Managing the drug discovery/development interface

Tony Kennedy

The transformation of drug discovery in the past decade will result in an expanding array of novel development candidates that will outstrip the development resources of even the largest pharmaceutical companies. A critical success factor for drug companies will be their ability to maximize the value of their development portfolios by focusing finite resources on projects with real potential. Successful management of the research-to-development interface will require better quality decision making in the selection of entrants to development and in portfolio management. Clarity in defining the product opportunity in the challenging new pharmaceutical marketplace will be crucial to such decision making.

There has never been a more exciting time to work in drug development. Dramatic advances in technology are revolutionizing the way drugs are discovered. Genomics, robotics, miniaturization, high-throughput screening and information technology are synergizing to accelerate the discovery of novel drug candidates. As a result, the number of potential drugs that could enter the development pipeline is likely to outstrip development resources. The 'innovation index' of portfolios is also likely to increase, as many new molecular targets are explored.

The marketplace for drugs is also changing dramatically. The decision makers and the decision-making process for prescription drugs have changed significantly in the past decade. Although the industry can argue that drug costs represent a small (<10%) and justifiable proportion of total healthcare costs, drug pricing and drug use have come under the spotlight as many countries try to constrain spiralling healthcare costs[1].

These dramatic changes in the science base and the market dynamics combine to pose a number of critical questions for drug development:

- What development strategies are needed to position novel drugs in the new marketplace successfully?
- How will development organizations cope with a marked increase in the input of development candidates?
- How will organizations choose between alternative development options?
- With the proportion of innovative projects in the portfolio mix increasing, how can the risk be managed?
- What are the implications for portfolio management?

This article will consider these questions from both conceptual and practical project management perspectives and will focus on the critical discovery–development interface, where many of these issues bite.

Target product profile

Successful drug development, ultimately, is about translating science into a worthwhile investment that provides value to a variety of customers and stakeholders. In order to be successful, customer needs must be both understood and fully reflected in the design specification for the product. The first (and the most critical) task undertaken by a new project team is to determine this specification, which is commonly termed the target product profile (TPP).

The TPP is the key strategic tool that guides drug development. The TPP describes the specification of the product

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Table 1. Format of the target product profile

Profile component	Information need	Basic example
Indication	Target patients and purpose of treatment	Reduced blood pressure in mild–moderate hypertensive patients
Efficacy	Minimum efficacy requirements – quantify minimum performance for the end points to be studied	Diastolic blood pressure reduced by >10 mmHg in 90% of patients Onset of response within 1 week of commencing therapy Blood pressure control maintained on extended therapy
Safety	Required safety profile Highlight class- or therapy-related side effects that this product must not have or set limits	Excellent safety and tolerability profile is a must No safety issues that would limit prescribing in this patient group
Dose regimen	Required dosing regimen	Must – twice daily oral dose Want – once daily dose
Dosage form	Specify the commercial form	Must – solid dosage form Want – tablet
Cost of goods/pricing	Specify the maximum cost of goods and pricing assumptions	Pricing assumption of £700–900/annum in major markets Maximum cost of goods supplied – £0.3/day
Registration and launch date	Planned date of regulatory submission and expected approval dates	Registration filing – December 2001 Approvals in December 2002 to June 2003 in major territories

intended to be introduced in the market. It defines the required efficacy and side-effect profile of the drug, 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 time of market introduction. It is the key design template for creating the development plan. It defines the performance requirements that enable the commercial organization to assess the market impact and estimate the commercial return (Table 1).

