



Review Article

RISKS AND OPPURTUNITIES IN DEVELOPMENT OF NEW DRUG AND QUESTION BASED REVIEW OF REGULATORY COMPLIANCE

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ABSTRACT

Pharmaceutical development is a costly, time exhausting and uncertain process that takes years to accomplish. In many instances patent protection expires before a new drug is approved for marketing. Most pharmaceutical firms in the United States and European Union (EU) depend on the exclusivity rights allotted under the U.S. Federal Food, Drug and Cosmetic Act (FDCA), and the corresponding EU authorities to recover considerable investment in the drug research and marketing approval process. Hence, pharmaceutical companies must understand and use the different forms of non patent exclusivity in both the U.S. and EU in order to win in the global marketplace. Pharmaceutical firms generally obtain patents on products long before their product candidates are ready to enter market. Since it can take up to 12 years for a firm to obtain market approval, it leaves little patent protection left on the product at the time of commercializing. To provide pharmaceutical companies with a chance to recuperate their investment in drug research and development and to induce continuing innovation, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have enforced numerous provisions to increase the period during which companies can market their drugs free of generic market competition.

Keywords: FDA, EMA, EU.

INTRODUCTION

Regulatory Affairs (RA), also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods). Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals. The success of regulatory strategy is less dependent on the regulations than on how they are interpreted, applied, and communicated within companies and to outside constituents [1, 2].

The Aim Of The Present Study Is The Risks And Opportunities Involved In The Development Of A New Drug. And To Discuss The Problems Arise During The Development and After Development [3, 5].

RISKS AND OPPURTUNITIES

As the pharmaceutical industry seeks to transform drug development, there is a growing consensus that traditional cost-cutting and productivity-enhancement methods have largely run their course. There are, however, an array of new business tools and platforms that can help companies leverage their assets more effectively in managing the three principal sources of risk that currently interact to push drug development costs higher.

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These are:

Portfolio risk: The uncertainty related to accurately assessing a candidate drug's clinical utility and value [5].

Operational risk: The logistical and management challenges involved in delivering robust clinical information about a candidate drug to the right sources, in a timely manner

Resource risk: Exposures arising from imbalances between the fixed-cost base that supports operations and the requirement to deliver clinical results that are useful and relevant to regulatory decision-makers.

Industry has little choice but to adjust to this segmentation of risk. New development models can help redefine the boundaries within the traditional pharmaceutical business model, and answer the key question of what a pharma company must own to gain competitive advantage, and what portfolio, operational, and resource risks can be hedged through risk-based partnerships.

Through changes that involve more structured access to resources, better deployment of capital as well as development of new monitoring and evaluation systems, companies will find they can shed the bureaucratic, large-scale, fully integrated business model and move to a nimbler, more modular way of leveraging resources to increase the value of their clinical programs and assets

Any risk-based transaction involves evaluating both the upside and the downside variance associated with expected outcomes. Exhibit I illustrates the major challenges and potential solutions for each of the three types of development risk—portfolio, operational, and resource [7, 8].

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1. Portfolio risk is the threat to moving assets through proof-of-concept and large Phase III studies, and on to the market in time to address imminent "patent cliffs." Current constraints—including P&L pressure, cuts in development funding, and increasing regulatory and reimbursement expectations coming from the payer community—are yielding more late-stage failures and forcing companies to

respond by concentrating risk in a limited number of development programs.

Increasingly, companies are mitigating this risk by building networks of allies with access to both capital and risk-based services. This approach stretches development budgets and releases the latent value in the portfolio without increasing exposure to failure. It provides more "shots on goal" through better focus and shared deployment of resources.

Attempts to mitigate **operational risk** have traditionally centered around outsourcing isolated elements of the clinical development value chain, such as data management and site startup. This parceled approach has often led to higher costs, a dilution of accountability, and massive inefficiencies throughout the process. Over time, this has institutionalized a risk-reward imbalance between partners that can undermine trust and create a disincentive to "manage out" an unacceptably high variance in operational outcomes.

In spite of the industry's greater focus on planning and budgeting for clinical trials, median time frames and sharp variations in clinical development costs remain unnecessarily high. When pharma was a high-margin business, these variations—a latent exemplar of organizational inefficiency—went largely unaddressed. But they are no longer possible to ignore, as the cost and operational unpredictability of trials are incompatible with today's less profitable business model.

