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Unfinished business: target-based drug discovery

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The switch in the mid-1980s/early 1990s from a phenotypic approach to a target-based approach to drug discovery has been followed by low productivity of new drugs entering the market. Reasons for the (necessary) switch and unsolved problems with both approaches to drug discovery are discussed. The S-curve theory of new technology development and introduction can act as guide as to when an upturn in productivity can be expected; this should occur during the next decade leading possibly to a new golden age of drug discovery.

During the 1990s the pharma industry placed an enormous bet. It bet that a target-based approach to drug discovery would be superior to the previous paradigm, which was largely observation-based, using what we now call a 'phenotypic' approach. The industry placed this bet by retooling and reorganizing with no actual evidence that the new approach would deliver the required levels of productivity. Ten to 15 years on, productivity as measured by new drug applications (NDAs) approved annually is at an all time low and company growth rates have fallen dramatically. The reasons for this are complex, but insofar as the change to a target-based approach was meant to overcome the looming decline in productivity, we know now that the bet did not deliver, at least in the short-to-medium term.

This review considers the reasons the switch was made and the relative strengths and weaknesses of the old and new approaches. In particular, it focuses on unsolved problems that will need resolving if drug discovery is to regain its luster. Finally it finishes on an optimistic note noting that knowledge gained during the past 15 years is likely to lead within a decade to the beginning of a new golden age of drug discovery.

Definitions: target-based and observation-based approaches to drug discovery

The 'observation-based' approach is the approach in which compounds are screened versus cells, tissues or even directly in whole animals with a read-out chosen as a surrogate of the response desired in humans. An 'active' eliciting the phenotype of interest is selected as a potential lead.

The 'target-based' or 'hypothesis-based' approach is the approach in which modulation of a selected biochemical mechanism is hypothesized to be potentially useful in treatment of a particular disease. The biochemical factor (enzyme, receptor, channel, etc.) may then be used directly in lead discovery using a screening approach or rational design. 'Actives' that may be selected as 'leads' for optimization are compounds that modulate the selected biochemical mechanism.

Advantages and disadvantages of the two approaches

Before the mid-1980s, the prevailing state of knowledge of human biochemistry meant that only a minority of projects could select with any confidence the appropriate biochemical mechanisms to target for drug discovery. In that situation the observation-led approach was the only feasible means [1]. Projects were largely chemistry-driven and biology was essentially a black-box. Relatively small numbers of compounds could be screened to generate leads, maybe a few dozen each week. In the absence of a mechanistic assay, and with primary screen data being generated in whole cell or tissue assays, structure–activity relationships (SARs) were complex for chemists to optimize, though they often did succeed. Project timelines, however, were usually long by today's standards; often lead optimization alone could take three to five years.

In retrospect we can see that this approach has the advantage that drug discovery projects always start with a lead compound and an effect of interest in a physiological system. The process of screening ensures that both biology and chemistry are in sync. Another

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potential positive is that lead molecules and eventual drugs may exhibit polypharmacy with resulting increased effectiveness.

This approach, however, has several important weaknesses:

(a) Chemists have to work with biological data which is a composite of many factors: binding to the (unknown) target of interest is measured but many other binding phenomena also influence the read-out such as cell absorption, protein binding, metabolism, etc. Some of these are essentially 'sites of loss' of the molecule and each molecule in a related series may experience differential loss, giving a very complicated picture. Moreover the efficacy read-out may actually be the result of polypharmacy; the molecule may be interacting with several targets, for example with enzymes, channels or receptors closely related in structure to that which is actually targeted. As a result SAR patterns may be very complicated and difficult to interpret during lead optimization.

(b) Lack of knowledge of the mechanism of action is a major impediment during early clinical trials. There is substantial risk that the mechanism may not be relevant to man. This risk can be overcome to some extent by testing human cells and tissues but it may not be possible to get a relevant assay for many diseases (this criticism can also be made of the target-based approach). Although attempts can be made to identify the mechanism of action of leads, historically this has rarely been successful during the timeline of the discovery or early clinical project.

(c) Another consequence of not knowing the mechanism of action of a drug as it enters clinical trials is that the risk of mechanism-based toxicity cannot be assessed. Therefore safety as well as efficacy in clinical trials can be something of a gamble. If safety issues are encountered in early clinical trials, it is often difficult to tell whether toxicity is 'off-target' and therefore potentially separable in a new molecule, or is mechanism-based and therefore inseparable from the desired effect of the drug. Decision-making on whether to continue the project is difficult in these circumstances.

