Editorial

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Personalized Medicine

A possible future for the pharmaceutical industry

"When all drug patents expire and there is a plethora of available medicines, the major pharmaceutical companies of the future would in essence be converted to the equivalents of today's manufacturers of generic drugs and biosimilars."

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Industry trends

For several decades, drug development has followed a proven formula of discovery and development that to date has generated the availability of 6572 US FDA-approved medicines that are offered in the USA for treatment of a variety of medical conditions [1]. Bringing a new drug to market is an extremely lengthy and costly process, beginning with drug discovery where a lead compound is identified which interacts and modulates the activity of a desired target that plays an important role in a particular disease pathway. The drug is then assessed and refined in the preclinical phase of drug development so that its solubility, stability, toxicity, pharmacokinetics, metabolism and dosage are established. Clinical development, where the effects of the drug are studied in humans, then proceeds through several distinct phases or trials. In a Phase I trial, safety and dosing are determined, usually in healthy volunteers. A Phase II trial then follows where an initial appraisal of efficacy and further exploration of safety in small numbers of diseased patients is determined. The most important part of clinical development is the Phase III trial where safety and efficacy are assessed in a sufficiently large number of patients. The details of the drug development and approval process can be further explored on the FDA website [2].

According to the FDA, approximately 400 original investigational new drug applications are received annually from pharmaceutical and biotechnology companies initiating clinical trials [3]. In spite of this continued high activity of new drug development, recent years have yielded a very small subset of investigational new drug applications that have actually led to approved drugs. For example, there were only 39 FDA drug approvals in 2012 and a mere 27 in 2013 [4]. This trend of fewer annual drug approvals has plagued the industry for the past decade and raises concerns for future prospects.

An additional important concern is the dramatic increase in the actual cost of therapeutic development. A drug that receives FDA approval typically requires over 10 years of effort from discovery research to regulatory approval, and product launch at a cost of approximately US$350 million [5]. But this analysis is for a single successful drug that is actually approved. The reality is that there is a failure rate for FDA approval of over 90% for all drugs that enter human clinical trials, which pushes the overall cost of drug development for the major pharmaceutical companies, who are developing multiple medications simultaneously, to approximately US$5 billion per drug [5]. These high risks and high costs make the current investment model unsustainable.

Another industry trend is the growing number of low-cost generic drugs that are becoming available. When a patent expires that has served to protect a company's branded drug from being marketed by others, any manufacturer can then reformulate, obtain regulatory approval, and market their own version of the drug under its chemical name without advertising. Because of market competition and less risk of regulatory

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approval, the generic drug is priced significantly lower than the comparable original branded version but the dosage, strength, route of administration, quality and intended use remain the same [6]. These factors have changed the market so that generic drugs are an attractive option for patients, physicians, payers and hence a growing business for drug developers.

Difficulties ahead in development of new drugs

There are several factors that have contributed to the significant rise in the cost of drug development. One contributing element has been the accessibility of many more potential drug targets, which leads to a significant increase in the amount of compound screening that can be performed for the same disease pathway. Prior to the availability of the human genome sequence, one estimate of the number of targets to which all approved therapeutic drugs have been developed was 324 [7]. But as a consequence of the mapping and DNA sequencing of the human genome [8,9] and the countless studies that have followed, it is now believed that over 10–15% of the 21,000 genes encoded by the human genome may be druggable [10].

In addition to having many more potential intracellular, cell surface and extracellular targets to choose from for compound screening compared with decades past, the number of compounds available today has also dramatically increased. Advances in both computational and combinatorial chemistry, have transformed the number of compounds that can be generated and evaluated from hundreds of thousands to tens of millions [11,12]. The combination of having an order of magnitude rise in the possible number of drug targets to choose from and several orders of magnitude upsurge in the number of drugs that can be screened has led to significant increases in the cost of drug development.

> "...major pharmaceutical companies are fostering a new era of consolidation..."

Another factor to consider in understanding why the cost of new drug development is escalating is that the 'low hanging fruit' have likely been picked [13]. In this analogy, the current approved drugs were easy to identify. But new efficacious drugs that may be functioning in the same disease pathway may reside higher in the tree. These are more difficult to get to and require investments of time, money and some luck. As there is significant risk of failure, major pharmaceutical companies hedge their success by operating multiple drug development programs at any one time, increasing the chances of getting an FDA approval but at an increase in cost.

Emergence of new business models

Fewer annual drug approvals and significant increases in the time and cost of drug development have painted concerns about the future of this industry as the historical business model is unlikely to be sustained. We have already seen changes in the industry such as the reluctance of big pharmaceutical companies to fund early internal drug discovery initiatives in an attempt to decrease front-end risk. They now prefer to outsource exploratory activities to third parties and to either license a therapeutic or acquire a small drug company at later stages when the compound is in late preclinical or early clinical development. These actions by the major pharmaceutical companies are fostering a new era of consolidation in the industry that extends beyond the purchasing of small companies to mergers and acquisitions of large peers. As this continues, we are destined to eventually see a small number of large drug developers selling therapeutic solutions to the market, who focus on clinical development and marketing, and many smaller companies whose main goal is to become acquired, as the prospects of actually developing and marketing a drug are slim.

> "...diagnostic and therapeutic industries may eventually become one and the same."

But industry consolidation driven by the factors outlined above is only the beginning of the changes to come. At some point in the distant future, the few remaining large pharmaceutical companies may have so many efficacious drugs on the market to treat all medical conditions that they may no longer need to pursue the development of new medicines. This may lead to successive stages of additional disruptions in the market. The first could be the disappearance of early drug discovery companies, which will no longer be formed by investors since the large remaining pharmaceutical companies would no longer be acquiring them. Private equity groups and other larger investor networks may temporarily step in lieu of large pharmaceutical companies and acquire many of the remaining small companies, restructuring them as a single larger entity to compete with the larger consolidated companies for market share. But even this scenario ultimately ends in consolidation, resulting in a small number of big pharmaceutical companies selling all the branded and patent-protected drugs.

Another significant market disruption may occur when all the existing drug patents held by the major pharmaceutical companies eventually expire. At this point, the value of each branded proprietary medication marketed by these companies would drop by an order of magnitude, as is the case today when generic

equivalents are allowed to enter the market following patent expiration and compete head to head. When all drug patents expire and there is a plethora of available medicines, the major pharmaceutical companies of the future would in essence be converted to the equivalents of today's manufacturers of generic drugs and biosimilars.

Can the major drug developers of today position themselves to stay in business in the future when generic drugs will be the only available option? One way is to launch or acquire their own generic drug manufacturing and marketing divisions; we are already seeing this trend in the industry. A world where lower cost generic small molecule drugs and biosimilars are used in virtually all of pharmaceutical intervention is great news for patients, physicians and payers, but the traditional profit margins of drug developers will greatly diminish. How can the pharmaceutical industry recoup some of this lost revenue? One way is to develop a new hybrid business model where one division produces and markets drugs while the other division provides valuable information to physicians on which specific drug or drug combination is best suited for a particular patient. This fused drug and companion diagnostic model is the hallmark of personalized medicine. Though we are seeing an increasing number of available drug and companion diagnostic combinations, the future may dictate that this will become the standard of care. We are already seeing the emergence of *ex vivo* personalized therapeutic models, particular in cancer, where patient biopsies are use to model their specific disease and predict the best drug or drug cocktail to use [14]. These types of approaches could represent early predecessors of the future where the diagnostic and therapeutic industries may eventually become one and the same.

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The author is a co-inventor on two provisional patent applications dealing with the design of microfluidic devices that can culture cells in three dimensions. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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