Several recent case studies show that limited control over operational risk significantly impacts clinical trial time lines, costs, and management overhead. Addressing this element of risk is therefore a key element in transforming the clinical development model to reduce time lines and cost variability—and to recapture time-based competitive advantage.

2. Resource risk arises from the misalignment between fixed, supply-side resources—including large, fully integrated business functions—and highly variable demand-side market fluctuations. Industry leaders are realizing the importance of using fewer fixed assets, and transforming fixed costs into variable costs. This involves moving specific parts of the business to a more differentiated base where clear lines of responsibility serves as a way to manage market volatility.

One emerging trend is for pharma leaders to build networks of allied organizations to absorb and integrate potential non-core functions, such as data management and sales forces. By transforming fixed costs in this manner, companies will find that they can limit exposure to redundant cost risks and respond rapidly in an environment in which change is a constant factor.

Although not insubstantial, direct cost savings from addressing operational risk are small when set against indirect reductions in overhead, recaptured opportunity cost and time based competitive advantage in reaching the market faster. Increased speed to market can yield overall savings of more than \$1 billion, for a mid-size development portfolio—not a trivial sum^[10, 11].

3. Root of the Problem: One-Off Outsourcing:

To understand the root causes of operational risk, Quintiles Consulting conducted interviews with cross-functional development teams at several companies. The survey found that respondents were outsourcing clinical development tasks in piecemeal fashion. The companies awarded tactical responsibilities in the clinical development value chain (such as data management or monitoring) to a range of vendors through a procurement process designed to minimize the cost of each step. After that, sponsors tended to recognize and pay for value based on completed "inputs" to the development process, such as the number of monitor visits or number of sites initiated.

4. The Solution: Better Focus on Outcomes:

Industry is exploring new approaches that reengineer the risk-reward imbalance through better alignment of incentives, that encourage a focus on outcomes-based metrics. These are more effective vehicles for delivery due to three factors: First, they increase the accountability of the service provider for solving operational problems, rather than simply taking direction from the sponsor; second, they encourage a deeper exploration of design and operational feasibility between the service provider and the sponsor prior to starting the trial; and third, they rebalance the risk inequity by imposing real penalties for late delivery of agreed outcomes.

5. Partnerships to Control Risk Exposures:

As part of the "risk trade" transaction, service providers must agree on a more equitable level of control over the design and execution of a trial, sufficient to keep the risk to an acceptable level for both parties. This usually involves a greater degree of integration in planning and design activities such as feasibility and site selection. As yet, no Big Pharma company has solved the problem of owning the entire risk in the value chain by working in alliance with service providers in that chain. Recently, however, several companies have launched transformation initiatives, some involving relatively radical departures like outcomes guarantees. While most of these initiatives are still in the pilot stage or apply only to a small part of the business, their rationale is already clear:

» To transform the rules of the game for drug development in order to unlock the latent value in the portfolio within fixed or shrinking budgets and development organizations

» To determine the optimal unit of outsourced work, who is responsible and accountable for delivering it, and what degree of autonomy/oversight is required to balance efficiency, control and risk. If the ultimate deliverable is an agreed outcome at a specific time, the new operating principles shift variable price inputs to the trial to fixed price outcomes, thereby redefining the answers to these questions.

» To mitigate the inherent risks in outcomes-based models. In order to do this, the traditional role of the sponsor and service provider will need to be explored. Changes will likely cover variables such as site selection, start-up/close-out timeliness, monitoring efficiency, and execution flexibility. Contracts will likely be based on the time value of outcomes.

Insights from the successes and failures of these pilot projects will lead to refinement of new operating models and usher in a new paradigm for drug development. In an era of constant change, those organizations that can nimbly manage the three dimensions of development risk (portfolio, operational and resource) will emerge as winners. The key question facing development leadership teams is how to rebalance risk to meet this challenge and ensure a project's viability and competitiveness.

It follows the steps as follows:

- a. Inclusion criteria.
- b. Statistical analysis of success rates.
- c. Time to research termination. Success rate trends.
- d. Therapeutic classes.
- e. Clinical phase attrition rates.
- f. Phases I and II but declined for phase III.
- g. Reasons for research abandonment.

i). Safety (eg, "human toxicity" or "animal toxicity"), efficacy (eg, "activity too weak" or "lack of efficacy"), and economics (eg, "commercial market too limited" or "insufficient return on investment").

