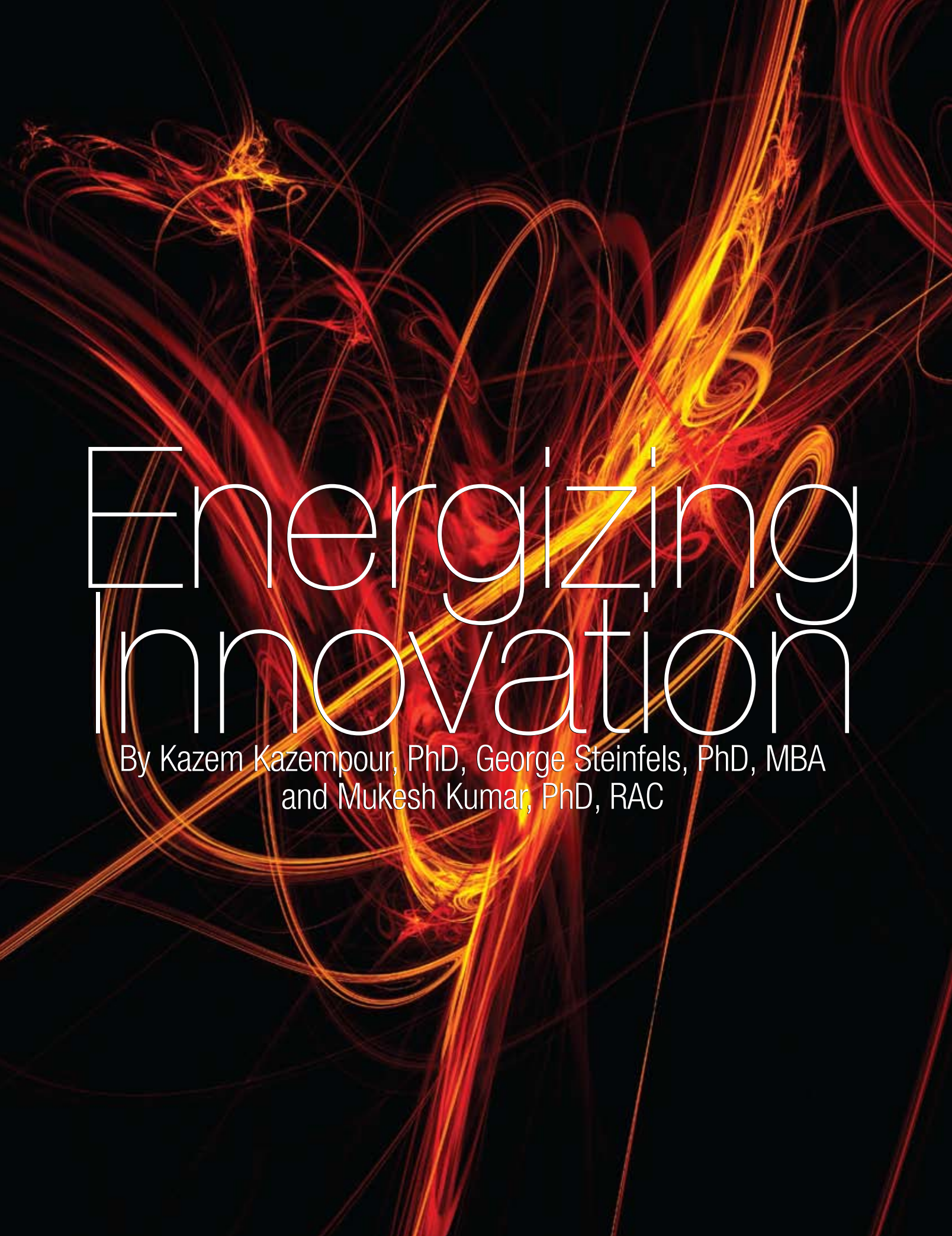

Energizing Innovation

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Former UK Prime Minister Harold Macmillan once said, "to be alive at all involves some risk." This statement is especially apt for a biomedical product development enterprise. Successful product development and commercialization require integration of multiple disciplines, each with its own complexities and risks. Drug developers need to worry about issues such as intellectual property, preclinical and clinical testing, business development and financial sustainability. Due to the logistics of the process, which could take up to 10 years and cost hundreds of millions of dollars, it is not surprising that most small and medium-size enterprises (SMEs) in the pharmaceutical industry do not end up with profits. And, since SMEs constitute more than 90% of this industry, that translates into a huge waste of money and resources. More importantly, SMEs are a major source of new products, either directly or indirectly, by licensing or selling their products to large enterprises.