With problems such as these, the phenotypic approach to drug discovery became less popular during the first half of the 1990s. By this time, human biochemistry had advanced to a point where the majority of projects could be based on a hypothesis about the involvement of a discrete biochemical mechanism in disease, and on this basis, target-based drug discovery became predominant in the industry. Both biologists and chemists welcomed the change. Biologists could offer much better assays, and these were very popular with chemists who now had excellent quantitative data to guide SAR analysis and drug design. Two new technologies in particular which were widely available from the late 1980s enabled the rapid retooling of the industry. The first was the rapid spread of recombinant DNA methods. The second was the commercial availability of low-cost fast protein liquid chromatography (FPLC) for protein purification. With these changes, biochemistry and molecular biology emerged as important disciplines in an industry that had previously been dominated by chemists and pharmacologists. It was now possible to screen compounds versus purified target protein, often using highly automated equipment and data analysis, at the rate of many thousands of compounds per week. Also at this time, drug metabolism and pharmacokinetics (DMPK) emerged as an important independent discipline with specialists working closely with chemists during the lead optimization cycle. With these supportive changes, chemists found lead optimization to be easier and faster, with lead optimization timelines dropping substantially: the previous timelines of three to five years have been replaced by one to three years now.

However, this new approach is no panacea, and experience has shown that there are a number of issues with the target-based approach to drug discovery:

(a) Targets selected may have poor disease linkage, unsupported by any animal or clinical data: they are 'unvalidated' and this can lead to a high failure rate downstream in the discovery phase or in clinical trials. In this respect, one of the major problems of the earlier observation-based approach has not been fully resolved.

(b) On the chemistry side, hits and leads are often difficult to find: it has taken the industry much longer than expected to develop lead discovery methods to a point where success rates are adequate. Even now, after more than 15 years of development of HTS and compound libraries, one can safely say that most projects could benefit from a broader range of lead molecules. Moreover, many targets have proven to be undrugable, at least with current knowledge.

(c) The ability to predict off-target effects has been poorer than expected despite this being one of the perceived advantages over the observation-led approach.

(d) Sometimes, molecules encounter *in vivo* assays representative of the human disease state quite late in the drug discovery process. Although this could be regarded as a choice made by project scientists, in practice, lead molecules selected from *in vitro* screens used in a target-based approach may have characteristics which make them inherently less suitable for testing in whole tissue or whole animal systems than those selected by phenotypic screening in more complete biological systems. The drug discovery process now has several extra steps before identifying a lead with an effect of interest in a whole physiological system modeled on the disease of interest. Most of the early phase of a project is based on drug–target interaction not on drug–organism interaction. This can lead to significant failures midstage in a drug discovery project when compounds eventually encounter whole animal systems.

(e) Because targets are precisely defined, many more companies are working on the same targets than was the case in the days of the observation-led approach. This means there may be much more overlap in company R&D portfolios than in earlier periods of the industry's history. This leads to conflicts in Intellectual Property (IP). Also, if those targets prove to be fruitless (and many do) then there is the potential consequence of industry-wide failure.

Productivity record

Concerns about the target-based approach were voiced by one industry manager as follows: 'For the past decade the pharmaceutical industry has experienced a steady decline in productivity and a striking observation is that the decline coincided with the introduction of target-based drug discovery' [2]. The correlation is observable, though we should be aware that other factors may also been important. Drug discovery has got tougher for reasons

