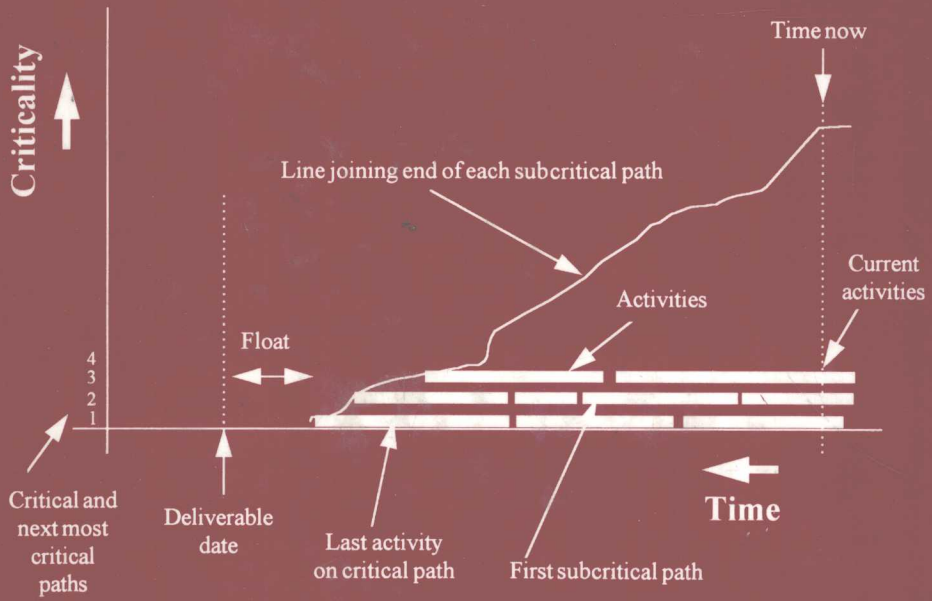
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 86

# Pharmaceutical Project Management




edited by
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# Preface

Drug development is a high-cost, high-risk, and lengthy enterprise. Most drug companies are actively exploring ways to accelerate and improve their drug development processes. Excellence in drug discovery has long been regarded as a hallmark of successful drug companies. It is increasingly recognized that this alone is not enough and must be coupled with excellence in drug development. The latter capability requires that a high-quality, well-motivated, and well-trained staff is in place, and that development vision is matched with good process and procedure.

Project management plays a pivotal role in achieving and sustaining excellence in drug development. The pharmaceutical industry has been relatively slow to implement project management techniques in comparison with other industries. In the past decade, however, most large drug companies have established project management groups with full-time staff whose professional responsibility is the management and planning of drug development.

Pharmaceutical project management has a broad scope encompassing strategic and operational management of individual projects and of the development portfolio. Within this scope reside challenges and opportunities in the management of information flow, personal and organizational

decision making, and risk and opportunity assessment. It includes day-to-day management and motivation of international project teams and management of joint ventures. It covers operational planning, which requires an understanding of the basic principles of networking, scheduling, and critical path analysis. It includes an understanding of intelligent resource management in the face of the high rates of project attrition and conversancy with techniques of steady-state portfolio analysis. Integration of planning for individual projects with the management of the total development resource pool presents particular challenges to most organizations. Some companies have made significant progress in recent years to harness the improved technology in information and planning systems to provide a multiuser distributed planning capability better able to support the project demand and resource supply interface.

*Pharmaceutical Project Management* highlights a number of topics of key importance to the successful management of contemporary drug development. The contributing authors bring a wealth of development experience drawn from a broad variety of companies to capture the diversity of approaches to project management. The scope of the book includes strategic and operational aspects of the drug development management at both project and portfolio levels. Basic concepts and the practical application of computerized planning techniques are considered. Issues and approaches to successful management of international project teams and for joint ventures are explored. Specific consideration is given to decision making in drug development in the context of management structures that vary significantly between companies. The application of project management to particular development areas is described for clinical trials and manufacturing groups. Also, development work is increasingly contracted out by the pharmaceutical industry, bringing with it specific issues to contractor and contractee. The issues and solutions of both parties are considered.

The audience for this book will most likely include those in drug development and project management, as well as pharmaceutical industry consultants and project managers in other industries, e.g., chemical and food.

Looking to the future, the impact of the dramatic pace of change in information technology on project management is considered. Last but not least, the future role of the professional project manager is discussed, including a review of candidate profile and training needs.

