Accelerating the Drug Development Process

Drug development time is money for some, life-and-death for others

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INTRODUCTION

For years, critics have said the FDA's medical device approval process takes too long, particularly when compared with the one in Europe. In the U.S., companies argue they lose valuable time and money as they seek to improve the lives of patients they serve.

This paper argues that the development process for experimental drugs could be accelerated without significantly endangering the Public’s health thus saving lives and cutting cost.

THE COMPETING EUROPEAN AND AMERICAN REGULATORY INSTANCES

A recent article entitled “FDA trashes European regulatory process”, published in Fierce Medical Devices, describes the fierce debate between the European and American regulatory instances on the drug approval process.

While industry lobbyists push for a more streamlined process to quicken the FDA approval time for certain high-risk devices and often seek approval in the EU first, the FDA claims that there is a safety benefit from the slower, more rigorous regulatory process in the U.S. It concludes that even if the EU system is quicker, it is far from better, as illustrated in the report the FDA issued: “Unsafe and ineffective devices approved in the E.U. that were not approved in the U.S.”

Richard Pazdur, the head of FDA’s Office of Oncology Drug Products, stated that “the EMEA is not the FDA of Europe, and the FDA is not the EMEA of the United States.” Many differences lies between the two regulatory bodies:

- The FDA is a centralized agency that oversees the drug development process in a single country, whereas the EMEA manages the approval process for many European nations.
- Clinical investigations of new drugs in the United States often compare the drug with a placebo. In the EU, the benefit-risk assessment has become increasingly based on comparisons between the new and existing drugs.
- A main difference between US and EU regulations lies in their perception of risk and how to manage it.
- Moreover, licensed officers carry out the FDA's risk assessment, while the EMEA holds companies responsible for it.

Nevertheless, there are growing similarities between the U.S. and the European regulatory systems. Both have the common objective of ensuring safety and efficiency of new products. They go over pending regulatory actions and proposed regulatory initiatives together. There is also a growing free exchange of documents.

In the mid-term, the differences between the two entities tend to be eliminated, and in the long-term a unique accelerated approval process could emerge. In November 2007, the EMEA and the FDA already adopted a common application form for drugs for rare diseases in both jurisdictions.
The International Conference on Harmonization (ICH) guidelines already lead to the creation of common technical document and pharmacovigilance. Open discussions are in place between both entities and there is hope that this will lead to an accelerated approval time both in Europe and the US.

DRUGS ACCESS TAKES TOO LONG

The Center for Drug Evaluation and Research (CDER), within the US Federal Food and Drug Administration (FDA), is responsible for evaluating and approving the introduction of new drugs to the market. However, their primary focus is to ensure drug efficacy and safety, with a secondary goal to accelerate new drug introduction. Although their mission is to keep dangerous and ineffective drugs off the market, about ten years ago at the height of the AIDS crisis, the CDER started reforming the drug review process to accelerate the availability of new drugs.

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA) to fast-track the review process of New Drug Applications (NDA). PDUFA requires the pharmaceutical companies to contribute directly to the cost of the review process by paying a fee to the FDA in exchange for agreed-upon accelerated review milestones and a faster review process based on surrogate end points to predict (vs. prove) a drug safety and efficacy. Under PDUFA, the CDER expects to review and act upon ninety percent of NDAs for standard drugs within ten months after the applications are received. According to the FDA, “PDUFA has allowed the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process.”¹

However, much is still to be done to reduce the length to introduce a new drug to market. Animal (pre-clinical) studies take three to four years to collect enough information to submit an Investigational New Drug Application (IND), followed by five to six years of clinical studies, and about one year for the FDA review of the NDA. The entire process takes, on average, seven to ten years before a new drug can be introduced to the market.
TIME IS MONEY FOR SOME, LIFE-AND-DEATH FOR OTHERS

Investigating and testing the safety and efficacy of new drugs is a costly endeavor for the pharmaceutical industry. According to Forbes, the average cost of bringing a new drug to market has reached $1.3 billion in 2011. Once a drug is approved by the FDA, pharmaceutical companies have just a few years to ‘monetize’ their R&D investment, until the expiration of the patent. The imminent arrival of the dreaded "patent cliff" has been haunting the pharmaceutical industry for. With patents on many blockbuster drugs about to expire, an estimated $250 billion in sales are at risk between now and 2015, according to data from EvaluatePharma.

