Steering a course through the technology maze

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Many of the new technologies currently transforming the way in which pharmaceutical R&D is performed consume far more cash and resources than traditional 'wet' bench science. They also carry a high degree of risk. It is therefore crucial that the industry finds systematic methods of evaluating them effectively. This article examines the strategic perspective and internal processes companies should adopt to ensure that they spend their money wisely. It also outlines a three-tier approach, based on decision analysis techniques, for objectively assessing specific technology options – including discovery technologies, which are notoriously difficult to evaluate – to build a technology portfolio.

At the end of the 18th century, epilepsy was regarded as a form of diabolical possession. Today, the physiological and pathological attributes of a single brain cell can be recorded and directly correlated to the gene expression pattern. Advances in medicine and technology have transformed our understanding of illness. They have also delivered a quantum leap in the scope and scale of pharmaceutical research. However, these advances have come at a price. Many of the new technologies use much more cash and resources than traditional bench science. They also require skills outside the industry's usual ken. Even worse, some fledgling technologies come without a proven track record, yet the promise they hold is so great that no pharmaceutical company can afford to ignore them.

Thus, the challenge the industry faces is to develop a systematic way of evaluating new technologies, building a suitable technology platform and managing the uncertainties inherent in a high-risk, hi-tech environment. We believe the answer lies in a complete change of approach.

The technology maze

During the past five years, sophisticated techniques such as single-cell differential gene expression, functional genomics, proteomics and automated target validation have rewritten what is known about medicine (for excellent reviews see Refs 1–3). They have also changed the drug-discovery process beyond all recognition. The future looks brighter still: with increasing use of *in silico* target selection and validation, virtual lead optimization, and improvements in preclinical simulation already on the horizon[4–6] [for an interesting example of simulation, visit Physiome Sciences website (http://www.physiome.com)], the industry will soon be able to perform much of its early work on computers.

However, this brave new world has a 'sting': the huge cost of the technologies that have helped to bring it about. A report published by PriceWaterhouseCoopers[4] (London, UK) shows that between 1991 and 1997, the R&D expenditure of the top 20 companies more than doubled (in nominal terms). The latest figures from the Tufts Center for the Study of Drug Development (Tufts University, Boston, MA, USA) confirm these findings, with costs per approved drug now estimated at $660 million (J. DiMasi, pers. commun.).

The discovery process accounts for a significant part of the bill. Even small-scale acquisitions such as a proprietary bioinformatics database can cost as much as $2 million, whereas larger investments, such as an integrated

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HTS platform, cost up to $50 million. So it is little wonder that some big pharmaceutical companies can spend a third of their overall discovery budgets on new technologies alone.

The cost of the hardware is by no means the only issue; many of the new technologies are equally expensive in terms of the resources they consume. (Indeed, some scientists are now beginning to realize that acquisition of a new technology is often the start of, rather than the solution to, a research problem.) When an experiment is performed at the single-cell level, for example, it typically involves comparing the expression of genes between healthy and diseased tissue at various stages of a particular disease. However, a plentiful supply of the correct type of tissue is often difficult to obtain. There are also inherent variations as a result of genotype, age, race, sex, an individual's specific drug regime, and the way in which the tissue has been collected and stored. Add differences in RNA and protein stability to these factors, and the number of iterations required to secure a statistically valid result becomes very large, as does the volume of data to be managed.

In short, the new technologies have transformed the way in which pharmaceutical research is conducted – for good and for bad. However, with greater understanding of the complexity of diseases, high attrition rates in clinical development, intense competition and shrinking periods of market exclusivity, most companies need all the help they can get. Hence, this demonstrates the importance of learning how to embrace the new technologies without incurring stratospheric costs or losing their way in the labyrinth of options presented by the various technology providers.

Starting with the business strategy

The ability to chart a safe course through the maze depends, in part at least, on a total change of philosophy. Too many companies start with the technology itself rather than what they are trying to achieve. They ask, 'What can we do with this wonderful new gizmo?' Alternatively, they say, 'Our competitors have it. So should we'. They do not ask, 'What is our business strategy? What fundamental research questions are we trying to answer? What technologies do we need to answer those questions and how will this technology help us to answer them?'