Project teams sometimes confuse what they hope to see in the performance of a development compound ('want') with the minimum performance that would provide for a viable commercial opportunity ('must')[2]. It is essential that a *minimum* TPP must specify the *minimum* performance for commercial viability. The desired or 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, then the whole TPP must be reviewed again to ensure the impact of the change is fully understood. The TPP must be

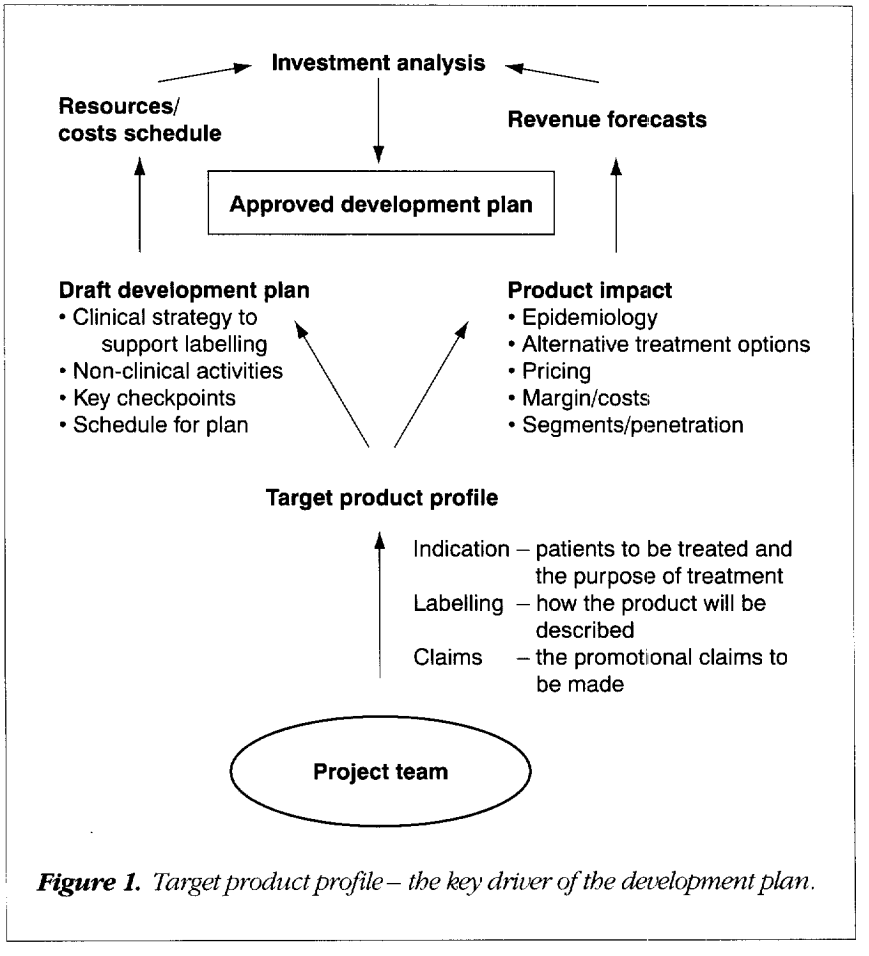

Figure 1. *Target product profile – the key driver of the development plan.*

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 dynamic, being affected both by internal and external factors. Internal factors can include both clinical and non-clinical development findings. External factors include, for example, new competitor clinical results. The TPP is therefore generally reset in development. The TPP is a contract between R&D and the commercial organization (Figure 1). The development investment is endorsed by the commercial organization on the basis that the TPP 'specification' is delivered to 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 can be justified.

Framing the TPP

The TPP is the 'pole star' on which the development plan is focused; it is of value only if it is both specific and quantitative. The TPP enables development checkpoints to be set based on the minimum performance established and 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 is for the project team to attempt a disease 'flow scheme' (Box 1) and/or a simple pictorial depiction of the patient 'flow' in a disease – a disease 'cartoon'. This would highlight how the disease is detected and how the disease progresses both acutely and chronically. The types of intervention possible (current and expected) should be assessed, including prophylactic approaches, surgical intervention and drug intervention. The outcomes of intervention and their problems should be considered.