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# 1

# Strategic Project Management at the Project Level

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## I. PROJECT STRATEGY OVERVIEW

Drug development is not a simple process. If honest, most newcomers to drug development will concede that their initial experience as a project team member for a development project is disconcerting. Unfamiliar technical acronyms fly around the room. Team members with greater development experience and knowledge of the project often dominate the discussion. The new team members probably will be glad to conclude their

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contribution to team discussion and to escape from their first team meeting without making fools of themselves. Drug development is more comprehensible if the team member has the good fortune to join a project team at its inception rather than, as is often the case, as a replacement team member. It is at the initial team meetings that the core early development strategy is decided.

Successful drug development depends on the quality of the development strategy. Ultimately, successful drug development is about translating science into an optimal investment proposal that provides value to a variety of stakeholders and customers. This can be achieved only be establishing a strategy which recognizes who the customers for new medicines are and addresses their needs. This will mean moving increasingly from designing "for" to designing "with" the customer. Health care provided in most countries has experienced significant change in recent years. Probably the greatest change to be faced in the future will be the expectation that new medicines will be not only safe and effective but also cost effective in the overall context of disease management.

Drug development strategy is concerned with establishing clearly set objectives for the development and life cycle management of an asset, recognizing critical hurdles to success, and structuring plans to achieve the best reward/risk for the investment. It requires a range of skill sets which include strong technical knowledge of drug development and understanding of development risk management. Project attrition rates are high, and it is important to understand why and when these can occur. The overwhelming majority of projects fail. A primary objective in drug development, therefore, is to eliminate from development, at the earliest time, projects that offer poor prospects for commercial return. Termination decisions are rarely made with certain knowledge which is why they are so often painful for teams and companies to take. It requires understanding of the importance of the target product profile (TPP) as a strategic tool and the need for its continuous review throughout development. The TPP definition is critical to the design of clinical development strategy. It is also the basis for establishing clear Go/No Go criteria for the compound through development.

It depends on good understanding of planning skills to ensure that alternative development scenarios are recognized and their impacts are fully explored. It also requires business skills to evaluate the investment opportunity integrating the key parameters of risk, time, cost, and return. At the core of all of this is knowledge of the disease area which enables the impact of a new medicine in the total scheme of intervening in the disease state to be assessed. If this analysis is at fault, all else is of little value. In an increasingly

cost-constrained environment, where cost effectiveness is a passport of access to patient groups, pharmacoeconomics will be a key strategic driver in formulating development plans.

It also requires an understanding of life cycle management. The commercial value of a product will be realized only by ensuring that the product benefits are fully exploited. New medicines will need to "earn their keep" by justifying price at time of market entry and by sustaining their competitive value during their life cycle. An investment in health economics studies will be needed to underpin this case. Opportunities may exist for developing better dosage forms and dose regimens and may also exist for switching Rx medicines to OTC. Finally it is essential to establish a clear postpatent strategy in good time.

In summary many skills are needed to create a strong development strategy. Generally a well-structured project team has these skills. The experienced project manager should have a broad awareness of many of these skill requirements. However, generally, his or her greatest contribution will be in harnessing the skills within the project team to build a robust and farsighted project strategy.

## II. DEVELOPMENT STRATEGY FROM CRADLE TO GRAVE

### A. Early Development Strategy

*1. Improving Input Quality to Development*

The quality and quantity of preclinical data provided by discovery groups to support the development of a new compound is often suboptimal. It is important to establish appropriate selection criteria for development because much time and resource can be wasted, subsequently, by the development organization in "patch and mend" strategies which more thought (and training) in discovery could obviate. This is not to advocate a fortress mentality with development playing a prima donna role to discovery. There has to be a reasonable balance with the onus of responsibility on discovery to provide a basic array of technical data to justify development and an onus on development to show maturity and reasonable flexibility. Specific data gaps in a development proposal may exist for good reasons (e.g., obtainable but will incur major delay) and can be addressed in development. Establishing reasonable criteria for development is also valuable to discovery groups though this may not be appreciated at the time! The selection criteria can be used to better discriminate between alternative lead candidates prior to development. Generally, lead candidates are selected on the basis of

structural activity studies focused on one or more biological activities. It also makes good sense to optimize development candidate selection by examining other preclinical data which will be critical for development. In each of the nonclinical development disciplines (chemistry, pharmaceutics, drug metabolism, pharmacokinetics and toxicology) key pieces of data may be obtainable at modest cost and to aid in selecting the best development candidate. Basic stability and solubility studies of a drug substance, at an early stage may reveal the need to select a better salt or an alternative candidate. Characterizing the basic pharmacokinetics may highlight a best option candidate. In vitro genotoxicity testing should certainly be undertaken early. Although additional resources are required to more fully profile a limited selection of development lead candidates, the payback in improved input quality to development will more than justify the effort.