Take the case of a company whose business strategy is to provide an integrated healthcare service for individuals with various types of diabetes. In the future, the company hopes to offer customized medicines, so it will clearly need pharmacogenomic data on the sub-populations and individuals most vulnerable to diabetes. Moreover, it will need to integrate that information into its entire R&D process. As part of its plans to provide a service and not just a range of products, the company might also need diagnostic tools to identify those who suffer from the various forms of the disease.

In other words, its business strategy should dictate the technologies in which the company invests. This approach ensures the development of a technology platform that genuinely supports the product pipeline, which is balanced in terms of risk and will deliver a real return on investment – a technology platform that serves, rather than subsumes, the company's objectives.

Creating a technology group

If the right starting point is vital, so is the creation of a technology group with a clearly defined remit, including the power to set technology budgets, scout for new technologies and make recommendations. Exactly how this group is constituted and at what level will depend on a company's specific organizational structure. What is crucial, however, is that the members represent different departments, products and therapeutic areas.

The technology group should also report to a steering group of senior scientists: firstly, to ensure that it genuinely understands the company's business strategy and evaluates the technological options accordingly, and secondly, to ensure that it maintains a truly unbiased stance. Many of the members of the technology group are likely to be technophiles and to press for investments in the areas of the business they understand best or find most interesting.

The advantage of this approach is that it creates a central conduit for dealing with every technology issue, regardless of the area of the business in which it originates. It also creates a clear point of contact for external technology providers and should therefore include a member from the company's licensing department. Most important of all, it creates a forum for identifying new technologies and technology providers that could add real value to the overall R&D strategy, including novel technologies that might ultimately even have an impact on the company's business strategy. Because some of the most innovative technologies are likely to come from the fusion of ideas from other hi-tech industries such as fibre optics, medical physics and telecommunications, the search should extend beyond the pharmaceutical industry.

Creating a technology portfolio and strategy

Once the technology group has been established, it will need to conduct an audit of the company's existing technology.

This should include an inventory of all the current resources – whether they are in-house or available through collaborations with external organizations. It should also identify any areas of expertise, redundancies, duplications and obvious gaps, either in terms of location or therapeutic area.

The technology group should then evaluate that list of resources, identify the key strengths and weaknesses, and develop a technology database that can be accessed by everyone in the organization. Obvious though this sounds, it is worth pointing out that some big pharmaceutical companies have as many as 100 technology-based collaborations, including small-scale ventures with academic institutions. Because details of those technologies are not widely disseminated, they often remain in the hands of the immediate user group.

The future is just as important as the present, as experience in other hi-tech industries has shown. The technology group should therefore draft a set of criteria for evaluating new needs and opportunities in the context of the company's long-term business strategy.

Whatever the particular technology strategy adopted by a company, it must also communicate that strategy to everyone in the organization (a growing challenge as big pharmaceutical companies become even bigger). It should include the criteria for evaluating any new technology, such as whether it adds value, what risks it carries and how it should be acquired. This ensures that the people working in the laboratories – those who regularly read journals, attend conferences and maintain links with the academic and clinical community – really understand what is required.