Box 1. A disease 'flow scheme'

Disease presentation
Burden of disease
1) Pain
2) Functional impairment
3) Productivity impairment
4) Burden on others

Diagnosis and intervention options
Specificity of disease diagnosis
Variability in disease progression

Intervention options
1) No intervention
2) Drug intervention
   – prevention
   – treatment
3) Surgery

Short-term outcome
Benefits of intervention
1) Burden of disease ↓
2) Cost of illness ↓
3) Sick leave ↓

Costs of intervention
1) Drug costs +/–
2) Surgery costs +/–
3) Indirect costs +/–
4) Adverse effects of intervention +/–

Long-term outcome
Benefits of Intervention
1) Long-term prognosis improved
   – Quality of life
   – Life years gained

Costs of intervention
1) Drug costs +/–
2) Post-surgical costs +/–
   – Complications

Secondary consequences of intervention

This 'holistic' analysis takes time – generally it will reveal important information gaps, a need to collect information and a need to involve external expertise to help understand the treatment context. However, the reward is a TPP of substance rather than a 'jump to the conclusion' profile that simply adds 5% to an efficacy parameter of what may be an irrelevant competitor 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 healthcare professionals who understand the appropriate patient needs.

The TPP is used by the project team to design the clinical development strategy, and to plan non-clinical activities. The definition of the minimum TPP provides a bridge linking product performance to investment decisions at project checkpoints with the hurdle height set to ensure commercially viable products.

Early development pharmacoeconomics hypothesis

Until relatively recently, TPPs focused essentially on defining the required clinical performance for a new drug. This was a viable analytical approach for a healthcare market in which clinical benefit was paramount, and cost was secondary. The industry viewed the prescribing physician as the key 'customer' for a new drug and focused heavily on providing this group with persuasive clinical trial information with well-trained sales teams and adroit publication and communication strategies.

In the new cost-constrained markets, the prescribing decision of the physician remains important, but it is circumscribed. Access barriers to drugs have come into place in an increasingly cost-conscious healthcare environment (Figure 2). In stark terms, the physician, although impressed by the

clinical benefit of a new drug, simply may not be able to prescribe it. A variety of mechanisms have emerged to constrain expenditure on healthcare, including the drug budgets. For example, health insurance schemes capitation fees (fixed price per head) introduce a strong competitive dynamic to seek cost savings at all points in the healthcare delivery chain. From the perspective of the drug company seeking to launch and market a new drug, a range of hurdles must be overcome if a new drug is to be successfully marketed; these include national reimbursement agencies, hospital formulary committees, managed healthcare organizations and national or local agencies with funding responsibilities.

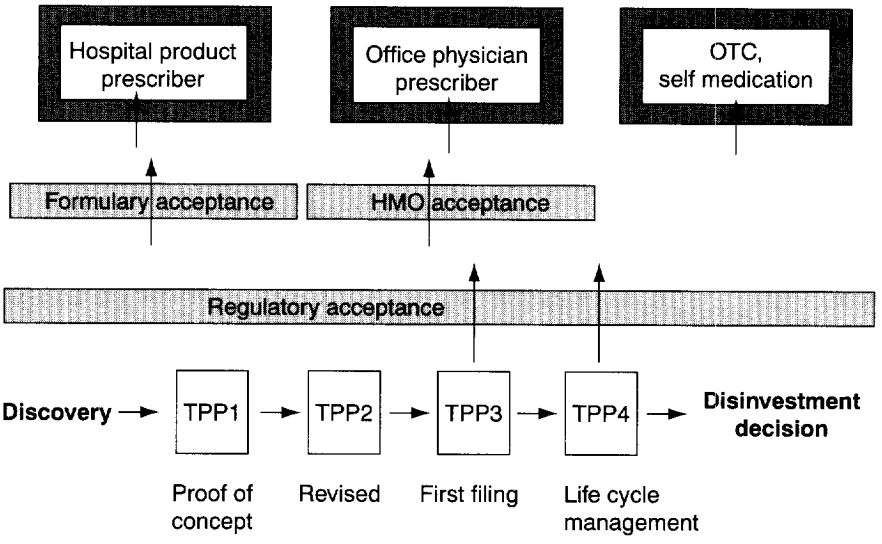

Figure 2. *Access barriers to drugs. The target product profile (TPP) needs to identify several different datasets (indicated by arrows through the barriers) to overcome the different barriers to product acceptance. HMO, health management organization.*

These diverse groups will be influenced by data to allow or even recommend use of a new drug but may also discourage or prevent use of a new drug by not including it in formulary listings or in reimbursement schemes. The type of information of interest to these groups differs to some extent, reflecting their differing roles and responsibilities. An awareness of the different perspectives of the 'customers' who ultimately guide drug use is essential to ensure that relevant data are collected to provide a 'passport' of entry (Table 2).