*2. The Product Profile—A Strategic Tool for Drug Development*

The key strategic tool which guides drug development is the Target Product Profile (TPP). The TPP describes the specifications of the product intended to be introduced into the market [1]. It defines the required efficacy and side effect profile of the product, how it is supplied, how it is to be used, in which patient groups, and for what purpose. It specifies the cost of goods and the time of market introduction. It is the key design template for creating the development plan. It defines the performance requirements which enables the commercial organization to assess the market impact and estimate the commercial return. Teams sometimes confuse what they hope to see in the performance of a development compound with the minimum performance that would provide for a viable commercial opportunity. It is essential to define a *minimum* TPP specifying the *minimum* performance for commercial viability. The expected product performance can also be defined alongside the minimum TPP, and commercial forecasts can be provided for both. The specific attributes within the TPP constitute a package. If a change is made in one attribute, the whole TPP must be reviewed again to ensure that the impact of the change is fully understood. The TPP has to be set in a specific time frame for launch because any change in schedule may result in an important change in the market environment, e.g., competitor launch.

The TPP is dynamically affected by internal and external factors. Internal factors can include clinical and nonclinical development findings. External factors include, for example, new competitor clinical results just released. Therefore, the TPP is generally reset in development. The TPP is a contract between R&D and the commercial organization (Fig. 1). The


**FIG. 1** Target product profile—key driver of the development plan.

development investment is endorsed by the commercial organization on the basis that the TPP specifications are delivered at an agreed time and cost. If the TPP "contract" is to be changed, this must be renegotiated and an endorsement for the new contract secured to ensure that further investment is justified.

The TPP is the pole star on which the development plan is focused. The TPP is valuable only if it is specific and quantitative. The TPP enables setting development checkpoints based on the minimum performance established in the TPP. The TPP should be defined by the project team because it is a multidisciplinary task. To frame the TPP, the team must define how the drug is intended to be used in the disease state. A good start for the project team is to attempt a pictorial (disease cartoon) depiction of the patient flow in a disease. This would highlight how the disease is detected and how the disease progresses both acutely and chronically. The types of

invention possible (current and expected) should be assessed including both prophylactic approaches, surgical intervention and drug intervention. The outcomes of intervention and their problems should be considered. This holistic approach takes time (generally this analysis will reveal important information gaps, a need to collect information, and a need to secure external expertise to help understand the treatment context), but its reward is a TPP of substance and not a "jump to conclusion" profile that simply adds 5 percent to an efficacy parameter of what may be an irrelevant competitive product. One benefit for a company in focusing on selected franchise disease areas is that good information bases and good understanding of specific diseases should already be in place with strong links to health care professionals who understand patient needs in these diseases.

*3. Target Product Profile—A Hypothetical Case Study: PRIONIX*

Usually it is not an easy task for project teams to draft a TPP. The types of issues encountered can best be illustrated in a hypothetical application. A new development candidate has been created for the following TPP analysis. Experts in rheumatic disease are asked to exercise leniency in their scientific scrutiny of the development support data which follows. . . .

PRIONIX is a novel compound that has advanced to development as an antirheumatic drug based on beguiling science not fully understood at a molecular level! It was shown that PRIONIX binds tightly in vitro to a small protein discovered in the joint fluid of patients with rheumatoid arthritis. Binding resulted in reduced cartilage degradation in a human in vitro joint explant system. Evidence from several clinical research studies demonstrated that the protein was a very potent proinflammatory factor and one whose concentration was a reproducible marker of active joint inflammation. Some animal work was done which highlighted limited bioavailability for PRIONIX: oral and IV studies established acceptable acute toxicity and demonstrated no significant issues in pharmacological safety studies. A decision was taken to develop PRIONIX.

The project team drafted the TPP. The key components of the TPP were addressed in defining the indication(s), the dose regimen, the required efficacy, acceptable safety, and tolerability profile. The maximum intended cost of goods was defined, and the time frame to market launch was projected.

Key competitor compounds in development and in the market were reviewed to ensure that the minimum criteria were adequate. The market dynamics in the period following launch were considered in detail to highlight events that could have a significant impact on prescribing the medication.