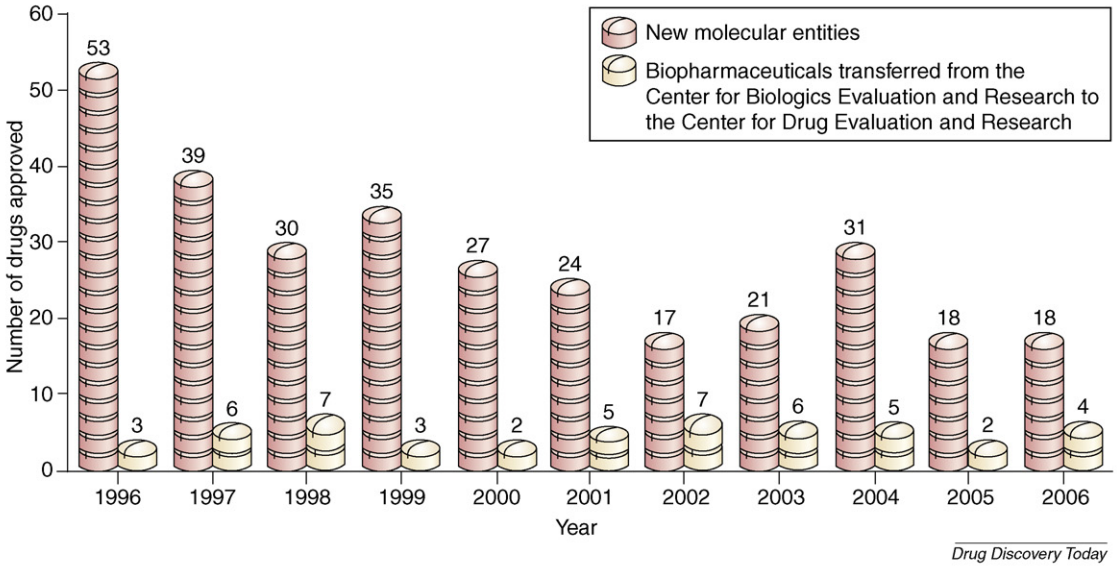

FIGURE 1

New molecular entities (NMEs) and biologic license applications approved by the US FDA by year. The number of NMEs approved in 2006 stayed the same as in 2005, with the number of approved biologics (4) still below that achieved in 2001–2004. Reproduced with permission from Macmillan Magazines Ltd [8].

which are common to any maturing industry. Previous efforts in drug discovery led to a substantial number of effective medicines. Pharmaceutical scientists seeking the next generation of breakthrough drugs face increased barriers in that the drugs now required are often either 'third-generation' drugs for diseases now moderately well treated, or 'first generation' drugs for 'difficult' diseases. Either way, scientists face higher hurdles. It is, however, certainly true that major changes were made to drug discovery processes over the past two decades without evidence of the likely success of the new approaches.

The productivity record (Fig. 1) following these changes has been well reviewed in the literature [3–7].

To recap briefly, productivity as measured by new drug approvals is running at a rate approximately half that a decade ago. According to Tufts Center for Study of Drug Development, marketing approval was received from the U.S. Food and Drug Administration for only 58 new drugs in 2002–2004, a 47% drop from the peak of 110 new drugs in the years 1996–1998. And the picture was no better in 2005 and 2006: all the companies in the industry achieved just 18 New Drug Approvals for new molecular entities (NMEs) by the FDA in 2005 and again in 2006, together with 2 biologic license applications in 2005 and 4 in 2006. The FDA reported that the decrease in approvals is because of a reduced number of NDAs [8].

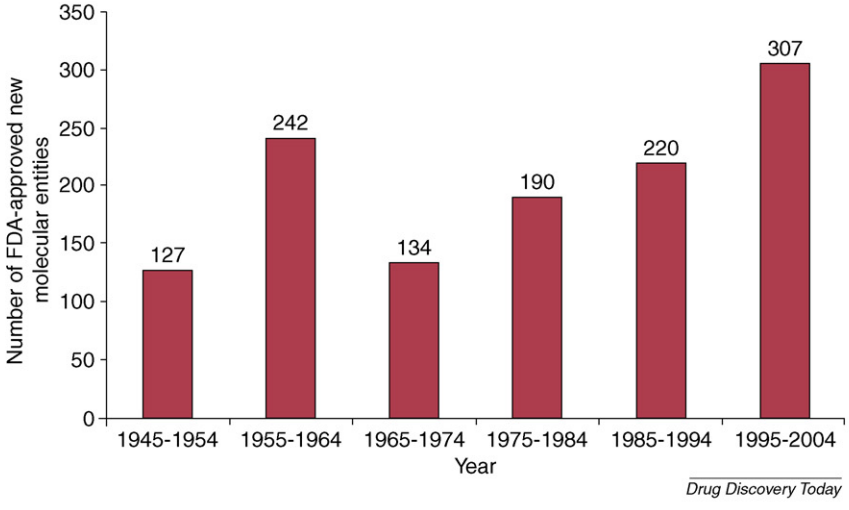

FIGURE 2

Industry performance (FDA-approved new molecular entities) over six decades. Reproduced with permission from [9].