'Value demonstration'

Savings in the drug budget can be made by the use of cheaper drugs offering equivalent benefit, by more effective use of existing drugs and by limiting access to drugs for which widespread use is unjustified. Cost saving, however, has to be assessed in the broader context of overall healthcare expenditure. For example, additional drug costs could be justified by reduction of hospital costs. The demonstration of cost-effectiveness of new medicines will be a critical success factor for commercial success in the future. This represents a difficult challenge for the pharmaceutical industry and society because 'value demonstration' is easily supportable as a concept but is far from easy to apply in practice. Although pharmacoeconomic assessments are increasingly undertaken, the lack of sophistication of some analyses has attracted increasing concern[3]. Some initiatives to improve the clarity and quality of pharmacoeconomic assessments have been taken, and guidelines were issued by a *British Medical Journal* Economic Evaluation Working Party in 1996 (Ref. 4). The discretionary nature of the methods used to analyse cost-effectiveness was specifically commented on by the *New England Journal of Medicine* in highlighting the need to minimize sources of bias[5].

The challenge that health economics poses for those engaged in designing a drug development strategy is profound. Many of the real benefits of a new medicine and its true cost-effectiveness will not be demonstrable within the scope of clinical trials supporting first registration, pricing and launch, let alone those limited trials conducted in early development. How, then, can pharmacoeconomics be of use in early development? An integrated health economics strategy is needed that both shapes the overall development strategy at all development stages (identifying the key economic consequences of the disease and the types of data that need to be collected in trials) and enables a constant reassessment of project viability as development data become available (quantifying the impact of the observed product performance in clinical studies). By focusing exclusively upon the 'primary' clinical end points of a study, important potential direct and indirect benefits of drug intervention may be neglected. For example, the granulocyte

Table 2. Pharmacoeconomics – interested parties and their concerns

Pharmaceutical company	• Early assessment of project opportunity/viability • Fearful of exclusion of drugs from formularies and health management organizations • Recognize need to invest in pharmacoeconomic studies but often sceptical of the impact of the investment on decision-makers
Pharmacists	• Play an important role in deciding which drugs are used in a hospital – involved in formulary decisions/treatment strategies • Assist in monitoring patient compliance
Patients	• Increasingly well informed and organized into pressure groups prepared to pressure clinicians and lobby governments • Global coherence of such groups is enhanced through use of the Internet to focus attention on their needs
Office physicians	• Increasingly cost-conscious • Generally concerned with the long-term patient outcome • Efficacy-focused, they are keen to see time-saving benefits (reduction in return visits)
Managed care organizations/ health insurance companies	• Want substantive real-world outcome data on which to base selection of cost-effective drugs; may lack the infrastructure to provide these data • Not easily impressed with small-scale pharmacoeconomic studies
Reimbursement agency	• Responsible for setting reimbursement level/co-payment for the drug • Concerned with the impact of new medicine on healthcare expenditure • Will set pricing that reflects the perceived cost-effectiveness of the new medicine

colony-stimulating factor Neupogen was successfully developed by documenting not just that the drug was capable of accelerating white blood cell recovery post-chemotherapy and reducing the incidence of febrile neutropenia, but also that as a consequence of treatment, the number of in-hospital days as a result of infection was reduced, there was saving in the antibiotic bill, and there was a reduction in the need to reschedule subsequent chemotherapy cycles for patients.