CDER Small Business and Industry Assistance (CDER SBIA):

Drug sponsors which qualify as small businesses can take advantage of special offices and programs designed to help meet their unique needs. The CDER Small Business and Industry Assistance (CDER SBIA) Webpage provides links to FDA laws, regulations and guidances that affect small business. Information is also provided on financial assistance and incentives that are available for drug development^[13, 14].

Laws, Regulations, Policies and Procedures:

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. With numerous amendments it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations (CFR):

Code Of Federal Regulations (CFR). The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug sponsors that are required under Federal law. The following regulations apply to the ANDA process:

- 21CFR Part 314 Applications for FDA Approval to Market a New Drug or and Antibiotic Drug.
- 21CFR Part 320 Bioavailability and Bioequivalence Requirements For more information on retention samples, please see Bioequivalence Study Retention Samples.
- Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Final Rule.
- 21CFR Part 310 New Drugs.

MaPPs:

CDER's Manual of Policies and Procedures (MaPPs) provide official instructions for internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures. MaPP documents to help prepare ANDAs are listed together on CDER's Manual of Policies and Procedures webpage.

- Chapter 5200 - Generic Drugs

The Cost of New Drug Discovery and Development:**i) Protection of intellectual property.****ii) Therapeutic competition.****iii) Generic competition.****iv) Public policy issues.****v) Summary of cost studies:**

This discussion documents that the rapidly rising cost of pharmaceutical R&D is due mainly to the increased cost of animal testing and conducting clinical trials. The best estimate of the costs of drug R&D today is likely to be that from the most recently available well-designed study; that is, US \$802 million. We also should note that improvements in the drug development process would yield significant improvements in this picture. DiMasi has calculated that a 25% reduction in clinical phase lengths would reduce total capitalized drug development costs by 16% (approximately US \$129 million). He also reports that improving success rates from the current 21.5% to 33.3% would yield a reduction of US \$221 million in capitalized cost per NCE.

vi) The societal value of pharmaceutical R&D investment:

A theoretical model demonstrating the connections between pharmaceutical R&D and societal value is shown in Figure 4. Any adverse disturbance to the scientific research, regulation or use of pharmaceuticals will have detrimental effects on social value. Likewise, any disruption in the flow of funding from sales to R&D will lead to diminished social returns. Figure 4 also shows that opportunities to improve societal benefits can come from multiple pathways, including a more efficient development process, a favorable regulatory environment, and improved use of drugs.

Regulatory Compliance:

Numerous studies have found that the drug development process is highly expensive and that these costs have trended significantly upward for decades. Many factors affect the cost of drug development, but two of the key basic elements are time and risk. Development times increased substantially from the 1960s through the 1980s but overall remained relatively stable during the 1990s. Development times did not directly contribute much to the rapid increase in pharmaceutical R&D costs in the past two decades. However, if clinical trials become larger and more complex, and the costs of inputs to the development process increase faster than inflation, the "time costs" associated with the investment of

resources in new drug development will increase in absolute terms, even if development times remain the same. Indeed, there is evidence that the clinical trial process has become more extensive and complex in the past few decades. Situation is similar for drug development risks. By development risk, we mean the likelihood that development of a drug will be terminated owing to efficacy, safety, or commercial concerns. High drug failure rates contribute substantially to R&D costs, whether or not these costs are otherwise increasing. The rate at which pharmaceutical firms successfully develop investigational compounds for marketing approval by regulatory agencies is an important indicator of the effectiveness of the drug development process. Processes and technological innovations that can improve the predictability of outcomes for new compounds can therefore significantly increase the productivity of new drug innovation.

Historical literature focusing specifically on the quantification of drug development risks is fairly robust. Fore mentioned research on drug development costs includes estimates of drug development risks. Early research on development risks suggested that clinical approval rates for self originated drugs in the 1960s were in the neighborhood of one in eight. Subsequent studies indicated that development risks fell in the 1970s, with approval rates averaging approximately one in five; the risk levels pertaining to the 1970s remained fairly stable to the mid-1990s.

Clinical approval success rates and clinical phase transition analyses for the investigational compounds that entered clinical testing between the mid-1990s and the early 2000s from the 50 largest pharmaceutical firms (as determined by sales). We analyze approval success rates and phase transition rate trends within this period for new compounds as a whole and by therapeutic class. The data are also stratified by product type (large molecule vs. small molecule) the results relating to phase transition rates (or their converse, phase attrition rates) allow us to examine whether pharmaceutical firms are "failing" drugs earlier in the development process and thereby (other factors assumed to be equal) potentially reducing overall development costs.

