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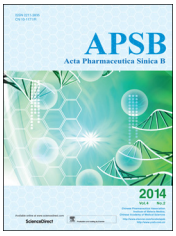

REVIEW

Research and development in drug innovation: reflections from the 2013 bioeconomy conference in China, lessons learned and future perspectives

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Abstract The enormous progress biotechnology, bioinformatics and nanotechnology made in recent years provides opportunities and scientific framework for development of biomedicine and constitutes a paradigm shift in pharmaceutical R&D and drug innovation. By analyzing the data and related information at R&D level over the past decades, developmental tendency and R&D patterns were summarized. We found that a growing number of biologics in the pipeline of pharma companies with successful products already in the market though, small molecular entities have primarily dominated drug innovation. Additionally, small/medium size companies will continue to play a key role in the development of small molecule drugs and biologics in a multi-channel integrated process. More importantly, modern and effective R&D strategies in biomedicine development to predict and evaluate efficacy and/or safety of 21st century therapeutics are urgently needed. To face new challenges, developmental strategies were proposed, in terms of molecular targeted medicine, generic drugs, new drug delivery system and protein-based drugs. Under the current circumstances, interdisciplinary cooperation mode and policy related to drug innovation in China were deeply discussed as well.

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1. Introduction

Bioscience is now rapidly expanding in the 21st century. Advances in biology/biotechnology, bioinformatics and nanotechnology provide opportunities and a scientific framework for biomedicine, which can have significant impact on conventional research and development (R&D) and drug innovation, even a revolutionary change. The objective of this article is to further discuss the aforementioned areas by reflecting on the Session on R&D in Drug Innovation during the Bioeconomy 2013 conference in China along with lessons learned and future perspectives, and their implications for the growth of biomedicine in China[1–20]. Big Pharma's challenges which are becoming opportunities for biotech and startup companies include: (1) R&D spending is growing faster than sales growth, (2) drug discovery is lagging relative to industry growth needs, (3) increase presence of large molecules in big pharma's pipeline, (4) increasing need for in-licensing products and technologies, and (5) blockbuster drugs are going off patent. As a result of these changes, the number of joint ventures and collaborations between academia, government and industry has exponentially grown in recent years.

Pharmaceutical innovation has led to a decline in industry productivity. Despite the increased investment in R&D by the industry, the number of new molecular entities (NME) achieving marketing authorization is not increasing. Over the past 20 years, the number of Investigational new drugs (INDs) approved by regulatory agency did not increase as anticipated with enhanced quality control level and strict safety assessment as well as many molecular targets identified, while those drugs currently applied in clinical for long time have demonstrated their values, suggesting that high investment, development of technology and "-omics", such as proteomics and genomics have not reduced the R&D risk effectively and enhance efficiency[1,2,8].

In light of these scenarios, various strategies have been adapted in order to increase R&D efficiency and productivity[8]. At the drug discovery level, increased use of bioinformatics and computer modeling along with accelerated proof of concept studies and enhanced input from commercial and marketing have proved to be useful. The use of biomarkers and translational research in clinical trials is regarded as a powerful tool and used broadly in the pharmaceutical industry. Implementation of risk mitigation strategies and exploitation of outsourcing and strategic partnerships can further improve R&D efficiency and productivity.

2. Innovation trends in biomedicine

2.1. Conventional R&D pattern with high cost, high risk and low productivity is not sustainable

The conventional R&D pattern in drug innovation started in 1960s and it is always accompanied by high cost, high risk and low efficiency. By analyzing the ratio of the number of drugs approved for marketing by Federal Drug Administration (FDA) to that of active ingredients/molecules at the drug discovery stage, it remained at approximately 0.01% (Fig. 1) that is "one in ten-thousand" molecules make it to the market indicating the need for tremendous investment in R&D as a result of the extremely high potential of failure in the course of drug development. High rate of failure in drug development continued despite demands in high drug product quality and safety assessment along with technological advances.

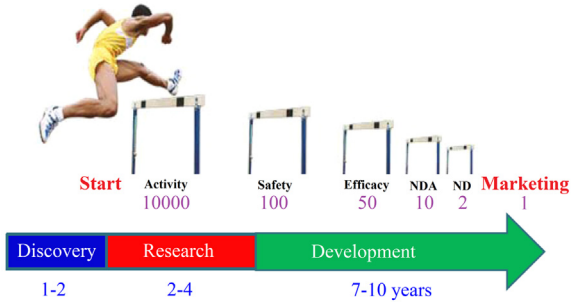

Figure 1 "One in ten-thousand" model for drug innovation of research and development.

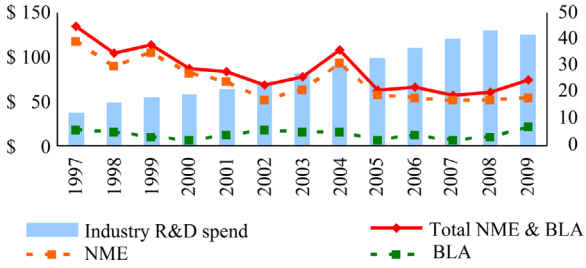

Figure 2 Comparison of new molecular entity and biological application since 1997 (Source from FDA websites, Evaluation Pharm).

The recently published data sourced from Bristol-Myer–Squibb and other 5 giant pharmaceutical companies revealed that of the 6 drug candidates that were terminated at phase III clinical trial in 2012, 4 were eliminated by efficacy and with the other 2 were safety issues. Efficacy and safety issues were considered as the main causes of failure at the stage of phase III. A molecule is not a drug, neither is active one and "druggability" is a key factor in the systematic process from molecule to drug, while translational research with "risk evaluation" is the decisive element. Unfortunately, this key problem has not been properly considered and addressed by multidimensional investigation through science, technology, policy, regulatory, ethnics and industry, analyzing bottleneck and other issues in common. However, a deep understanding of the issues using traditional models of drug development R&D and focusing on key challenges and opportunities is critical to building and adapting new innovative models of drug R&D.

2.2. Developing small molecule drug is still the mainstream approach

The nature of the pharmaceutical industry is such that the main driver for its growth is innovation[21]. Biomedicine R&D is becoming increasingly challenged due to lower productivity and thus pharmaceutical companies have opened their R&D organizations to external innovation[14,15,20].

Fig. 2 compares new molecular entities and biological applications from 1997 to 2009. R&D spending was increased more than 3-fold since 1997 while NME approvals dropped by 44%. This trend is expected to continue given increased regulatory scrutiny; NME approvals decreased by 4.8% 1997–2009, while R&D spend increased by 10.7%; 45 NMEs and therapeutic biological applications (BLAs) were approved in 1997 which fell to 25 in 2009; in 2009, the industry spent a total of $125 billion (BN) R&D *vs.*