In early development, a pharmacoeconomic strategy can be developed with modelling based on epidemiology studies and how disease management is practised in the major territories. This helps to focus clinical development strategy and highlights the types of data that best demonstrate product value. This type of study can be undertaken in Phase I (or indeed earlier as strategic support to the discovery engagement in the disease area). Early in development, studies should be performed to further define current practices of disease management. This should address the best alternative options of disease intervention and the 'real world' direct and indirect costs and benefits of such interventions. This work provides a basis for assessing the differential impact of intervention with a new drug. By conducting such studies early in development, the findings are available to shape the pivotal efficacy Phase IIIa study strategy.

Many companies, despite the evident difficulties, are recognizing the need to establish a pharmacoeconomics strategy much earlier in development than before. This may help to identify the best instruments to document product value and may reveal that some drugs are not likely be commercially viable because the observed clinical performance is unlikely to translate into cost-effective benefits justifying reimbursement. In cases where a drug is potentially being developed for more than one type of clinical indication, an early pharmacoeconomic analysis may highlight the best indication to target.

Selecting the right projects

Improving the scientific and technical input quality

The quality and quantity of preclinical data provided by discovery groups to support the development of a new compound is often suboptimal. This may in part be a consequence of the intense pressure on discovery groups to feed new candidates into development. It is important to establish appropriate selection criteria for development because time and resources can subsequently be wasted by the development organization in 'patch and mend' strategies, which more thought (and training) in discovery could prevent.

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 not to fall into the trap of 'box ticking' for entrant acceptance. Specific data gaps in a development proposal may exist for good reasons and can be addressed in development. For example, information may be obtainable but its acquisition would incur major delay. Establishing entry criteria for development is also of value to discovery groups because these can be used to better discriminate between alternative lead candidates. Lead candidates are generally selected on the basis of structure–activity studies focused on selected biological efficacy parameters. It makes good sense to optimize development candidate selection by also examining other preclinical data that will be critical for development. In each of the non-clinical 'development disciplines' (chemistry, pharmaceutics, drug metabolism, pharmacokinetics and toxicology) key pieces of data are obtainable at modest cost and aid selection of the best development candidate. Basic drug substance stability and solubility studies may reveal, at an early stage, the need to select a better salt or an alternative candidate. Investigation of drug interaction liability is technically feasible and may help in the selection process. *In vitro* genotoxicity testing should certainly be undertaken early. In each of these areas, there is scope to establish screening assays requiring modest drug quantities. While additional resources will be required to profile a limited selection of development lead candidates more fully, the pay back in improved input quality to development will more than justify the effort.

Improving the strategic input quality

There may be good strategic reasons not to progress a compound into development. Choosing the best development options requires medical vision, driven by the basic science, combined with the creativity to conceive how markets could be transformed and reshaped by breakthrough therapies. It is not about fitting pieces into jigsaws; in many cases it will be possible only to make a preliminary assessment of product potential at the proof-of-concept stage with an early read out from clinical trials. In some cases, however, it may be possible for teams to recognize (in the 'disease cartoon' analysis and its translation into the TPP and the supporting clinical trials design that will deliver the required product labelling) that the prospects of delivering a product with value in a particular disease setting are marginal. This 'strategic filtering' of research and development opportunities is difficult to achieve and requires the integration of scientific, clinical, technical, commercial and regulatory skills; it represents a high level competency for any R&D organization.

Proof-of-concept and criteria for full development

The minimum TPP created in the development plan should be used to define the checkpoints and 'go/no go' criteria for the indication. The criteria chosen should balance realism and rigour. This is easier to say than to do, and some specific comments are appropriate:

- The data available at early checkpoints will be limited.
- Dosing will be of short duration.
- Patient numbers enrolled in studies will be small.
- Dose regimens will not be optimized and hence neither will be the efficacy delivered.
- It is possible that dynamic markers will have been studied rather than the intended clinical end points.

It is important not to fall into the trap of mindlessly extrapolating market required labelling to early checkpoints. This applies particularly to ultimately desired statistical statements for which early trials will not have been powered.