Although the term "drug" is used throughout this article, the ideas described apply equally to drugs, biotechnology products and medical devices.

Drug product development is different from any other high-tech venture. First, medical products are highly regulated. Substantial safety and efficacy must be demonstrated in a battery of expensive and time-consuming nonclinical and clinical tests. The number of marketing applications for novel drugs submitted to the US Food and Drug Administration (FDA) has declined in recent years. FDA has faced pressure from Congress to tighten its oversight of drug safety since the withdrawal of Vioxx from the market in 2004. The agency's ability to analyze data for potential safety problems has improved, and it is especially vigilant when evaluating drugs for chronic conditions—drugs that people will be taking daily for many years.[1] Incidentally, chronic indications are also very attractive to drug developers due to their potentially large markets and high returns on investment.

Furthermore, pharmaceutical and biotechnology products offer several financial exit strategies before the product is commercially viable. The value of the underlying intellectual property accumulates over time as it reaches the stage of development at which it can be monetized via licensure or sale to other companies. In fact, the smaller the company, the more likely it is to exit product development early.

Among the primary concerns of drug development enterprises are developing a strategy that reduces risk of failing to gain regulatory approval and securing financial investment in their ventures. Despite the obvious challenges, with a well-planned strategy, drug development can be an extremely lucrative business. Currently, several large pharmaceutical companies are experiencing tough times; several blockbuster drugs are scheduled to go off-patent and product pipelines are drying up, making it difficult to replace major revenue earners. SMEs with small teams and focused development cycles offer the promise of attractive drugs. Large corporations are increasingly relying upon smaller developers for new products. Some large companies are even changing their internal processes to mimic those of smaller companies. GlaxoSmithKline recently announced its plans to break R&D into smaller teams that will compete for funding in a manner similar to start-ups.[2] Some large, US-based companies are also increasingly going outside the US and Western Europe for new discoveries and potential products.[3]

Role of Strategy

Strategic planning for product development can make or break a company. Because drug development is a multi-step process, with each step dependent upon the success of the previous one, a small error at any stage can translate into huge losses. Strategic plans need to include not only the obvious issues such as the required tests, and manufacturing and logistical issues, but also such business development issues as potential product profile, market intelligence and competitive position.[4]

Technology Status Analysis

A thorough, periodic analysis of all available information is critical to evaluate development status. This includes a review of all the preclinical experiments, characterization of components, status of competing products, etc. Discerning a drug's mechanism of action plays a critical role in its regulatory lifecycle. Drugs with unknown or unclear mechanisms of action, unknown targets within the human body or unreliable animal models are categorized as high-risk products both by the European regulators[5] (EMEA) and FDA, leading to an automatic requirement for more complex and expensive tests. Hence, all currently available information—both internal and in the public domain—should be reviewed to keep scientific background information current. This analysis should be done periodically to maintain the ability to adapt to changes in the information. FDA prides itself on being a "science-based regulatory agency." The ability to logically explain the basis for safety and efficacy of a product goes a long

way toward building the agency's confidence in a product under review, and increasing the chance of a favorable response.

Target Product Identification

Biological technologies usually have several applications, but at the beginning of development, a company can focus on only one or a few applications. It is important to conduct feasibility analyses where pros and cons of potential target products are evaluated side by side based upon available resources (financial and intellectual), potential to acquire new resources, timeline for development, and the expected timing and size of return on investment. For example, an antibody-/antigen-based product might have applications in therapeutics, diagnosis and research. While a therapeutic application could potentially lead to much larger financial benefits, it would take a long time and require more investment than a research tool or diagnostic kit. Similarly, a drug might show promise in a high-risk, chronic indication, e.g., a cardiovascular application, as well as an orphan drug indication. Compared to the chronic indication, the return on investment might be smaller for the orphan indication; however, the latter offers an easier path to approval and quicker return. Moreover, getting one indication approved will create a market history, making the subsequent addition of more indications easier. It also offers a stronger attraction for investors for future development due to increased credibility.