We examined the investigational drug pipelines of the 50 largest pharmaceutical firms as determined on the basis of sales in 2006. Several data sources were consulted, but the core source for the compound list was the IMS R&D Focus investigational drug pipeline database. We supplemented that database with information from two other commercial pipeline databases (iDdb3 and Pharma projects), as well as from CSDD investigational drug, approved drug, and investigational biopharmaceutical databases that were derived, in part, from confidential company surveys, published regulatory agency documents, online company pipeline lists, and Internet searches.

i) Inclusion criteria**ii) calculation of success-rate estimates****iii) success-rate trends****iv) Success rates by therapeutic class****v) Success rates by product type****vi) Drug Development Challenges and recovery**

- Drug development is a lengthy, complex, and costly process, entrenched with a high degree of uncertainty that a drug will actually succeed.
- The unknown pathophysiology for many nervous system disorders makes target identification challenging.
- Animal models often cannot recapitulate an entire disorder or disease.
- Challenges related to heterogeneity of the patient population might be alleviated with increased clinical phenotyping and endotyping.
- Greater emphasis on human data might lead to improved target identification and validation.
- There is a lack of validated diagnostic and therapeutic biomarkers to objectively detect and measure biological states.
- Unfamiliarity with current regulatory processes for investigational new drug (IND) applications can be resolved through pre-IND meetings.

Drug Discovery and Development Pathway:

The process of drug discovery and development beginning with target identification and validation. A target can be a protein, DNA, or RNA that causes or contributes to disease. Its validation consists of demonstrating that modulating the target has a

therapeutic effect. Assay development follows target validation and is an objective method for screening putative compounds to determine interaction and/or modification of the target. After an assay is established, the next step is to find compounds that actively engage

the target. From a pool of potential compounds, a few select leads that demonstrate a relationship between chemical structure and target-based activity in a biochemical or cell-based assay are generated.

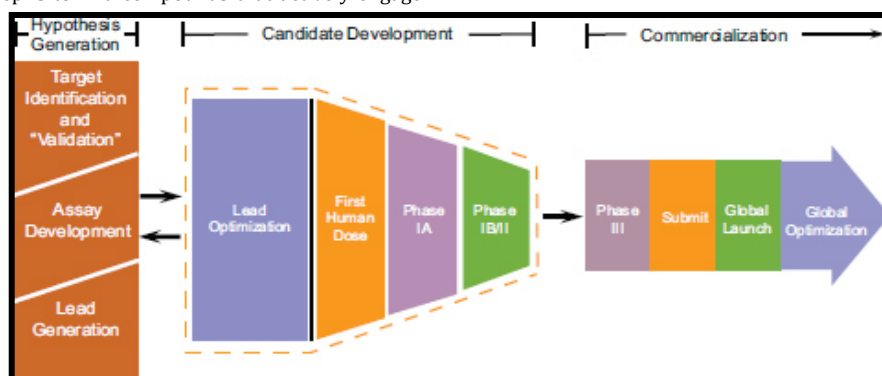


Fig. 1: Overall drug discovery and development process

The process of moving from target identification to lead generation is often done entirely without animal studies, said Potter. Potential compounds, for example, can be generated through binding/functional, biochemical, and cellular or cytotoxicity assays. High-throughput screening through a large compound library can identify multiple compounds. Progressing to a lead compound(s) can involve complex cellular assays, toxicological surrogate assays, biopharmacological surrogates, and surrogates for absorption, distribution, metabolism, and excretion (ADME).

Potter noted that animal models are often used first to narrow the number of lead compounds to one or two candidates that can proceed into clinical trials. The lead compound(s) is tested in animals for its pharmacological and toxicological properties. Animal tests for efficacy—as opposed to safety—are, in most cases, not required prior to first-in-human testing, a point repeatedly stressed by several workshop participants. After a lead compound is generated, it undergoes further testing to optimize physicochemical

and pharmacological properties, especially potency and selectivity. Optimization is an elaborate process that can be costly and time-intensive. Despite the resources (e.g., time, personnel, and finances) devoted to generating lead compounds, Potter observed that many fail during optimization.