Hence a major factor in the return on investment (ROI) of drugs is the relatively short window of time a company has the monopoly of the market. According to a new study from consulting firm Oliver Wyman published in Life Science Leader magazine, the value generated by $1 invested in pharma R&D has fallen by more than 70%. To illustrate, in 2008 Genentech launched Herceptin (trastuzumab) HER2+, a breast cancer treatment, and earned $1.287 billion in revenues the same year. In theory, just a one month delay in getting the drug approved could have cost the company more than $106 million in lost revenues.

Needless to say, in addition to saving lives, an accelerated development process would have a beneficial effect on the cost of the drug. Thus a streamlined process for drug development can have a positive impact on the cost of developing new drugs or approving existing drugs to treat different diseases. Development process improvements leading to faster drug access must however be balanced with potential risks they may pose to public safety.
SAFETY CONCERNS

The concept of accelerating new drug access is appealing, but the question is: What phase of the development process should be accelerated and how, all while preserving public safety?

Let’s review the drug development process for potential inefficiencies. Today, robotics and High Throughput Screening (HTS) are used to speed up hits in Primary Assays. Just like robotics and HTS revolutionized the industry about fifteen years, computer simulation offers the potential to accelerate the pace of pharmaceutical research. This new technology is called ‘in silico’ as an analogy to biological experiments performed in living organisms (‘in vivo’) and in test tubes or Petri dishes (‘in vitro’). No matter how promising the ‘in silico’ technology is, according to the FDA “while computers give chemists clues to which compounds to make, they don’t give any final answer. Compounds made based on a computer simulation still have to be put into a biological system to see whether or not they work.”

Once a hit is identified and prioritized, the molecule of the New Medical Entity (NME) with the greatest promise is selected and refined during animal studies, focusing on its Therapeutic Window and pharmacokinetic properties. The success rate of animal studies is very low, however, with only one in one thousand compounds that enter animal studies found suitable for clinical trials.

Assuming a drug is shown to be safe enough to begin clinical trials, Phase I proves whether or not a drug presents an unacceptable level of toxicity. In this phase, the health of twenty to eighty healthy male subjects receiving the experimental drug is compared to a control group, with similar subjects, receiving treatment with an inactive substance (placebo). Once a drug is deemed to be safe “enough”, Phase II tests the drug’s effectiveness and is administered to a few hundred subjects afflicted with the target disease. Safety continues to be studied during this phase. Because the clinical phases are critical to ensure a drug’s efficacy and safety in humans, they follow a rigorous and lengthy scientific process that offers little prospect for improvement or acceleration.

This leaves Phase III and the FDA review process as candidates for shortening the drug development process.

PHASE III & NDA REVIEW PROCESS IMPROVEMENTS

Phase III are complex, multicenter studies potentially involving several thousand subjects. Their goal is to authoritatively assess a drug’s effectiveness and side effects against the currently available therapies, if such exist. To scientifically prove result repeatability, the FDA often requires two successful Phase III trials. Because of their large size, geographical distribution and the complexity of studies undertaken, they have a good potential for process improvement and acceleration.

Computer systems have been used in the past decade to capture and analyze study information. However, these systems are hard to use and not integrated with other clinical systems such as Safety Systems and Clinical Trial Management Systems (CTMS).

Pharmaceutical companies should aim to raise productivity by:
- Using integrated systems to capture and analyze information submitted to the FDA.
- Speeding up subjects recruitments. The length of clinical trial for drugs treating life-threatening diseases could be reduced to one year by improving subject enrollment.
- Running multiple phases III in parallels
- Embedding FDA investigators in studies

CONCLUSION

Although some fear that safety could be jeopardized, experimental drugs still take too long to develop, delaying their access and increasing their cost. Industry professionals need to find innovative solutions to accelerate the drug development process while ensuring public safety.
REFERENCES


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