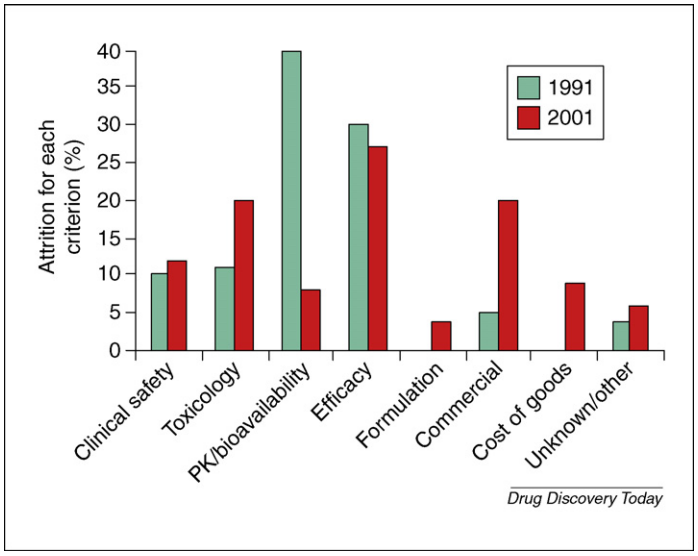

FIGURE 3

Percentage comparison of the reasons for R&D project losses in 1991 and 2001 (% projects lost). Reproduced with permission from Macmillan Magazines Ltd [12]. Equivalent data analyzing reasons for failure of biological products is not available, possibly because of the recent development of these types of product and the small sample size; however, two publications have indicated that overall survival rates are higher [5,13].

It has been argued by authors taking a longer-term view that our industry has actually achieved a steady *increase* in productivity over the past six decades with positive impact of human health and longevity. This is illustrated in Fig. 2, which shows increasing productivity decade-by-decade since the 1940s [9]. This chart, however, hides the fact that most of the NMEs recorded for 1995–2004 were registered early in that period with a clear drop in drugs registered since the turn of the century as illustrated in Fig. 1.

One notable fact is that in recent years (data for 2004–2005), the number of molecules each year entering clinical development (Investigational New Drugs; INDs) increased steeply, yet failure rates in clinical trials appear to have increased as evidenced by the declining ratio of NDAs to INDs [10]. Notably, the failure rate in phase 3 trials, the time of highest expenditure, has risen dramatically: approximately half of drugs reaching phase 3 have failed in recent years compared with less than 20% in earlier periods.

With R&D cycles extending to 8–12 years, these NDA success rates must reflect decisions and practices from the early to mid-1990s, including those discussed above.

Reasons for drug losses

The overall productivity record begs the question 'why are projects and drugs failing'? The reasons for attrition have been well studied within companies and by independent bodies. Several analyses have been published [11,12] and these will be briefly summarized here. Note that the data used in these analyses come from large pharmaceutical companies; there is no current evidence to indicate whether small biotechnology companies are more or less efficient in their R&D efforts.

Cumulative attrition in the discovery phase is approximately 80% and this means that only about one in five drug discovery projects succeeds in selecting a compound for clinical trials [11]. Cumulative attrition in clinical development – the high-cost part of drug R&D – is even higher at over 90%. Fewer than one in ten clinical projects succeed in delivering a product to market. Overall, throughout the R&D process fewer than 1 in 50 projects succeeds in getting a drug to market [11].

Comparison of the reasons for R&D project failure over the decade 1991 (the tail-end of the old paradigm) to 2001 indicates