Once optimization is complete, first-in-human testing can begin with a Phase Ia clinical trial in which a single dose of the drug is given to healthy volunteers. This is followed by Phase Ib trials, which consist of multiple escalating doses to establish safety, steady-state pharmacokinetics, and maximum tolerated dose. There is increasing use of Phase Ib trials to provide evidence of efficacy in order to establish proof of concept (POC).¹ Potter noted that a typical POC clinical trial is a small controlled study conducted at fewer than 4 sites with less than 100 subjects/patients. If the drug succeeds at POC, clinical trials then proceed to larger Phase II and Phase III trials, which consist of randomized, usually placebo-controlled arms, to ensure safety and efficacy [15, 16].

Table No. 1: Stages of Drug Development

Stage	Method	Purpose
Preclinical	Animal, in vitro, and laboratory studies	Testing toxicity, efficacy, pharmacokinetics, and pharmacodynamics
Investigational New Drug Application		
Phase I	Healthy human volunteers (~20–100)	Testing the safety of a single dose (Phase Ia) and multiple doses (Phase Ib) of a drug; also includes pharmacokinetics and maximum tolerated dose
Phase II	Patients (~100–300)	Assessing safety and efficacy
Phase III	Patients (hundreds to thousands; typically 1,000–2,000)	Assessing safety and efficacy
New Drug Application		
Phase IV	Varies	Postmarketing surveillance

After successful completion of Phase III and submission of a new drug application (NDA) to the U.S. Food and Drug Administration (FDA), a drug becomes eligible for marketing. Even with marketing approval, a drug continues to be studied through postmarketing surveillance to ensure safety.

Current Drug Development Challenges:

- ❖ **Unknown Biological Mechanisms and Biomarkers of Diseases**
- ❖ **Translational Failures Using Animal Models**
- ❖ **Lack of Clinical Phenotyping and Patient Stratification**
- ❖ **Inability to Rely on Published Data**
- ❖ **Pipeline Challenges**

Reddy expressed the view that there are several pipeline problems plaguing large pharmaceutical companies. During the past 15 years, companies have steadily increased expenditures on research, but the number of new drug approvals has dipped. Adrian Ivins, director of the Harvard NeuroDiscovery Center at Harvard University, noted that during this timeframe, only a small handful of nervous system drugs were approved, despite a growing market coupled with unmet need when organization looks to invest in a particular drug, it uses a checklist of questions to gauge the risk of investment, including

- Has the drug target been identified (versus a drug identified in a phenotypic screen)?
- Has the target been validated as a way to arrest the disease?
- Are the biochemical interactions of the drug candidate known?
- Is there information about dose dependence in animal models?
- Has safety of administration on a chronic basis been shown?
- Can the drug cross the blood–brain barrier?
- Do toxicology studies show it is a safe drug?
- Is there a sufficient therapeutic window?
- Are drug purity and stability acceptable?
- Is there good protection of intellectual property?

Multiple challenges can impact the drug development pipeline, originating with the lack of understanding of underlying biological mechanisms of nervous system disorders. Lawrence Goldstein suggested that the field identify key bottlenecks in the pathway and become better at tolerating a certain amount of uncertainty and risk to improve therapeutic development.

Khan noted that biologics are regulated differently from small molecules in the following ways:

- Biologics may not need to be tested for genotoxicity.
- Biologics may not need to be tested in two species, because sometimes only one species is pharmacologically relevant.
- Biologics may not need to be tested for antidrug antibodies, especially if no toxicity is observed at an adequately high dose.
- The criteria for an adequately high dose may be different.
- The assessment of pharmacodynamic effects in toxicity studies may be helpful.
- Acute-dose toxicity studies may not be adequate to support a single-dose clinical trial if a long half-life of elimination in humans is anticipated.

CONCLUSION

United States FDA and European medicines agency have enforced numerous provisions to promote innovation by introducing exclusivity strategies which will exclude innovator from unnecessary competition from others. Within the exclusivity period no other application related to the drug product is accepted. In this span of time innovator will be the monopoly in market and no other will compete with his product. The expected revenue fall of major drug companies as they face patent expiration of key drugs, the decline in new product introductions, ongoing cost-containment efforts in healthcare expenditures in established markets in the United States and Western Europe, and pharmaceutical industry growth in emerging markets, have laid the foundation for innovator-drug and generic-drug companies to develop strategies to respond to these changing industry fundamentals. The net result is a blurring of the traditional strategic boundaries between innovator-drug and generic-drug companies. Innovator-drug companies are seeking to diversify and build their positions in generics, which includes product positions in emerging markets. In turn, the major generic-drug companies have to decide how to best avail themselves of the large opportunity resulting from the wave of patent expiries as well as their own diversification into new drug development.

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