The primary purpose of setting go/no go criteria is to provide an answer to the question – do the data available at this time justify further investment in the project? For some projects competitor products may have helped to define the checkpoint hurdle height. For some pioneer products demonstration of dose-related activity against selected markers in early studies may be as much as can reasonably be achieved to encourage investment in the next stage of development.

When should the key checkpoint for full development to the market be set? This will vary by project. For an antibiotic, Phase I pharmacokinetics, safety and tolerance may be enough to set a good probability of success for the project. On the other hand, some prophylaxis studies require very large patient numbers to determine efficacy, and it may be only at the completion of Phase III scale trials that project viability is established. Key go/no go project checkpoints, when they occur and how criteria are quantified, are very much project-specific and indeed shape the investment risk profile for a project. For some projects, the development risk is frontloaded and for some it is backloaded (Figure 3). The outcome at go/no go checkpoints is not, of necessity, go or stop. Phase II data may reveal that the dose response has not been adequately explored or Phase I studies may reveal poor pharmacodynamic results but also suboptimal

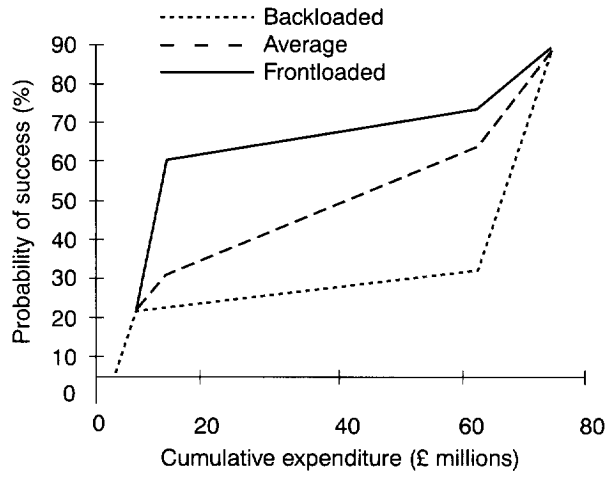

Figure 3. *Risk profiles for drug development projects.*

bioavailability for the formulation studied. In each case, plans can be redesigned to achieve a successful outcome albeit with delay to the project.

Risk management strategy

Attrition in early development

Some data on why projects fail in early development have been published by the Centre for Medicines Research (Figure 4). Anti-infective projects comprised some 77 of the 198 compounds included in this survey and 'distorted' the overall picture because unsatisfactory pharmacokinetics were responsible for nearly all anti-infectives terminations but accounted for only 7% of other categories. If the anti-infective drugs are excluded, the major single reason for failure by far was lack of adequate efficacy (46%).

It is a salutary fact that most development work is either aborted or completed but never reported. Indeed, many people in development never work on projects that become products in their whole careers. The impact of attrition is well illustrated in Table 3. This is a steady-state portfolio, a mathematical model that has as its key parameters the failure rate at each development phase and the time taken in each phase. The model is framed around the objective to bring one new chemical entity to market each year. Based upon the indicated phase durations and failure rates, the portfolio would contain about 23 compounds with most residing in early development. If the speed of development is slower, the size of the portfolio to sustain to one new market entrant per year must increase. The failure rate is generally very high in early development, particularly so in Phases I and II.