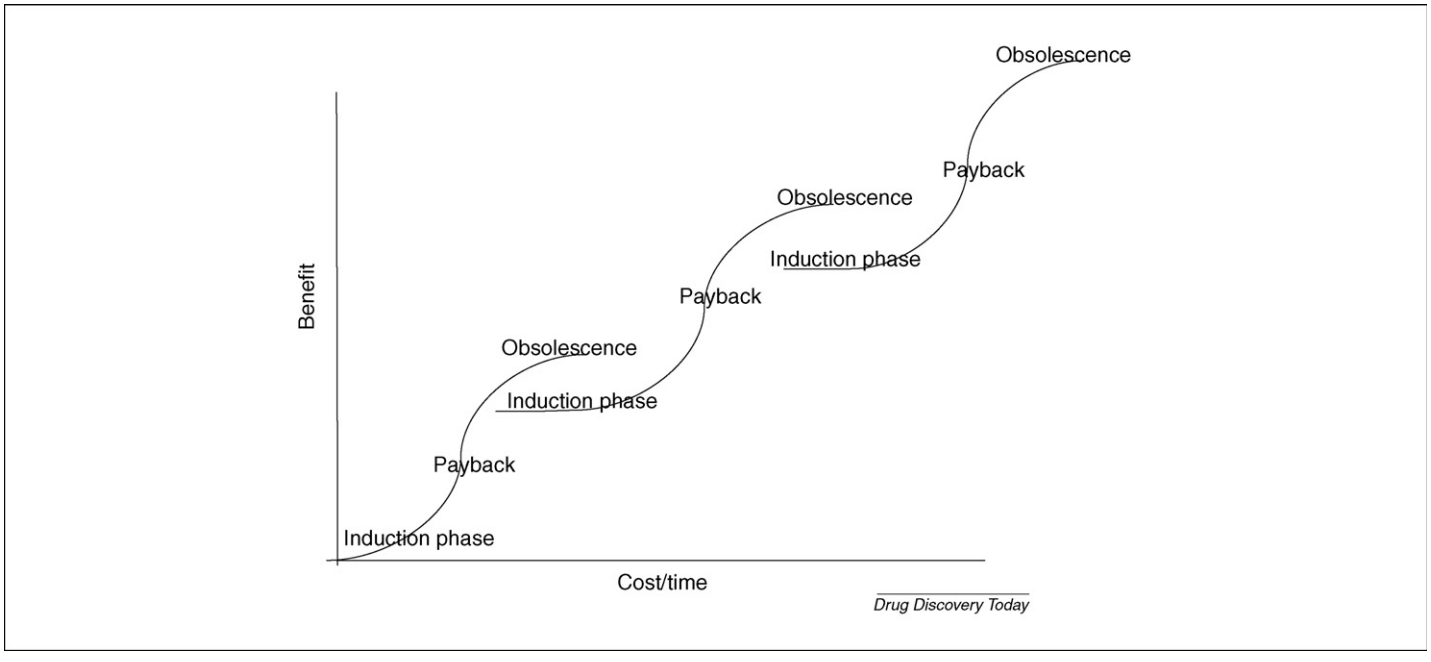

FIGURE 4

Successive waves of technology investment, maturity and obsolescence. Reproduced with permission from The Thomson Corporation and David Brown: Editorial opinion: [14].

TABLE 1

The five main reasons for project failure

Reason for failure	Description
Target mechanism	The chosen target mechanism fails in animal or clinical studies
Lead molecule	There may be either total failure to find a lead that can be optimized or 'hits' are selected as leads that later prove nondrugable
Drug safety	The final drug candidate selected from the lead series fails to pass regulatory toxicology requirements at IND stage
Clinical ADME	Adverse events or poor pharmacokinetics are observed in clinical trials that were not predicted by animal studies
Clinical efficacy	Failure to demonstrate the efficacy expected from animal studies or results from earlier smaller clinical trials

that the introduction of new methods had done little to change the reasons for small-molecule losses (Fig. 3).

Losses because of drug efficacy have not improved even though target-based drug discovery was particularly intended to reduce the incidence of this cause of loss. Similarly, the approach was intended to reduce losses because of problems with toxicology and clinical safety, yet both these causes of loss appear to have increased over the decade. And project terminations for commercial reasons increased dramatically: this is possibly for nonscientific reasons such as elimination of projects as companies have merged and then focused on projects targeting larger market size. Note also that this may be a marker supporting the author's comment above that the target-based approach may be driving significant overlap of company R&D portfolios, leading to abandonment of potential drugs in late clinical development when competitors achieve drug registration more rapidly. Finally, cost of goods (COGs) appears to be of rising concern. The rise in COGs – which represents the cost of bulk drug production – may parallel the increase in difficulty of finding good lead molecules such that more complex structures are being accepted into lead optimization with consequences downstream for commercial pricing.