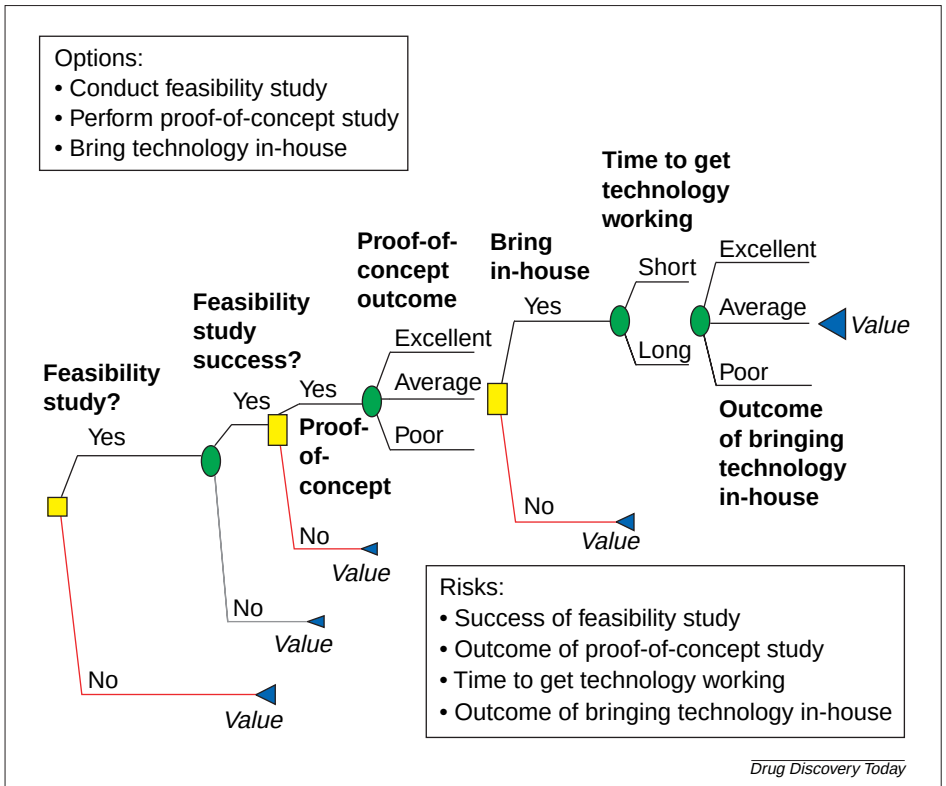

Figure 1. *Typical Level 2 decision tree. The yellow squares represent decision points or events over which the company has control. The green ellipses represent uncertainties or outcomes over which it has no control. The blue triangles represent the points at which it calculates value, although value can be calculated at any of the 16 nodes in this figure. The decision path goes from left to right, representing a typical sequence of events. Clearly, as the company progresses along the decision path, the overall risk is reduced. In this example, the company is considering moving its HTS platform to a miniaturized 1536-well plate format, in line with its business strategy to screen more targets with more compounds to increase the product pipeline. Rather than attempt a full conversion, it first conducts a feasibility study on a well-characterized reporter system. If this is successful (what a successful outcome is has to be precisely defined), it might test the approach in a variety of cell lines and assay formats. It will then make a decision on whether to bring the technology in-house and how that should be done. Value and risk can be assigned to any of these scenarios.*

Putting the right processes in place

The right philosophy, the right structure and the right people are all crucial elements in managing the technology maze. This is further to the right processes for acquiring, installing and integrating new technologies. This includes processes for seeking new technologies, fast-tracking the development and registration of intellectual property and managing the impact of new technologies on the company's information systems and architecture.

It also includes processes for incorporating new technologies into the organization, something that is often less straightforward than it appears. It is not only a matter of training particular staff to use a new technology. In many cases, the technology changes parts of the R&D process itself, especially the parts of the process nearest to the area in which the technology has been introduced. It might involve

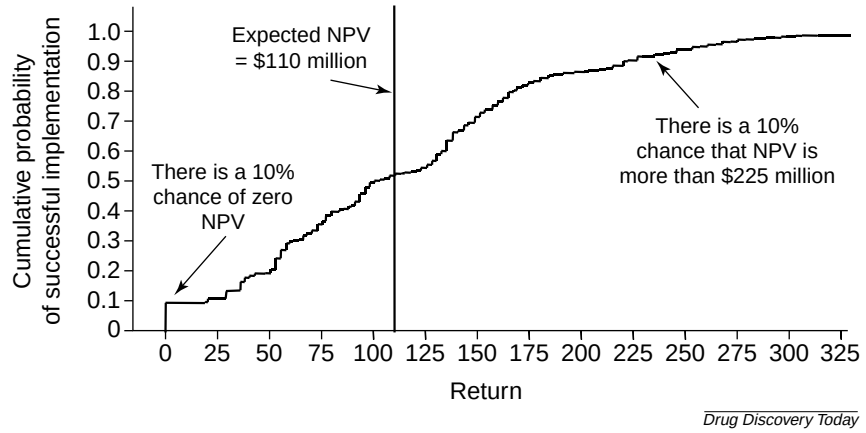

Figure 2. *Defining the value of a technology via a risk profile. Any individual technology can be risk- and value-profiled. In this example, the returns (calculated as future cash flows discounted to present value) from the 16 scenarios in Fig. 1 are plotted against the cumulative probability of successful integration of the technology. The mean expected return is $110 million. However, there is a 10% chance of a return of $225 million and a 10% chance of a zero return. With some technologies, there is a chance of a net loss. In general, the steeper the curve, the lower the risk, but this must be balanced against return as part of a portfolio approach. Abbreviation: NPV, net present value.*