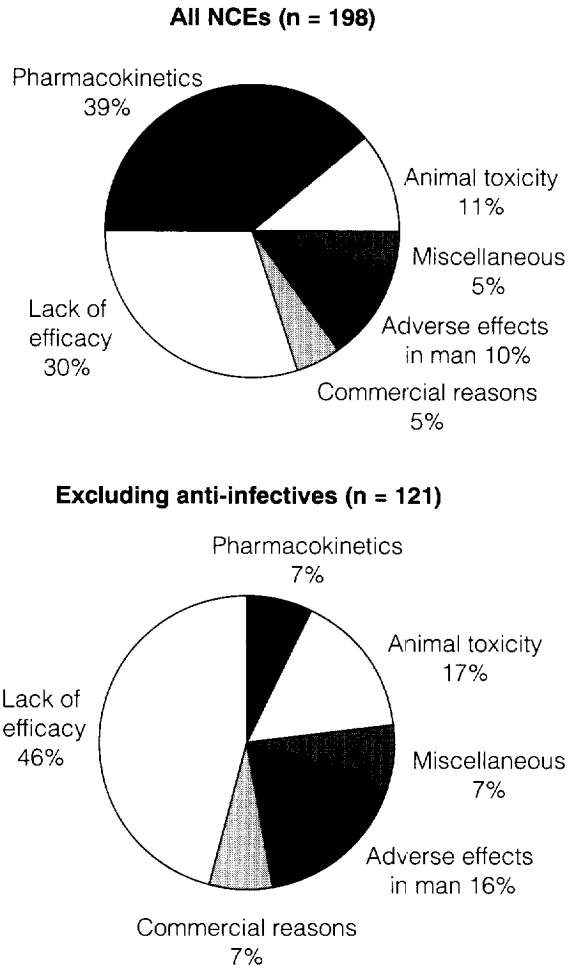

Figure 4. *Why do projects fail? The reasons for the failure of 198 new chemical compounds (NCEs) in clinical development are shown. If anti-infective compounds are excluded the failure profile changes significantly. (Source: Centre for Medicines Research.)*

Table 3. Project failure and the portfolio

	0	Phase I	Phase II	Phase III	NDA
Input	9	7.5	2.5	1.25	1
Output	7.5	2.5	1.25	1	
Elimination	1.5	5	1.25	0.25	
Elimination rate	1/5	2/3	1/2	1/5	
Phase duration (years)	1	1	1.5	2	
Probability of NDA	11%	13%	40%	80%	
Steady-state portfolio: goal of 1 NDA/year	9	7.7	3.75	2.5	

It is vital to cull weak projects as soon as possible. It is increasingly recognized that terminating projects is something to be regarded as an achievement and not failure. Because resource utilization increases considerably at each phase, postponement of termination decisions not only wastes resources on a redundant project but also denies resources to other projects. Termination decisions are difficult at any development stage, but become increasingly difficult in later development because investor expectations are often factored into the company share price.

Backup and follow-up strategy

Discovery and development strategy must be closely integrated to ensure success in bringing products to market. Backup compounds in essence offer no tangible differentiation from the lead compound in development whereas follow-up compounds do. The high failure rate in development demands that a well planned backup strategy is in place. Sometimes this strategy is simply to identify a backup candidate and await the phone call from development notifying failure of the lead. Some companies adopt a more aggressive parallel-track strategy progressing more than one candidate into development from a discovery programme to 'hedge the risk'.

Does this make sense? Would taking another member from the same series into development address this? This leads into a debate on chemical class, pharmacological class and idiosyncratic non-class-related effects of drugs. In principle, a parallel-track strategy might be valuable; for example, better access to the receptor sites or better binding kinetics may be evident within 'same series' candidates. Moreover, toxicology findings, adverse events in man and pharmacokinetics together account for 40% of the reasons for project terminations. These may have nothing to do with 'intrinsic pharmacology' and may be idiosyncratic. So in principle 'molecular hedging' to overcome the reasons for technical failure makes sense. But there is no such thing as a free meal, and the following must be considered:

- How much time is saved by an aggressive parallel-track strategy?
- At what cost?
- At what stage would a single lead compound be selected for full development?

Development costs escalate dramatically in late development. So in general terms, 'hedging' in early development makes sense from a cost/risk perspective. Parallel track development in Phase 0 and Phase I might save 1–2 years against a sequential strategy. The cost/risk and value contribution relationships for alternative strategies can be modelled. Such modelling generally supports parallel early phase development but with a 'holding rule' that a single candidate be advanced for major clinical efficacy trials.

