple of reasons. One is that a crystal structure does not always properly reflect how a protein molecule behaves in vivo. It is not unreasonable to envision that the chemical compounds designed to inhibit or enhance the activities of the protein in solid, crystalline forms in vitro may not produce the same pharmacological results in vivo in an aqueous environment. In addition, more often than not, medicinal chemists found it difficult to develop new chemical structures for the rational approach due to many practical reasons. This led to the development of combinatorial chemistry to provide large, diverse libraries of compounds for drug discovery to increase a sheer chance of luck or hit. A decade later few would argue that the current approaches for drug discovery harnessed with automated crystallography equipments and mass production of new chemicals with combi-chem machinery are working efficiently. It is true that all those recent technologies and findings with -omics (genomics, proteomics, metabolomics) offer new angles for achieving rational drug design. By the same token, however, these also add more complexity and data overload to the chemists and biologists who are already overwhelmed with those generated previously. No doubt that scientists made a great progress in understanding diseases from both the level of the whole individual entity down to the molecules to cellular organelles and genetic levels. But they haven' t had figured out yet all that' s necessary for drug development. In order to utilize the unprecedented amount of data generated, the data must be translated into knowledge that can readily be of use for both drug discovery and development. Data and knowledge management becomes increasingly important due to these obvious reasons. The key issue now is figuring out which information is worth putting together with other information as well as finding ways to communicate efficiently with the various data platforms. In other words, data mining and management are becoming the name of the game for drug discovery in this era of mass production of chemicals and high throughput capabilities.

2. In silico drug design

In silico drug design technologies should aid in analyzing complexity in biological system, as long as the technologies are based on a thorough understanding of relevant biological phenomenology. Some have argued that these technologies will enable drug manufacturers to accelerate the selection process, and could save hundreds of millions of dollars and two to three years in drug development time with increase in

their overall chance of success. It should be recognized, thou, that the in silico approach has its value in supplementing and supporting rather than replacing the current drug discovery and development processes. Some pharmaceutical companies have established various ambitious plans to cut down the cost and time for new drug development. For example, Bristol Meyer Squibb launched a five-year development time plan from a product' s first synthesis to marketing. In the plans, it will take only one and half a year from first synthesis to phase II clinical studies, of which materialization remains to be seen.

3. Gene-based drug design and personalized medicine

According to recent studies, somewhere between 20 and 40% of patients are prescribed a drug that has no beneficial effects on their medical conditions. Furthermore, tens of thousands of people die every year from adverse drug reactions, which could be in part from inadequate dosing regime, and millions more suffer from uncomfortable and sometimes dangerous side effects. Many of these treatment failures and adverse events could be avoided or at least minimized, if drug response could be understood in molecular levels, to be more exact, in genomic levels. The majority of gene-based therapies are under investigation for the treatment of cancer followed by infectious disease. At least 20% of current pharmaceutical research activity is on gene-related programs, and around two thirds of these are still in the preclinical stage, suggesting that most gene-based treatments will not be commercially available for several years. Nonetheless, more than 100 products are in various stages of clinical evaluations.

Conclusion

Despite the promise of personalized medicine from rational and gene-based drug design, many pharmaceutical companies become wary of the impending changes in the way new drugs will be discovered, developed and prescribed. Just imagine the financial damage the pharmaceutical industry has to endure if 1 billion dollar drug currently turns out to be efficacious in only the 20% of patients with the appropriate genetic profile, for instance. On the other hand, companies that adopt the personalized medicine paradigm early on could find the ways to maximize sales and profits by discovering and commercializing medicines that work in close to 100% of an adequately defined patient population. This would mean fewer treatment failures, almost guaranteed success in treatment, and a premium pricing advantage. The ever increasing financial burden and new paradigm shift in medications urge the pharmaceutical industry figure out the ways to address all those questions and concerns, and successfully draw social and political support, which would, hopefully, in turn lead to a better quality of patient life and an extra return on investment.