It should be noted however that drug discovery has certainly got more difficult as industry scientists focus increasingly on more complex diseases than in earlier periods, such as Alzheimer's disease, various cancers and stroke. Animal models for these diseases are not well correlated with human disease and the risk of failure in clinical trials is consequently higher than experienced with earlier generation of drugs. This points to a key need: better animal models of the complex diseases currently research by the industry to reduce attrition rates in clinical trials.

One glimmer of hope is indicated by Fig. 3: it appears that failures for pharmacokinetic reasons have reduced, and many in the industry will be well aware of significant improvements in knowledge and practice that has led to this positive result.

An additional pressure on the industry that is not represented in Fig. 3 is because of increased regulatory hurdles. Over the years there has been a steady drift toward greater regulation and in particular requirements for both safety and efficacy have been increased. Clinical trial sizes have steadily increased in response such that both costs and timelines have inflated. This undoubtedly is another factor behind the reduction in recent years in the number of drugs entering phase III that go on to successfully achieve approved NDA status.

Overall, we can summarize five main reasons why projects fail (Table 1). Failures can be due to the target mechanism chosen proving to be not relevant in animal or clinical studies; to failure to find a good lead molecule; to drug safety in that the chosen molecule fails to pass regulatory toxicology studies; to poor pharmacokinetics in man and to failure to demonstrate efficacy in clinical trials.

It is notable that these are much the same reasons that drugs failed before the target-based approach was adopted, despite the fact that this new paradigm was expected to overcome some of these problems.

For the future, the key issue is whether we are making progress in learning how to reduce losses. Even though the record during the first full decade of use of the target-based approach could be regarded as disappointing, it could be argued, based on S-curve theory of new technology introduction, which is discussed below, that this is too short a time-span to observe significant improvements and that we are still in the induction phase of the new technology; and that over the coming decade we are likely to see the benefits of the investments made.

S-curve theory of technology development

Previously, the author has argued [14] that the S-curve theory of technology development, introduction and payback can act as a guide to a realistic expectation of the rate of impact of the 'new technology' of target-based drug discovery. The S-curve theory states that technology performance increases with investment but eventually reaches a plateau where further improvement would either be impossible or prohibitively expensive. Achievement of higher performance requires a discontinuous switch to a different technology, which in turn follows its own S-curve (Fig. 4) of development through three phases: first, induction phase as the technology is being developed and tested; second, payback phase as the successful modes of the technology are widely adopted; and third, senescence phase when the technology has been played out and needs replacing by a more productive technology itself entering the payback phase of its own S-curve.

The new technology may well start at a performance level below that of the old one, but it has the potential to overtake its predecessor. In the context we are discussing here, the old technology of a phenotype-based observation-led approach reached its obsolescence plateau in the late 1980s following several decades of productive service to the industry. The new target-based approach should then have taken over. However, my view is that the new technology was not ready; it was still in the induction phase rather than the payback phase when the industry made the switch in the early to mid-1990s. We suffered a discontinuity in the waves of S-curves (Fig. 4) because, though we needed the new technology to be at least starting its payback phase, it was actually still early in its induction phase when the industry switched over to it. Moreover, and this is a key point, note that the induction phase appears to

extend to 15–25 years according to all the best research done on this topic [15,16]. This indicates that the target-based approach may fully mature into its payback phase in the next decade rather than this one. So a key point here is that our industry has been suffering a period when one S-curve of technology had peaked and plateaued before the new technology (the target-based approach founded on molecular biology and the human genome) was mature, that is before it reached the payback part of the S-curve. I believe this is at least one reason why productivity has fallen and is an explanation of the recent malaise in our industry.

Conclusions and perspective

In summary, there are unsolved problems with the target-based approach to drug discovery, and current evidence indicates that it has yet to fulfill its potential. There are grounds for hope as steady advances in technical solutions and in implementation are being made. This is occurring also with the phenotypic approach which may receive something of a renaissance for some aspects of drug discovery [1]. Overall I agree with the conclusion of Schmid and Smith [9] that 'we are now seeing the first products emerge from the new approach', and that 'a key requisite in this achievement was the evolution of a knowledge-base in a range of areas'. This is descriptive of the final stages of the induction phase (Fig. 4) and the beginning of the payback phase of the S-curve of new technology introduction. We must, however, not expect immediate rapid increases in NME registration because the 15–25-year induction phase may not be fully played out yet. The S-curve theory suggests that productivity increases in small-molecule drug discovery are more likely to be achieved consistently in the next decade.

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