different inputs or outputs; it might even alter the links in the chain. Thus, people working elsewhere in the organization might also have to change the way in which they work.

Assessing technology options

Although the biggest challenge might be human, there are plenty of others with which the industry must contend. Technology providers constantly bombard large pharmaceutical companies with a wide range of so-called 'solutions' at various stages of maturity and therefore, objective assessment of the options is essential. Most companies base their assessments on cost; in fact, strategic impact, organizational scope and time to maturity are more important considerations. Our research also suggests that a three-tier approach is best.

Level 1. Mature technologies with little strategic or organizational impact

Level 1 applies to technologies with relatively little strategic impact or organizational scope and thus a correspondingly low level of risk, or uncertainty about the value they can add (e.g. antisense technologies). Here, the decision-making process (provided that it is coordinated) should take place as far down the hierarchy as possible. It is not a good use of resources if senior managers are spending time assessing local investment decisions.

A simple qualitative data file records the nature and maturity of the technology, its links to the company's business or technology strategy, the benefits it is expected to deliver and a brief history of any tests that have been performed to determine how robust it really is. This information is also logged on a central database so that, if the technology is subsequently acquired, everyone in the organization knows of it. Conversely, if the technology is rejected, nobody wastes time re-evaluating it.

Level 2. Developing technologies with considerable strategic or organizational impact

Level 2 is very much more quantitative and applies to technologies with greater strategic and organizational scope, or those that are less mature and therefore inherently more risky (e.g. miniaturization of HTS to 1536-well plate format). It involves defining the options a company faces at every stage of the decision-making process; measuring the risks associated with each option, calculating the costs and revenues arising from each outcome, and creating a value profile. (The probability of a successful outcome is determined by the scientists and subsequently reviewed.)

The crucial point about the process is the fact that it relies on the collection of real data. However, at this level (unlike Level 3), the data might be based on a generic set of assumptions about costs, time and other types of value, supported by information specific to the technology under consideration (see Fig. 1).

Suppose, for example, that the company is offered an opportunity to evaluate a new piece of target validation technology that complements its business strategy. The first question it faces is, should it conduct a feasibility study? That is, should it test the technology on one or two highly validated reporter systems in very robust assays at low throughput? If it decides not to do so, it learns nothing more – so the value of this option is zero. If it decides to do so, the technology can prove excellent, average or poor. (Defining exactly, and quantitatively, what these terms mean is part of the process; it ensures rigour and consistency across the organization.) The value of doing the feasibility study therefore depends on the particular