When picking target products and indications, all available incentives should be considered. An orphan indication might qualify for additional incentives such as priority FDA review and the waiver of FDA fees (application, establishment and product). The *Food and Drug Administration Amendments Act*, signed into law in September 2007, created a unique incentive to encourage development of therapies for "tropical diseases," including infectious diseases that disproportionately affect poor and marginalized populations, for which there is no significant market in developed nations. Developers of such therapies will receive a priority review voucher, entitling the holder to a six-month FDA review of another application that would otherwise be reviewed under FDA's standard 10-month review clock. The priority review voucher may be used or sold by the company receiving it for an application "submitted after the date of the approval of the tropical disease product application." These vouchers offer an excellent "bonus" source of revenue for companies—including those located in tropical regions—to develop much-needed therapies and then use the vouchers to reduce time-to-market of their own products or cash them in by selling them to another enterprise.

For first products, a company needs to pick safer targets in terms of development requirements and the risk of regulatory agency rejection.

Resource Management

Most SMEs have limited resources. Even in large companies, resources are becoming increasingly constrained. It is important that the available technical and financial resources be allocated appropriately. For example, access to an animal facility or a well-equipped wet-lab should not lead to more experiments than are necessary. More often than not, differences between regulations and guidance documents are not clear to drug developers. While regulations are binding requirements, guidance documents represent FDA's current thinking on the topic and are not binding on the agency or a company. An alternative approach to that suggested in guidance can be used if it satisfies the requirements of the applicable statutes and regulations. FDA strongly recommends that a company create a product development plan based upon what is feasible for that product, and discuss it with the agency before implementation. So long as there is a scientific explanation for the strategy supported by appropriate internal or publicly available documentation, FDA is willing to consider alternative approaches. One size does not fit all; FDA considers all new products to be unique, requiring individual consideration. This allows a company to manage its resources to maximize its resources. Another frequent error committed by SMEs is building expertise in areas that can be more efficiently and financially beneficially outsourced. For example, running a clinical trial requires a lot of resources that could cost more than outsourcing the work to a contract research organization (CRO).

Business Development

Like all businesses, drug development involves not only a smart idea but also the ability to attract potential customers. These could be investors (public and private), potential licensees and end users, i.e., consumers. A SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis forms the basis of the marketing strategy for a drug development enterprise. This is basically a summary prepared in a way that can be easily interpreted by the financial and business advisors who play a critical role in investment organizations. While strengths and weaknesses are easy to list based upon available information, opportunities and threats to the product can, at best, only be predicted because they

arise from unforeseen competitions or changes in scientific scenarios. Efforts should be made to create a fair assessment, balancing the positive and the negative information. These business development activities are critical not only to keep current investors updated, but also to create viable exit strategies should the company decide to monetize the equity built into the product.

Monetizing the Technology

The fact that bringing a new drug to market takes about 10 years and costs approximately one billion dollars has been well publicized. What is seldom noted, however, is that this estimate is a composite figure that includes the costs of failed drug projects. The drug development process can be categorized into distinct milestones, each of which can be based upon well-calculated risk and yield a handsome return on investment.

Licensing the Patent

The first milestone is securing intellectual property (IP) rights. Issuance of a patent demonstrates the technology's uniqueness, non-obviousness and application, offering an opportunity to license the same to another party. However, patents do not necessarily imply or demonstrate commercial viability and also are usually secured at an early stage of development; hence lower returns are expected.