Such events could include introduction of new diagnostic tools (which might increase or decrease the patient pool), major competitors going off patent with an impact on pricing, and regulatory and market interventions which could restrict use. This analysis identified the major factors which could affect market penetration and commercial success.

In discussing the TPP, it was recognized that, on the basis of the biological data, PRIONIX might offer benefit as an anti-inflammatory agent and as a disease modifying agent or both. The team recognized that the minimum TPP for an anti-inflammatory agent and a disease modifying agent would be very different. PRIONIX could occupy different segments in the market. If the clinical benefit offered was solely anti-inflammatory efficacy, the TPP must identify features differentiating PRIONIX from the best alternative anti-inflammatory drugs currently marketed (NSAIDS) or in development. A review of the literature highlighted that these drugs offered prompt onset of anti-inflammatory and analgesic actions and variable patient response [2] and that some offered a convenient oral once daily dose regimen. It was noted that several agents were already generic and low priced. Important weaknesses were the poor tolerance of NSAIDs and, in particular, the poor gastrointestinal side effect profile. It was suggested by experts that the latter is class related (through modulation of an arachidonic acid cascade). Significant switching in prescribing of NSAIDs was evident, indicating patient dissatisfaction.

The team believed that PRIONIX with its novel mode of action, potentially, could offer key benefits over the NSAID class by providing consistent efficacy and better tolerability. These features were of more than sufficient benefit to the patient to offset a need for once daily oral dosing. The *minimum* competitive TPP chosen by the team would deliver a product with at least as good anti-inflammatory efficacy as NSAIDs but with a slower speed of onset (i.e., one month). The dose regimen was more frequent at t.i.d. than the many o.d./t.i.d. products on the market. However, it was considered that the key benefit of significantly improved GI tolerability provides a real breakthrough for patients and encourages long-term compliance. It was recognized that PRIONIX, in contrast to NSAIDs, probably would not offer benefit in many other nonrheumatoid inflammatory conditions. To crystallize its thinking, the team drafted the labeling statements it intended for PRIONIX. The clinical trials needed to support these labeling statements were carefully reviewed in considering trial size and powering.

Development plans were prepared, which included definition of clinical endpoints and the quantitative performance required. The planning work established that it would take five years to develop PRIONIX to registration.

Phase 3a trials would be powered to demonstrate at least as good efficacy as the selected NSAID comparative drugs with significantly reduced GI side effects. A good commercial opportunity was predicted. An enthusiastic commercial group was already starting to draft promotional copy "PRIONIX - THE FIRST ANTI-INFLAMMATORY YOU WANTED TO STAY ON"....

However, the minimum TPP for a true disease-modifying antirheumatic (DMARD) drug would be very different. The potential patient groups included adult and juvenile rheumatoid arthritis patients. Review of the marketed disease-modifying drugs revealed inconsistent delivery of efficacy and very significant side effects. The toxicities of these drugs resulted in their second-line positioning, and they were generally used only during active disease episodes. Benefit, when seen, was slow in onset. If PRIONIX was a true, disease-modifying agent, which retarded joint destruction, this would be a long awaited treatment breakthrough. In these circumstances, dose regimen convenience would not be critical in the TPP, though an oral disease modifying anti-rheumatic drug was highly desired. An intramuscular route of administration would be acceptable if adequate oral bioavailability did not prove achievable. The drug would likely be dosed even if side effects were evident but, depending on their incidence and severity, could be limited to second-line use with a more limited commercial potential. The team agreed on a minimum TPP for the DMARD. Table 1 compares key features of the minimum TPP for PRIONIX as an anti-inflammatory and as a disease-modifying anti-rheumatic agent.

A development plan was created. It was recognized that demonstrating disease-modifying activity convincingly would require extended clinical studies during which joint erosion would be carefully monitored. Development to the registration point as a DMARD agent would take six and a half years. The commercial group saw a strong opportunity to justify pricing in an area of clearly unmet medical need, where a strong pharmacoeconomics case could be made.

The potential vulnerability of the investment was recognized on two counts. First, this was a project for which heavy investment would be made prior to proof of its DMARD efficacy. Secondly vaccine and other novel anticytokine projects were in development ahead of PRIONIX. The internal research view of these competitor strategies was skeptical—much promised—nothing delivered—and advised that all the other players were long shots—other than PRIONIX!

The team considered the scenarios of PRIONIX as a DMARD with and without acute anti-inflammatory activity. This raised some important