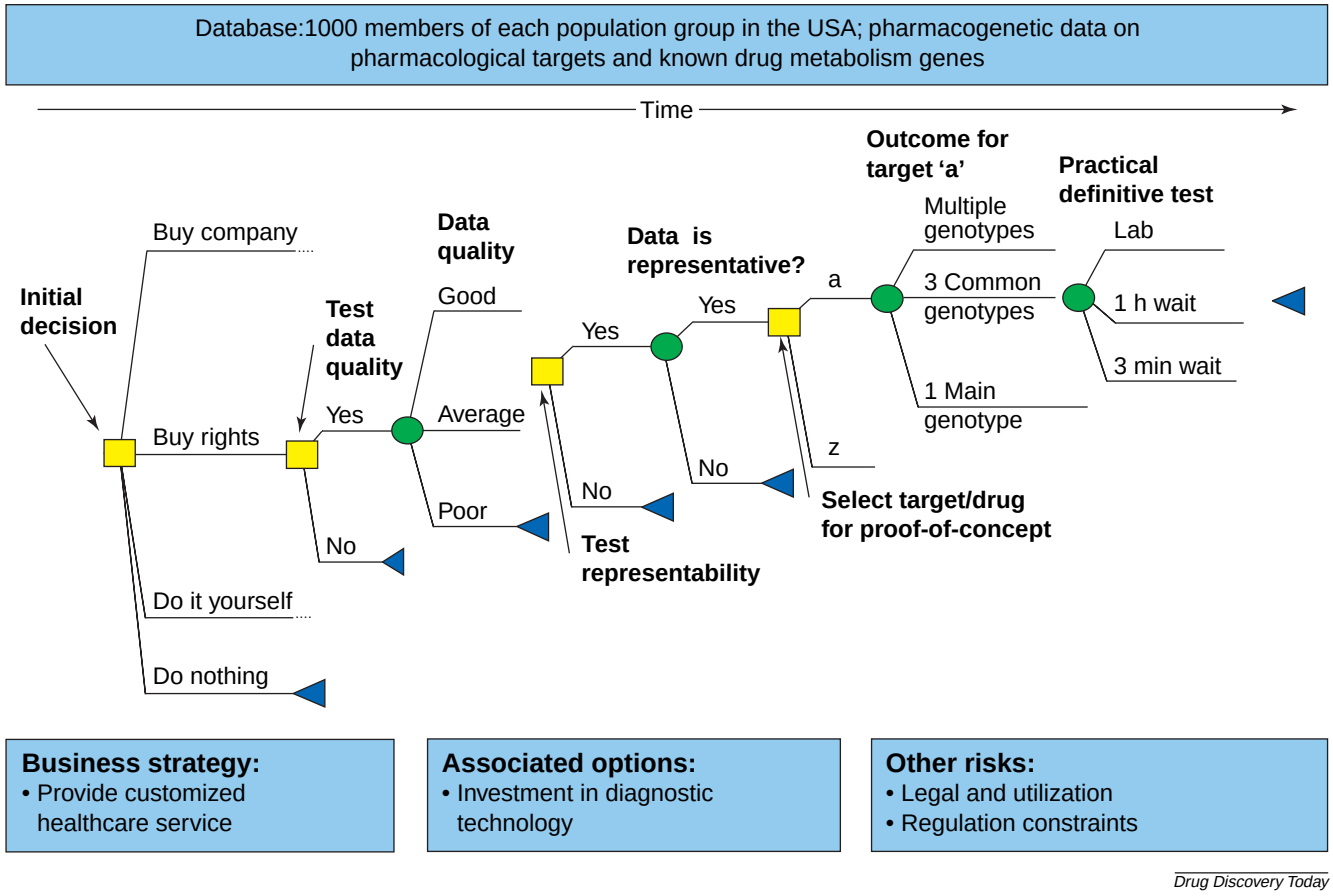

Figure 3. *Typical Level 3 decision tree. Here, a company is considering whether to access a pharmacogenetic database in line with its business strategy of providing a customized healthcare service. The decision is shown in yellow, the risk in green and the value in blue. The overall approach is exactly the same as in Fig. 2. At this level of strategic and organizational impact, however, the process is more involved. A working group with strategic knowledge will define the key decision paths (only one is shown here for clarity) and then collect and analyze as much data (internal and external) to support the decision analysis. The advantage of this approach is that associated options, such as investment in diagnostic technology to support the business strategy, can also be factored into the overall value assessment. Risks such as legal constraints and regulatory issues can likewise be considered. Having gathered as much information as possible, the group will then work the scenarios through and make a decision based on the risks and value of each. It is important that once this is done, action is taken to implement the strategy.*

outcome. However, the likelihood of each outcome can be quantified, thereby enabling the company to make an informed decision.

Suppose that it goes ahead with the feasibility study and the results are excellent. The company now faces a second decision: whether to perform a proof-of-concept study (that is, test the technology against target genes in a variety of cell lines and assays at high throughput). Again, the value of this study depends on the outcome, but the relative probability of getting a (precisely defined) good, average or unsatisfactory result can be quantified. The same is true of any subsequent options, such as whether to bring the technology in-house.