Discovery Through Phase 1 Clinical

Following demonstration of the scientific concept in a research lab, a product goes through a series of validation steps in the preclinical setting, along with component characterization and manufacturing process optimization, before first-in-man clinical studies. A good regulatory strategy calls for discussions with FDA before commencing the first clinical study under an Investigational New Drug (IND) application. The Pre-IND meetings are critical; they help develop an understanding of FDA's concerns regarding the product and deficiencies in the information up to that stage. Preliminary discussions with FDA regarding possible ways to satisfy the agency's concerns also can be held during the Pre-IND meeting and subsequent follow-up discussions, if required. These discussions provide firsthand information about what FDA perceives as weaknesses and strengths in the research conducted to date and planned for the future. This information can be used to plan the development path and raise capital for the clinical trial. Successful completion of the first clinical trial aids investor confidence in the product. At this stage, a company can either raise capital for future testing or exit by licensing or selling the technology to another enterprise.

This milestone is the most attractive time to sell the technology for SMEs that have not gone through the drug approval process. It may be financially attractive to some foreign-based firms—particularly those from Asia (primarily China and India)—as the investment required for IP, preclinical testing, the pre-IND meeting and first IND submission are not very high compared to what is required for the later stage, larger trials. This also provides a system for developing know-how in key processes that can be used later for full-scale innovative product development without investing in long-term, expensive ventures.

Phase 2 Through Regulatory Approval

Subsequent product development steps are more expensive and take longer to show results. At the same time, these steps add more monetary value to the IP with each success. Depending upon the product, several clinical trials of increasing size and complexity may be required to demonstrate safety and effectiveness. It is critical to keep FDA reviewers involved throughout the process to get timely feedback. US regulations allow for several meetings with FDA to facilitate timely discussions with the agency, thereby avoiding costly mistakes. Drug developers are well advised to utilize as many opportunities as possible to discuss the current status of the results with FDA. Each confirmation from the agency that results are on the right track adds enormous confidence in the developer and may help raise capital. Since FDA/sponsor discussions are confidential, the onus is on drug developers to present the information in a fair and balanced manner.

Branding, Marketing and Sales Partnerships

The commercial product development process that includes product naming and branding, marketing and advertising campaigns, and sales support generally are beyond the capabilities of a small drug development enterprise. Large pharmaceutical companies have extensive experience in these areas and a partnership could enhance the product's market success. One of the most important aspects of these partnerships is the timing of execution. A product near approval with a good regulatory track record offers the best returns. Ideally, brand build-up and marketing should start as early in the life of a product as is reasonable. Starting too early could impact the company's credibility for future products if there is product failure, while starting late might result in taking more time to reach the target market size.

Conclusion

Innovation drives the US biomedical industry, with all its risks and potential benefits. Drug development is also a necessity, linked directly to the quality of life. The enormous strides in developing therapies for various ailments in the last few decades have led to longer life expectancies and healthier lives throughout the world. Although drug development is very complex and expensive and takes a very long time, this industry does offer some key advantages. First, it is science-based, so careful planning and good teams can substantially increase the chances of success. Second, successful products have secure returns on investment, no matter what the pressures on the economic markets. With medical insurance and government-supported medical plans increasing worldwide, more and more patients are getting access to newer treatments. Third, products can be developed anywhere, but they are sold everywhere. Diseases are no longer limited by geographic or economic boundaries, and the development processes are increasingly being harmonized. An effective treatment can be developed in a region more comfortable for the innovator company and sold worldwide, increasing profitability. Lastly, legislators and regulators throughout the world have started to appreciate the need for developing therapies and nurturing this industry. Since the bulk of this industry is comprised of SMEs, several incentives now target small businesses. Therefore, it is not surprising that so many entrepreneurs take on the task of developing new products.

However, certain practices need to become a part of the training for SMEs. The major issues are described in this article. It is the dream of any drug developer to create a blockbuster drug, making more than a billion dollars in revenues per year; but only a small fraction of all drugs fall into this category. Drugs generating $25–$800 million in revenues per year comprise 95% of the market. Also, SMEs need to develop business plans that take advantage of the many incentives and resources available specifically to them. This article has discussed orphan drugs, pediatric indications and tropical diseases as examples. Depending upon the geographic region, there could be many more.

With the extensive and rapid flow of information, harmonization of processes all over the world, growth in training resources and globalization of the drug industry—both development and market—there are far more opportunities available to introduce new therapies, to help patients, and to be efficient and successful in this industry. Good planning, smart strategy and business acumen now are the keys to success.

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