In the real world, limited capacities in early development are often totally occupied with drug candidates from alternative discovery programmes. The opportunity cost therefore has to be considered in a portfolio context where the added value of early parallel lead development may be less than developing lead candidates from other programmes. When only one lead is put into development, and it is then terminated, the delay may result in loss of a competitive position. It may be necessary to replace a failed lead not with a backup but with a follow-up candidate to re-establish a competitive position in development. If a company is serious in its intent to establish a franchise in the market, it must sustain a discovery effort focused on follow-up candidates throughout development.

Making it happen

Discovery team and project team

Good project teams play a critical role in early development. When a decision is taken to progress a new compound into development, a project team is generally formed to bring additional expertise into play to establish an early development plan. It is essential that continuity is maintained by the involvement of key discovery scientists as active participants, not only to maximize the knowledge base on the lead candidate, but also to provide a close coupling back to discovery for a strong backup and follow-up strategy. This transition is facilitated if there is already a close involvement of the core development strategy groups with the discovery groups in the predevelopment period. The team representatives often found in an early team are shown in Box 2.

The greatest value the early project team can offer is to generate quickly and efficiently the critical data to support an informed further development decision on the asset. Project teams 'know the compound' in a way that more distant senior managers seldom can. This is potentially both an advantage and a disadvantage. Closeness to the compound means that detailed facts are known, but closeness to the compound can also mean that a broader judgement is lost to unreasoning compound advocacy.

Box 2. The early development team

- Project Director

Plus representatives from:

- Chemical development
- Discovery
- Drug kinetics/ metabolism
- Formulation development
- Health economics
- Marketing
- Medicine
- Regulatory affairs
- Toxicology

To quote an experienced project director comparing drug development to horse racing:

> 'I do not see it to be the role of project teams to lift the horse over the fences'

Most development decisions, like those in the rest of our lives, are not taken in a state of total knowledge. The smart thing is to know when to bail out and do something better.

Project management and the project director

Effective project management has a critical role to play in successful drug development. Drug development strategy is about establishing clear objectives for the development of an asset, recognizing critical hurdles to success and structuring plans in such a way as to achieve the best reward/risk for the investment. It requires a range of skill sets that include strong technical knowledge of drug development and understanding of development risk management. It requires an understanding of the strategic importance of the TPP and how it should be used in the continuous review of project viability throughout development.

Effective project management also depends on a good understanding of planning skills to ensure that alternative development scenarios are recognized and their impacts are fully explored[6]. In adition to this, business skills are required to evaluate the investment opportunity, integrating the key parameters of risk, time, cost and return[7].

At the core of all of this is the knowledge of the disease area, which enables an assessment of the impact of a new medicine in the total scheme of intervention in the disease state. If this analysis is at fault, all else is of little value.

Summary

Many skill sets are needed to create a strong development strategy. These skills are generally present in a well-structured project team or are accessible to the team from within or outside the organization. The greatest contribution of the project director is to harness the skills and talents within the project team to build a robust and far-sighted strategy for the project and to work effectively with the team and line functions to deliver the plan.

To revisit the questions posed at the start of this article:

Q. What development strategies are needed to position novel drugs in the new marketplace successfully?

A. Pharmacoeconomic strategy needs to be integrated earlier into development planning with greater awareness of customer needs. The TPP should be designed increasingly *with* customers (for example, involvement of patient self-help groups in team discussion on the burden of disease).

Q. How will development organizations cope with a marked increase in the input of development candidates?

A. By improving the quality of the input function with better strategic and technical filtering. In addition, by sharpening decision-making criteria to cull weak projects earlier.

Q. How will organizations choose between alternative development options?

A. By improved strategic visioning achieved by closer integration of discovery, development and commercial analytical processes, and recognition that 'interesting' science does not automatically translate to worthwhile medicines.

Q. With the proportion of innovative projects in the portfolio mix increasing, how should risk be managed?

A. By a strong commitment to backup and follow-up strategies. For some projects, by staging the investment to obtain proof-of-concept data before progression to full development.

Q. What are the implications for portfolio management?

A. Business analytical tools will need to be used more intelligently to aid selection of the best value portfolio mix of projects. If nothing else, this will provide transparency in decision-making, which itself plays an important role in gaining organizational commitment.

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