In short, this way of valuing a technology effectively mimics the process of trying to steer a path through the maze. It enables a company to measure the costs (including the initial expenditure and milestone payments) involved in each potential outcome, and the level of uncertainty associated with each. The company can then calculate the value of each outcome, by weighting the projected future cash flows according to the likelihood that it will occur. Collectively, this establishes the probable return on investment from a particular technology, given all the associated risks.

Figure 2 shows how the information can be plotted on a graph. The technology in question has a mean expected

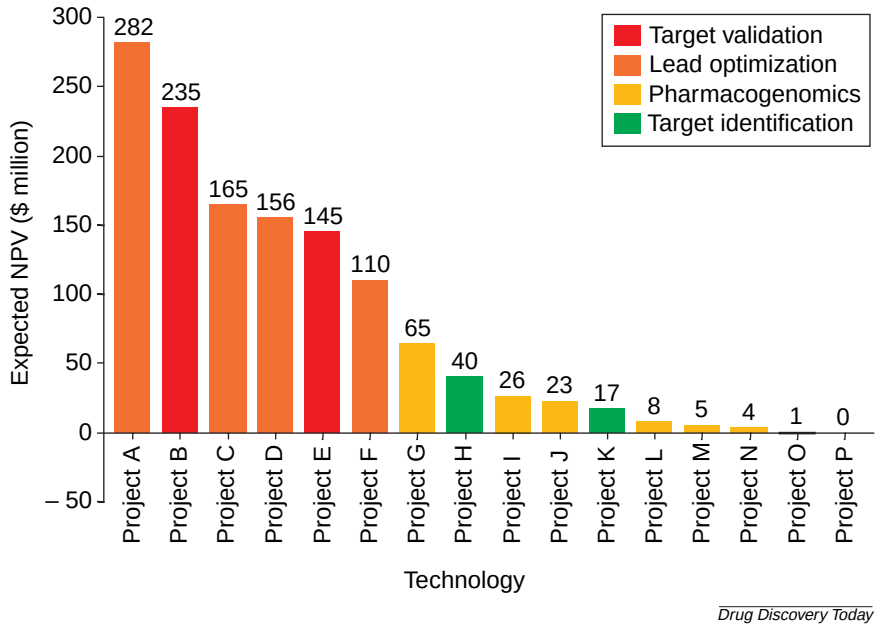

Figure 4. *Defining the expected value of technologies on a project-by-project basis. It is recognized that one of the dangers of new technologies is simply that they move the bottlenecks in the drug discovery process. In general terms, target validation and lead optimization are key value-adding steps but also the major bottleneck for most companies. In this assessment, companies that understand their processes and the associated metrics can shape their technology portfolios to address these key process steps. Abbreviation: NPV, net present value.*

net present value (NPV) (or future cash stream discounted to reflect various factors, including the time value of the money) of $110 million. However, there is a 10% chance that it will generate nothing and a 10% chance that it will generate more than $225 million.

Level 3. Embryonic technologies with potentially great strategic or organizational impact

Even Level 2 is insufficient for projects with acute strategic importance and huge organizational scope. Level 3 uses the same techniques as Level 2, but takes them several stages further. One key difference, for example, is the degree of detail involved in the collection and analysis of data on the potential risks and rewards of the technology in question.

Consider the case of a company that has been offered the opportunity to acquire a database containing pharmacogenetic information on 1000 representatives of each racial group living on the West Coast of the USA. Given that the company's business strategy is to develop a customized healthcare service, it needs pharmacogenetic data to accomplish its research objectives. The technology fits its strategic objectives and is thus worth evaluating.

In this example, the first decision the company must consider is whether to buy the organization that has produced the database, buy the rights to the data, build a similar database itself or do nothing (see Fig. 3). Having identified these options, it can evaluate them in terms of the risks and value associated with each.

Take the risks associated with buying the rights to the data; these clearly include the quality of the data itself. The company must therefore decide whether to test the data before handing over any money. Of course, it does not know at this stage whether the data are good, average or poor, but it can define each outcome relatively precisely and calculate the relative likelihood of each.

Say the quality of the data proves average. The company must then decide whether to test how representative it is. In practice, this is probably the point at which it would have to decide whether to buy the data, but what follows shows the power of the approach. If the data proved representative, the company might decide to perform further tests. It might, for example, want to check the pharmacogenetic implications for various targets in its early discovery portfolio. A particular target might apply to one main genotype (the most desirable outcome), several common genotypes or multiple genotypes (the least desirable result). Based on its knowledge of a particular target, the company might also want to assess the likely functional impact of the various polymorphisms on protein function and drug binding, and to measure other risks such as the uncertainty of developing a practical diagnostic test or the legal and regulatory dangers.

In other words, Level 3 applies where the technology is embryonic or promises to have an enormous impact. It enables the technology group to evaluate individual technologies or technology choices and define the key decision points, to build a case for securing the capital to acquire a particular technology, and to assess the risk–return profile. It also enables the group to assess the most important technologies in the context of the company's whole technology

portfolio, including where the risks and rewards are most concentrated.

Figure 4 shows the expected value of the various technologies in a typical portfolio, measured on a project-by-project basis. Figure 5 shows the resulting risk–reward profile for an entire portfolio, given the successful integration of those technologies. The portfolio represented here is balanced to support the high-value bottlenecks in the discovery process; it demonstrates how companies with clearly defined discovery processes and clear metrics can redesign their technology portfolios based on tangible data, not just 'gut feel'. Moreover, as long as they assess the relevance of those data periodically, they will find they can re-use much of them to evaluate subsequent opportunities, thus increasing the consistency of the decisions they make and the resulting technology portfolio.

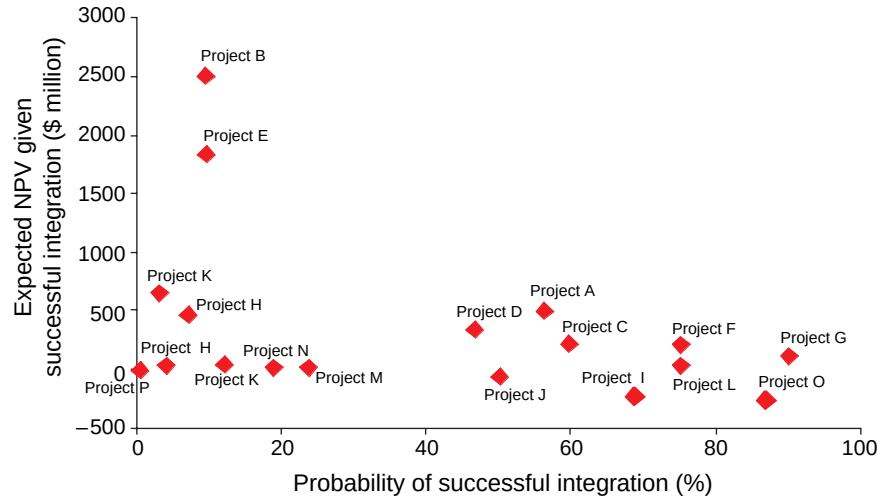

Figure 5. *Building a risk–reward profile for a whole portfolio. When a technology asset has been established, it should be managed and assessed as part of a portfolio in which risk and return are assessed as an on-going process in line with the business strategy. Once the company has taken a decision on risk, the portfolio should be rationalized. New technology options are assessed in the same way and compared with the overall technology portfolio, and investment decisions are taken accordingly. Given finite resources, this approach offers the best way of optimizing technology to deliver a company's business strategy. Abbreviation: NPV, net present value.*

Conclusions

This pragmatic combination of structural and statistical techniques offers the pharmaceutical industry numerous advantages. It provides a consistent and objective system for assessing new technologies, measuring and minimizing risk, and tracking an entire development portfolio. It accommodates different levels of investment and assessment, and ensures that such investment is firmly tied to a company's strategic goals. Above all, it is suitable for discovery technologies, which are notoriously difficult to evaluate. In short, it reduces the potential for expensive mistakes at a time when the stakes have never been so high.

The huge cost of discovering and developing new drugs is perhaps the single most important factor behind the latest bout of mega-deals – and the success with which the industry giants can convert their R&D dollars into truly innovative treatments will determine which will win. Those that learn how to make more and better products will be able to pick their partners; those that fail to do so will be left in the cold.

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